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REVIEW® of Ophthalmology

April 2016

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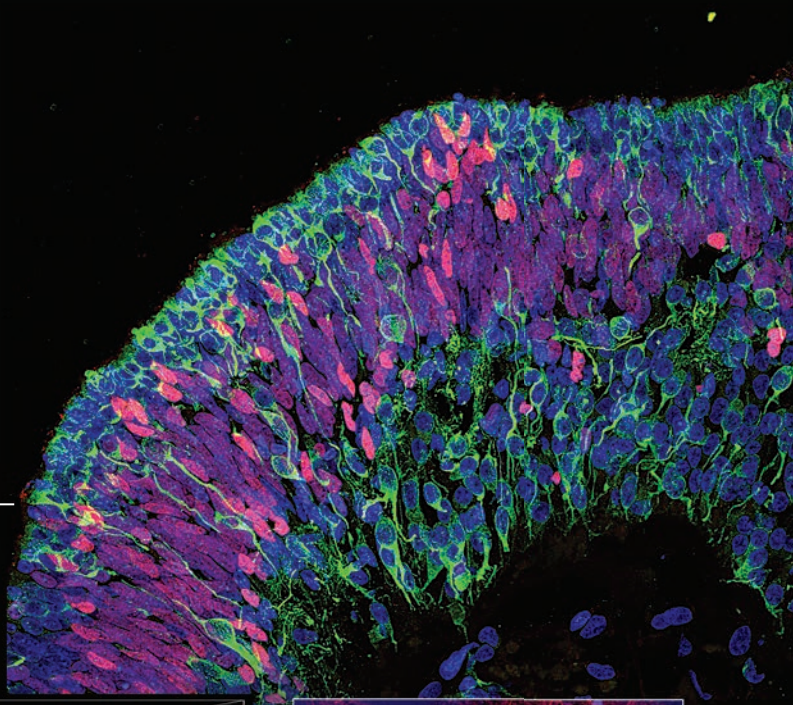
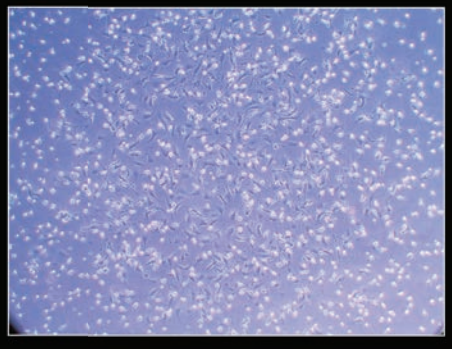
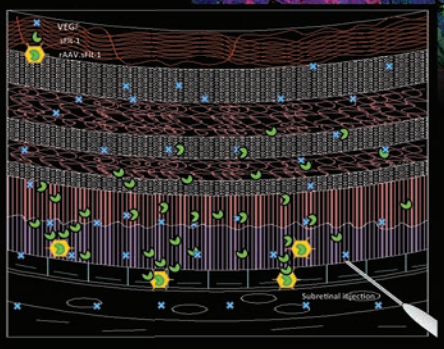
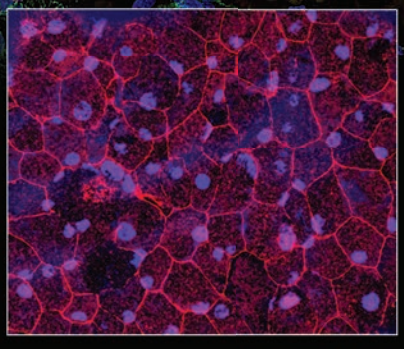
FIVE YEARS OUT

What's ahead for stem cells and gene therapy.









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REVIEW NEWS
Volume XXIII • No. 4 • April 2016

Dietary Vitamin C Appears to Slow Development of Cataract

A diet rich in vitamin C helps slow the progression of cataracts, suggests a new study published online in *Ophthalmology*. The research also shows for the first time that diet and lifestyle may play a greater role than genetics in cataract development and severity.

Researchers at King's College London looked at whether certain nutrients from food or supplements could affect the development of cataract. They also tried to find out how much environmental factors such as diet mattered as compared to genetics.

The team examined data from more than 1,000 pairs of female twins from the United Kingdom. Participants answered a food questionnaire to track the intake of vitamin C and other nutrients, including vitamins A, B, D, E, copper, manganese and zinc. To measure the progression of cataracts, digital imaging was used to check the opacity of their lenses at around age 60. The second measurement took place on average 10 or so years later but was only performed on 324 pairs of twins.

Both vitamin C and manganese were associated with a 20-percent risk reduction for cataract at baseline. After 10 years, the amount of lens opacity increased in all subjects, as expected. But researchers found that women who reported consuming more vitamin C from foods had a 33-percent risk reduction of cataract progression.

Genetic factors accounted for 35 percent of the difference in cataract progression. Environmental factors, such as diet, accounted for 65 percent. These results suggest genetic factors may be less important in the progression of cataracts than previously thought. Not enough data was available on the various vitamin supplements consumed to adequately study their individual effects.

IUPUI Researchers Use Stem Cells to Identify Cellular Processes Related to Glaucoma

Using stem cells derived from human skin cells, researchers led by Jason Meyer, PhD, assistant professor of biology, along with graduate student Sarah Ohlemacher of the School of Science at Indiana University-Purdue University Indianapolis, have successfully demonstrated the ability to turn stem cells into retinal ganglion cells, the neurons that conduct visual information from the eye to the brain. Their goal is the development of therapies to prevent or cure glaucoma.

In addition to glaucoma, this work has potential implications for treatment of optic-nerve injuries of the types incurred by soldiers in combat or athletes in contact sports.

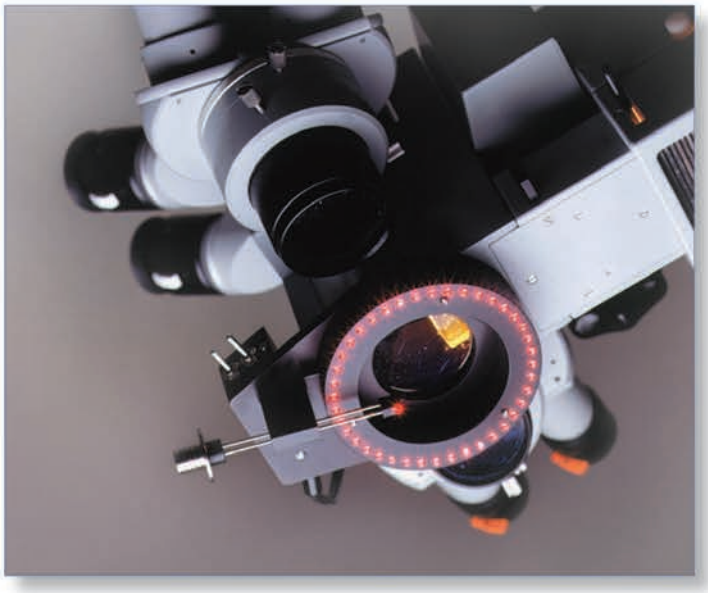
In the study, which appears online in advance of publication in the journal *Stem Cells*, the IUPUI investigators took skin cells biopsied from volunteers with an inherited form of glaucoma and from volunteers without the disease and genetically reprogrammed them to become pluripotent stem cells, meaning they are able to differentiate into any cell type in the body. The researchers then directed the stem cells to become RGCs, at which point the cells began adopting features specific to RGCs—features that were different in the cells of individuals with glaucoma than in the cells that came from healthy individuals.

Glaucoma is the most common disease that affects RGCs. When these cells are damaged or severed, the brain cannot receive critical information, leading to blindness. The National Institutes of Health's National Eye Institute estimates that glaucoma affects more than 2.7 million people in the United States and more than 60 million worldwide.

"Skin cells from individuals with glaucoma are no different from skin cells of those without glaucoma," said Dr. Meyer, a cell biologist and stem cell researcher, who also holds an appointment as a primary investigator with the Stark Neurosciences Research Institute at the Indiana University School of Medicine. "However, when we turned glaucoma patients' skin cells into stem cells and then into RGCs, the cells became unhealthy and started dying off at a much faster rate than those of healthy individuals.

"Now that we have produced cells that develop features of glaucoma in culture dishes, we want to see if compounds we add to these RGCs can slow down the degeneration process or prevent these cells from dying off. We already have found candidates that look promising and are studying them. In the more distant future, we may be able to use healthy patient cells as substitute cells as we learn how to replace cells lost to the disease. It's a significant challenge, but it's the ultimate—and, we think, not unrealistic—long-range goal."

For a further update on stem cell research, see p. 26.



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How dietary vitamin C inhibits cataract progression may have do with its strength as an antioxidant. The fluid inside the eye is normally high in vitamin C, which helps prevents oxidation that clouds the lens. More vitamin C in the diet may increase the amount present in the fluid around the lens, providing extra protection.

"The most important finding was that vitamin C intake from food seemed to protect against cataract progression," said study author Christopher Hammond, MD, FRCOphth, professor of ophthalmology at King's College London. "While we cannot totally avoid developing cataracts, we may be able to delay their onset and keep them from worsening significantly by eating a diet rich in vitamin C."

Aerie Presents Rhopressa Safety Update

Aerie Pharmaceuticals reported an update including further details on the safety profile for Rhopressa QD, a novel once-daily eye drop being tested for its ability to lower intraocular pressure in patients with glaucoma or ocular hypertension. The company previously reported interim topline 12-month safety and efficacy data on Feb. 17, 2016, for Aerie's second Phase III registration trial for Rhopressa QD, indicating that the drug had a positive safety profile with sustained efficacy through the 12-month period. The company expects to submit the NDA for Rhopressa QD in the third quarter of 2016. Among the safety update highlights:

• Detailed 90-day safety data from Rocket 1 and Rocket 2 for Rhopressa

REVIEW of Ophthalmology
EDITORIAL STAFF

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

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

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

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

Chief Medical Editor
Mark H. Blecher, MD

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

QD were shared with the Food and Drug Administration during the pre-NDA meeting that was held in October 2015.

• Based on the Rhopressa QD safety and efficacy data reviewed by the company to date, and in consideration of the adverse event and efficacy profiles of other products currently in the market, the company believes that product candidate Rhopressa QD continues to have significant potential.

• Patients with contraindications to timolol, or beta blockers in general, or otherwise presenting with cardiopulmonary issues, were excluded from both Rocket 1 and Rocket 2. Based on Centers for Disease Control & Prevention data from 2011 and 2014, an estimated 47 percent of the U.S. population older than 65 years of age has heart disease and chronic obstructive pulmonary disease, all of which are contraindications to timolol.

• Since it is not systemically absorbed, Rhopressa QD has not shown any drug-related systemic effects, nor has it generated any serious adverse events. Every other product in the adjunctive market for glaucoma and ocular hypertension has a history of drug-related systemic effects. Rhopressa is being positioned to compete in the adjunctive market, which represents approximately half of the prescription volume for glaucoma products in the United States.

• The most prevalent adverse event for Rhopressa QD was conjunctival hyperemia, the large majority of which was considered mild. Fifty percent of Rhopressa QD patients experienced hyperemia at some point during the trial; however, only 10 percent of the patients in the trial had hyperemia at each visit over the 12-month trial period.

• Other adverse events, including corneal deposits, conjunctival hemorrhages, blurry vision and reduced visual acuity, all of which have been observed in safety data for other marketed products, were commonly sporadic or self-resolving for the 118 patients on Rhopressa QD for the 12-month period in Rocket 2.

Slides posted to the Aerie website (aeriepharma.com) include an in-depth analysis, including images where applicable, of the Rhopressa QD adverse events noted in the safety data.

Drug Repurposed To Treat Pterygium

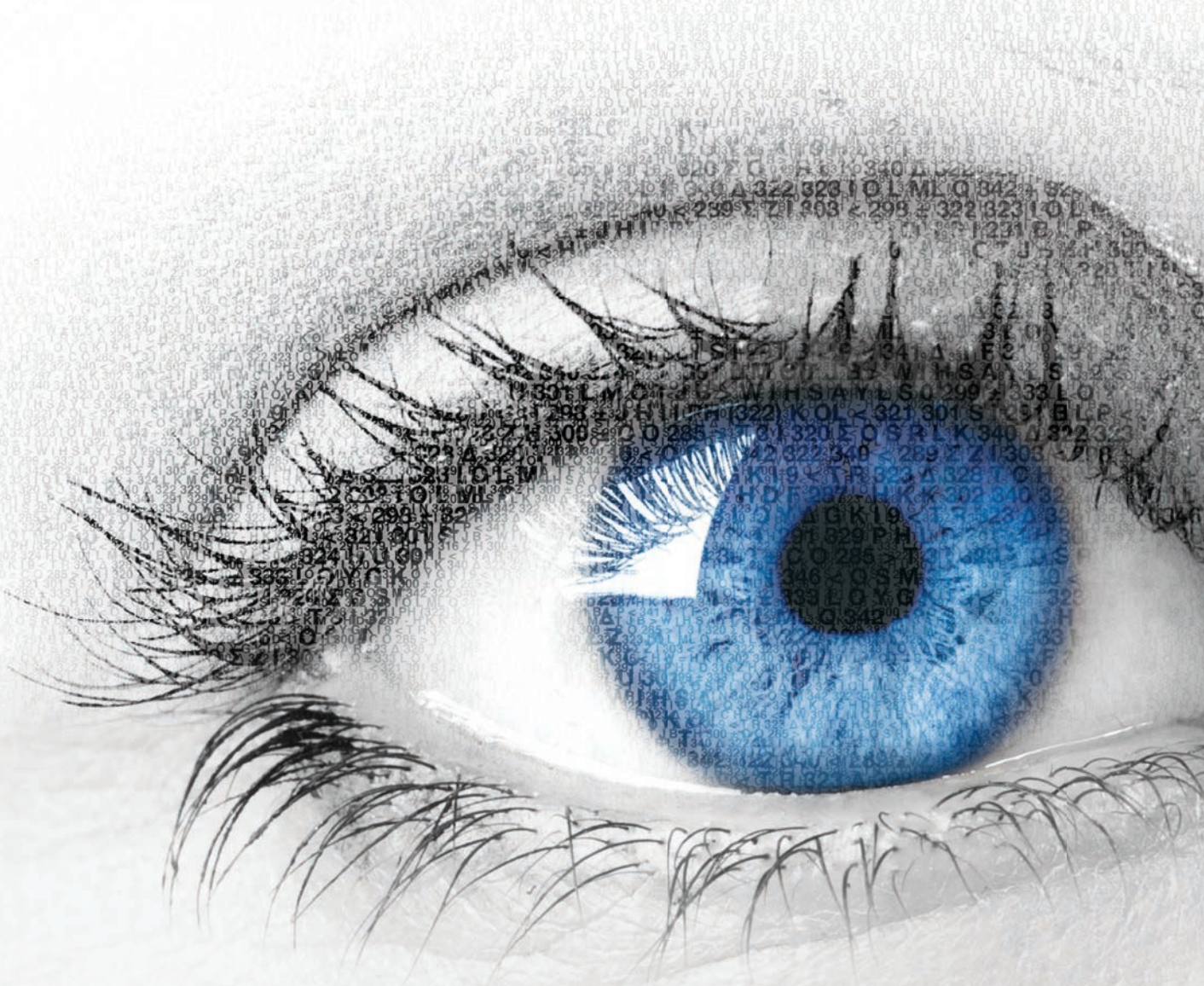
At the Israeli Society for Vision and Eye Research conference on March 10, the MedInsight Research Institute and Center for Drug Repurposing at Ariel University presented the latest findings on positive user-reported outcomes of the repurposed drug dipyridamole in treating pterygium and related dry-eye symptoms.

Dipyridamole is a cardiovascular drug, used for the past 55 years for treating angina and preventing stroke. It also has wide applicability for eye disorders, having been researched for various eye ailments over the past four decades, including diabetic retinopathy, ocular hypertension and retinal hemorrhage. In 2014, MedInsight published the first case report of a pterygium patient being successfully treated with dipyridamole eye drops.

In the findings presented at ISVER, researchers analyzed outcomes of dry-eye symptoms reported by patients with pterygium. Using the Ocular Surface Disease Index, the researchers found that there was a maximum reduction in OSDI scores averaging 52.4 percent during the course of treatment for 25 patients. Some patients reported a complete resolution of symptoms. Photographic evidence showed marked antiangiogenic effects and regression of the pterygia.

"These results are very exciting,"

(continued on page 25)



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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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INDICATION AND USAGE

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IMPORTANT SAFETY INFORMATION

- BEPREVE® is contraindicated in patients with a history of hypersensitivity reactions to bepotastine or any of the other ingredients.
- BEPREVE® is for topical ophthalmic use only. To minimize risk of contamination, do not touch the dropper tip to the eyelids or to any surface. Keep the bottle closed when not in use.
- BEPREVE® should not be used to treat contact lens-related irritation. Remove contact lens prior to instillation of BEPREVE®. Lenses may be reinserted 10 minutes after BEPREVE® administration.
- The most common adverse reaction occurring in approximately 25% of patients was a mild taste following instillation. Other adverse reactions occurring in 2%-5% of patients were eye irritation, headache, and nasopharyngitis.

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Please see the accompanying full Prescribing Information for BEPREVE® on the following page.

Reference: 1. BEPREVE [package insert]. Tampa, FL: Bausch & Lomb Incorporated; 2012.

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For product-related questions and concerns, call **1-800-323-0000** or visit **www.bausch.com**.

BEPREVE®
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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

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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.

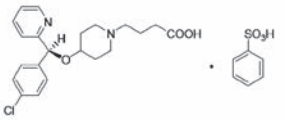
8.3 Nursing Mothers
Following a single 3 mg/kg oral dose of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection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

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

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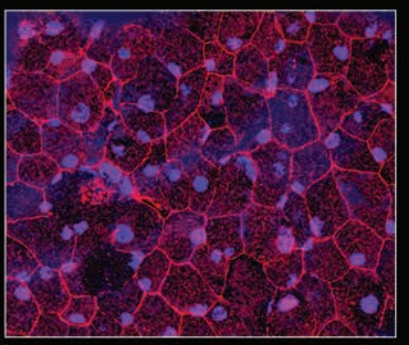

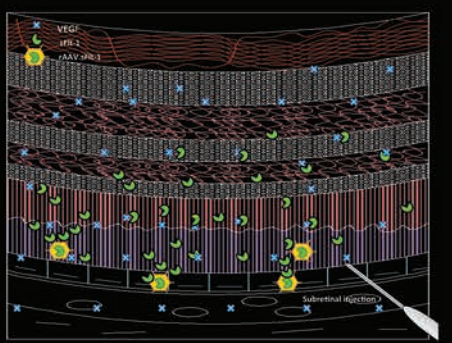

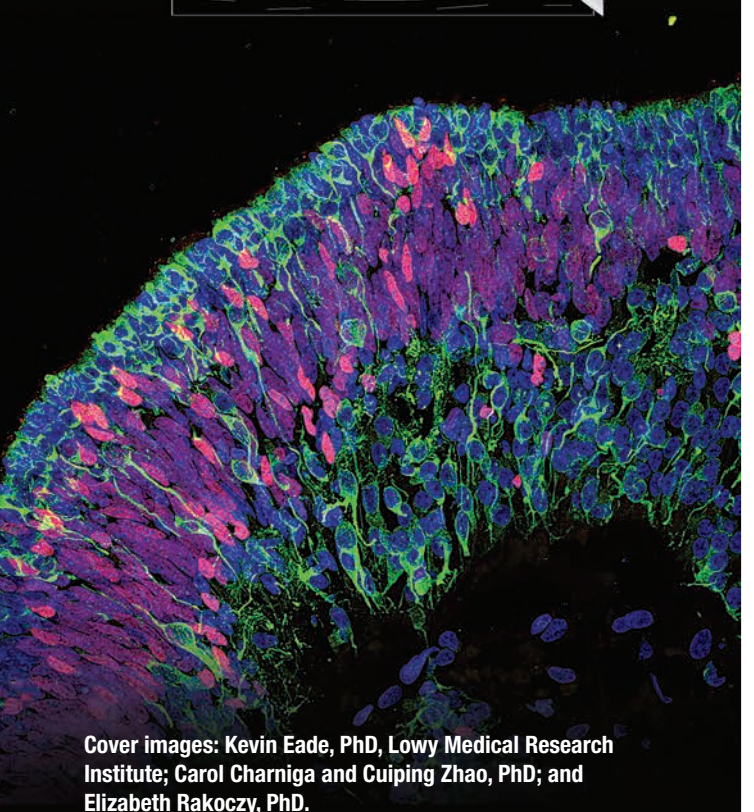

Cover images: Kevin Eade, PhD, Lowy Medical Research Institute; Carol Charniga and Cuiping Zhao, PhD; and Elizabeth Rakoczy, PhD.

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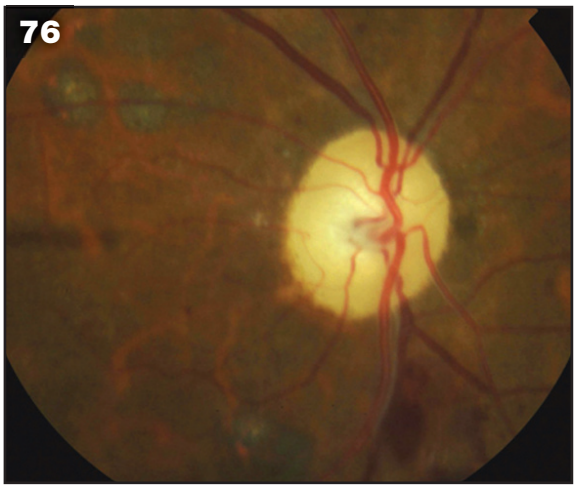
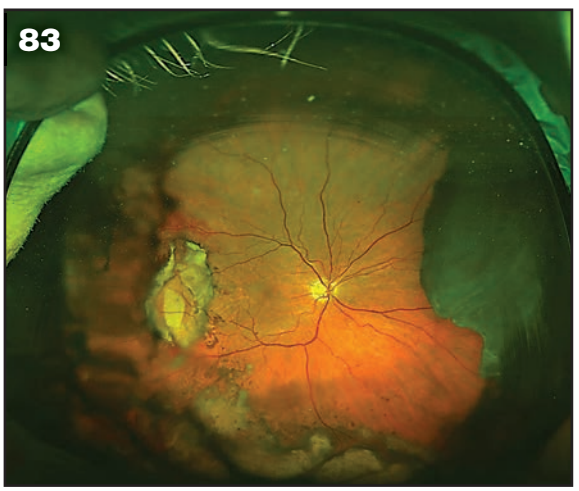
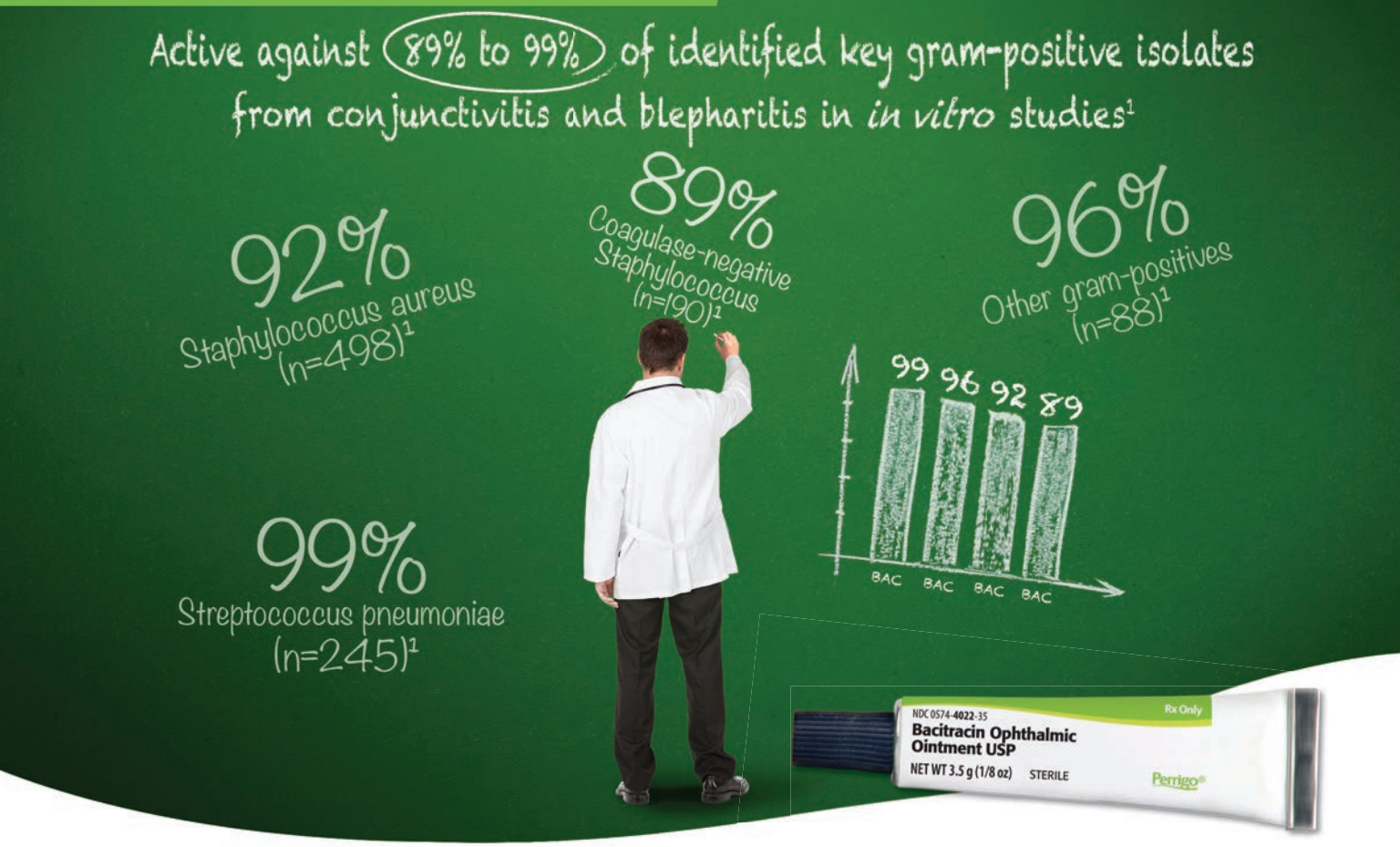




BACITRACIN OPHTHALMIC OINTMENT USP



***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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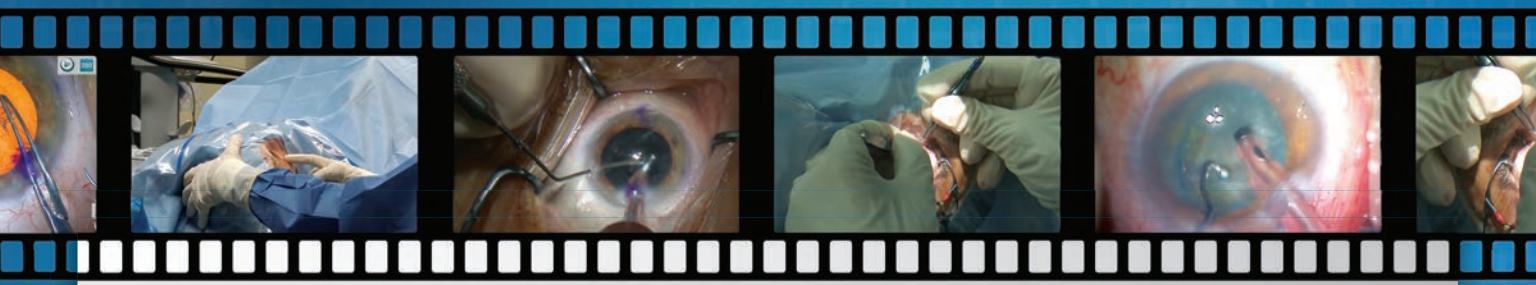

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Episode 4: "Severe Zonule Laxity: The Zonule-Friendly Technique"

Surgical Video by:
Richard J. Mackool, MD

Pseudoexfoliation and a large nucleus that masks zonule laxity is the situation with this eye in which the anterior capsule behavior during capsulorhexis doesn't alert the surgeon to the true status of the zonule. Using Trypan Blue, 360º viscodissection, a back crack technique, special techniques to rotate the nucleus, capsule retractors and a CTR, I am able to perform zonule-friendly phaco and IOL insertion in an eye that continues to bring surprises throughout the case. The video is necessarily a bit long but I think you will really enjoy this one!

Introducing: MackoolOnlineCME.com

Richard J. Mackool, MD

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

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

CME Accredited Surgical Training Videos Now Available Online: www.MackoolOnlineCME.com

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

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

Episode 4: Learning Objectives

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

1. To anticipate and appropriately respond to evidence of zonular laxity during phacoemulsification
2. To achieve familiarity with the advantages provided by capsule retractors in eyes with zonular laxity
3. To be aware of methods to insert and remove capsule retractors

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.

Credit Designation Statement
IAHB designates this live activity for a maximum of .25 *AMA PRA Category 1 Credits™*. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

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New Ways to Catch Keratoconus Preop

Surgeons say using the technology you have can help yield more accurate pre-LASIK screening results.

Walter Bethke, Managing Editor

In the medical realm, sometimes you don't need a new piece of technology to help you make a diagnosis, but instead just need to use your current technology in a new way. This is the idea behind a pair of pre-LASIK screening approaches. One method takes the data many surgeons are acquiring preop to calculate a new parameter that can be key in keratoconus: asymmetry. The other uses existing data to get an idea of how altered the cornea will be postop, which is a risk factor for ectasia. Here's how the approaches work.

The Asymmetry Index

Lima, Peru, ophthalmologist Maria Henriquez says that detecting an asymmetry between a patient's eyes, rather than just focusing on one eye, might help catch keratoconus preop.

"Keratoconus is a bilateral disease," Dr. Henriquez explains. "However, unlike glaucoma, which usually gets a bilateral evaluation, keratoconus doesn't get a bilateral analysis. So, we performed a study to analyze the tomography parameters in eyes with keratoconus in order to develop a bilateral asymmetry index."

In a prospective study presented at the 2015 meeting of the American Society of Cataract and Refractive Surgery, Dr. Henriquez and her co-workers used the Pentacam to analyze 424 patients (748 eyes). Of these patients, 294 had bilateral keratoconus, 50 had high myopia or astigmatism, 30 had forme fruste keratoconus, and 50 had low ammetropia and were used as a control group. The researchers studied 30 parameters, including central corneal thickness, pachymetry at the thinnest point and posterior elevation at the thinnest point. Among other results, they found that the mean asphericity asymmetry in the keratoconus group was 0.36 µm compared with 0.05 in the high ammetropic group ($p<0.001$). The mean steep keratometry asymmetry in keratoconus was 2.26 D compared with 0.48 D in the high-ammetropic group ($p=0.01$), and the mean anterior elevation asymmetry at the corneal apex was 7.34 µm compared with 1.61 µm in the high-ammetropic group ($p=0.03$). Asphericity had an area under the receiver operating characteristic curve of 0.97 in discriminating between keratoconus and high-ammetropic eyes.

Dr. Henriquez says the results showed there's a greater asymmetry in eyes with keratoconus than in normals or eyes with high refractive errors. "With the model we developed," she explains, "if we compare very early keratoconus—defined as both eyes having K values less than 48 D—with normal eyes, we've found a sensitivity and specificity of 0.92. However, when we add a non-asymmetric variable called the Final D, a percentage derived from logistic regression of all the parameters, sensitivity and specificity increases to 0.98."

There are certain patient presentations that can confound the asymmetry index. "If a patient has had previous surgery in one eye but not the other, you're going to find a larger asymmetry value, but it's not keratoconus.

"We've calculated the normal asymmetry value in the normal population," Dr. Henriquez continues. "This value plus two standard deviations is the normal range. If the value is outside this, the risk is increased. This is similar to OCT glaucoma detection systems."

The asymmetry index isn't currently on a device, but Dr. Henriquez says

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- **Avoid reimbursement difficulties by using broadly covered OMIDRIA and the OMIDRIAssure™ services (OMIDRIAssure.com)**

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.

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

Visit www.omidria.com

OMEROS

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

she and her colleagues are working with Oculus at the moment, though no agreement has been finalized. If a surgeon doesn't have access to a Pentacam, or doesn't want to wait until the index comes to that device, he can do the asymmetry calculation, though it will be more involved. "You have to look at the parameters I suggest in our paper in order to calculate the asymmetry, and you can get the normal value for comparison because it's published in our paper.[1] You can compare the asymmetry value you get with the normal value. It will be more difficult to do, but you can do it."

Percent of Tissue Altered

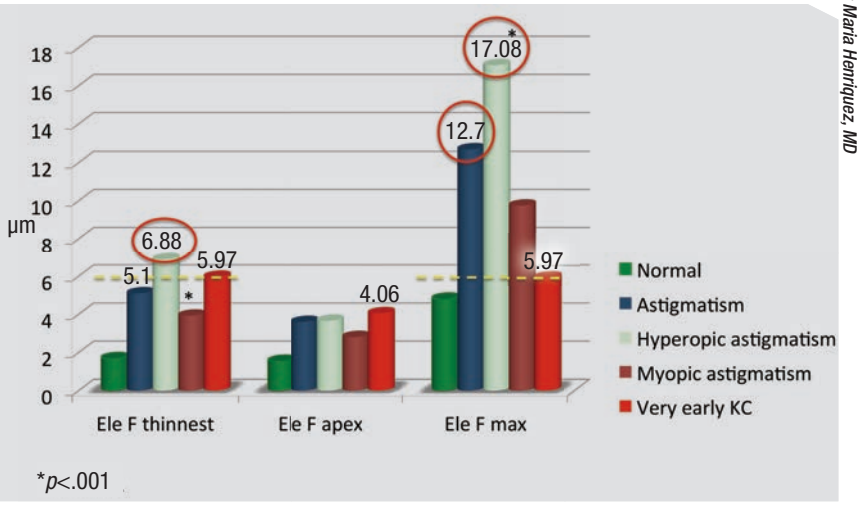
Marcony Santhiago, MD, PhD, of Rio de Janeiro, Brazil, acknowledges that parameters such as the residual corneal bed post-LASIK and the flap thickness play roles in ectasia risk, but thinks they're just part of the equation. More important, he argues, is the percentage of the tissue that's altered by the entire procedure.

Dr. Santhiago says PTA is represented by the following equation: PTA = (FT+AD)/CCT. In the equation, FT is flap thickness, AD is ablation depth and CCT is the preoperative central corneal thickness. "This concept, in my opinion, better describes the interaction between flap thickness, ablation depth and corneal thickness," Dr. Santhiago says. "Our studies show that, in eyes with normal preop topography, PTA has a higher prevalence, presents the higher odds ratio and a higher predictive capability for ectasia risk than the values of residual stromal bed, central corneal thickness, ablation depth or age.[2] In our studies, the risk of ectasia rapidly increases with a PTA higher than 35 percent—with 100-percent sensitivity—and its combination of sensitivity and specificity peak when PTA is equal to or higher than 40 percent." He adds that, in eyes with abnormal topography, less tissue alteration is necessary to induce ectasia. "Even subtle signs of abnormal topography are associated with ectasia after minimal tissue removal, and therefore there is no safe limit in such a situation."

Dr. Santhiago says PTA may be more than the sum of its parts, since it combines the effects of the flap and the ablation. "There is a common thought that the flap thickness is the only factor responsible for ectasia, or that ectasia only occurs in eyes that have the so-called, 'thicker-than-expected' flaps," he says. "We conducted a study to specifically address this matter. We investigated groups perfectly matched for PTA and flap thickness: In the first group were eyes with the same PTA, some of which developed

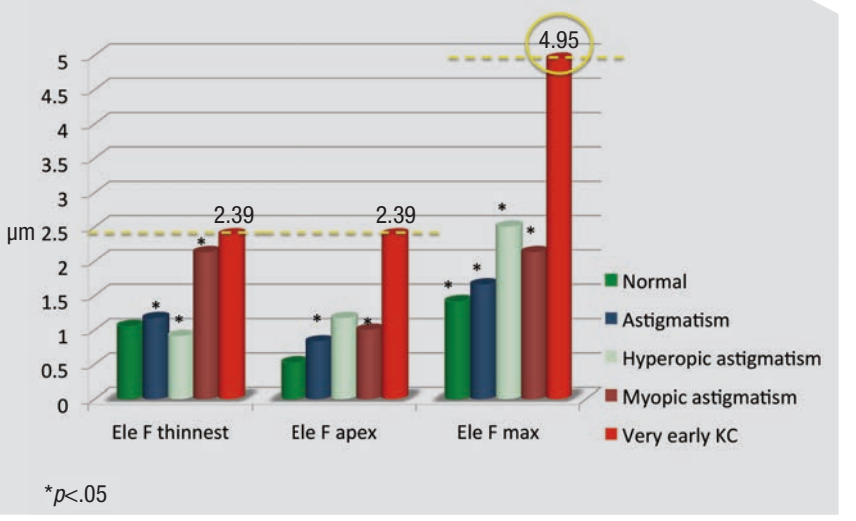
Figure 1. Highest Values from One Cornea's Analysis

Images: Maria Henriquez, MD



When the front surface elevation values of a high-ammetropic cornea are analyzed, astigmatism and hyperopic astigmatism stand out more than very early keratoconus.

Figure 2. Asymmetry Analysis Highlights Early Keratoconus



When a bilateral evaluation of the cornea from Figure 1 and its fellow is performed, suddenly the very early keratoconus stands out as the highest value.

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ectasia and some of which didn't; and in the second group were eyes with the same flap thickness, some of which developed ectasia and some of which didn't. In the first group, we did find that the group that developed ectasia had thicker flaps. In the second group, the patients who developed ectasia had a greater ablation depth. Therefore, we found that the LASIK flap had a greater impact than ablation depth, but that thicker flaps alone were insufficient to create ectasia unless coupled with greater ablation depths—meaning high PTA values. As a result, it appears that PTA presents higher discriminative capabilities than each of the variables that comprise it."

Dr. Santhiago says the same goes for the metrics of residual bed thickness and central corneal thickness, which many surgeons initially used as guideposts for screening. "Residual bed thickness theoretically informs you about the remaining load-bearing tissue after surgery, but 250 or 300 µm would mean different biomechanical changes depending on how much tissue you've altered to reach that value," he explains. "This concept was proposed assuming that the cornea had a homogeneous distribution of tensile strength, which isn't true. Since corneal tensile strength is not uniform throughout the central cornea, but instead has a progressive weakening in the posterior two-thirds, it seems reasonable that a ratio or a percentage wouldn't only be more representative of the actual change that has occurred, it's also a more individualized metric. This concept is the basis for PTA."

The Santhiago PTA display is a feature available on the Ziemer Galilei, which isn't approved by the Food and Drug Administration. However, it's conceivable that a surgeon with a reliable pachymeter could do the calculation himself to get a better idea of a patient's risk for developing ectasia. "As a risk factor, the weakening predicted by a high PTA, or any other factor, doesn't mean that ectasia will occur in all high-risk eyes," Dr. Santhiago notes. "It merely means these eyes carry an increased risk. It seems logical, though, that the balance of risk should be weighted toward minimizing it, especially when other excellent procedures are available. If PTA is the only risk factor, the surgeon should change to surface ablation and the patient would fall within safe limits." REVIEW

Dr. Santhiago is a consultant to Ziemer. Dr. Henriquez has no financial interest in the products discussed.

1. Henriquez MA, Izquierdo L, Belin MW. Intereye asymmetry in eyes with keratoconus and high ammetropia: Scheimpflug imaging analysis. Cornea 2015;34:10:S57–S60.
2. Santhiago MR, Smadja D, Gomes BF, et al. Association between the percent tissue altered and post-laser in situ keratomileusis ectasia in eyes with normal preoperative topography. Am J Ophthalmol 2014;158:1:87-95.

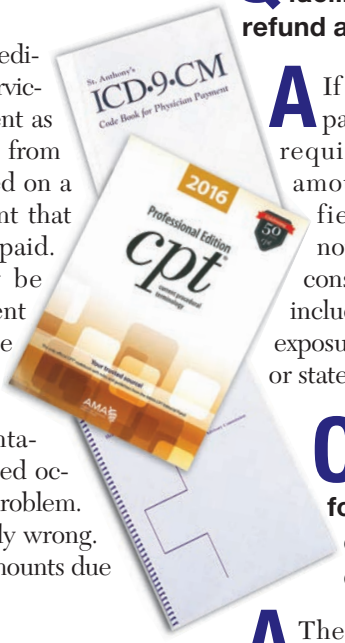
Donna McCune, CCS-P, COE, CPMA

When Your Medicare Cup Runneth Over

Overpayments: a look at the causes, the variety of correct responses and how you can prevent them in the future.

Q Is there a definition of an "overpayment"?

A The Centers for Medicare & Medicaid Services defines an overpayment as money received, usually from a third party payer, based on a claim for reimbursement that should not have been paid. An overpayment may be all or part of the payment received. It may be the result of an unintended mistake or caused by intentional misrepresentation. It may be an isolated occurrence or a recurring problem. Overpayments are clearly wrong. They are not disputed amounts due to differences of opinion.



Q Are there common causes resulting in overpayments?

A There are a variety of causes, including:

1. poor chart documentation that does not support the medical necessity for services;
2. upcoding eye exams; and
3. unbundling of services described by one inclusive CPT code.

Q Is the provider or facility expected to refund an overpayment?

A If you identify an overpayment then you are required to refund that amount within a specified time frame. By not doing so, there are consequences that could include fines and criminal exposure under federal and/or state law.

Q What is the time frame for returning an overpayment once discovered?

A The Patient Protection and Affordable Care Act §6402(a) requires return of an overpayment within 60 days after the date on which the overpayment was identified.

However, on February 11, 2016, CMS published a final rule, CMS 6037-F, requiring providers and suppliers to return overpayments within 60 days of identifying it. The consequences for not returning an overpayment within this time frame could include potential False Claims Act liability, Civil Monetary Penalties Law liability and exclusion from federal health care programs. If CMS or its contractors determine an overpayment exists and issue a demand letter, providers and suppliers are required to adhere to CMS procedures outlined in the demand letter.

Q Is an attorney required to make a refund of an overpayment?

A Not usually. If a significant amount of money is involved (e.g., >$10,000, or >20 percent of annual payments from the payer), it may be advisable to arrange the refund through an attorney with expertise in health law.

Q What is the process for voluntarily refunding overpayments to Medicare and other payers?

A Voluntary refunds of overpayments should be directed to the payment correction unit of the Medicare administrative contractor, or to the specific department of a third party payer that handles refunds. Many

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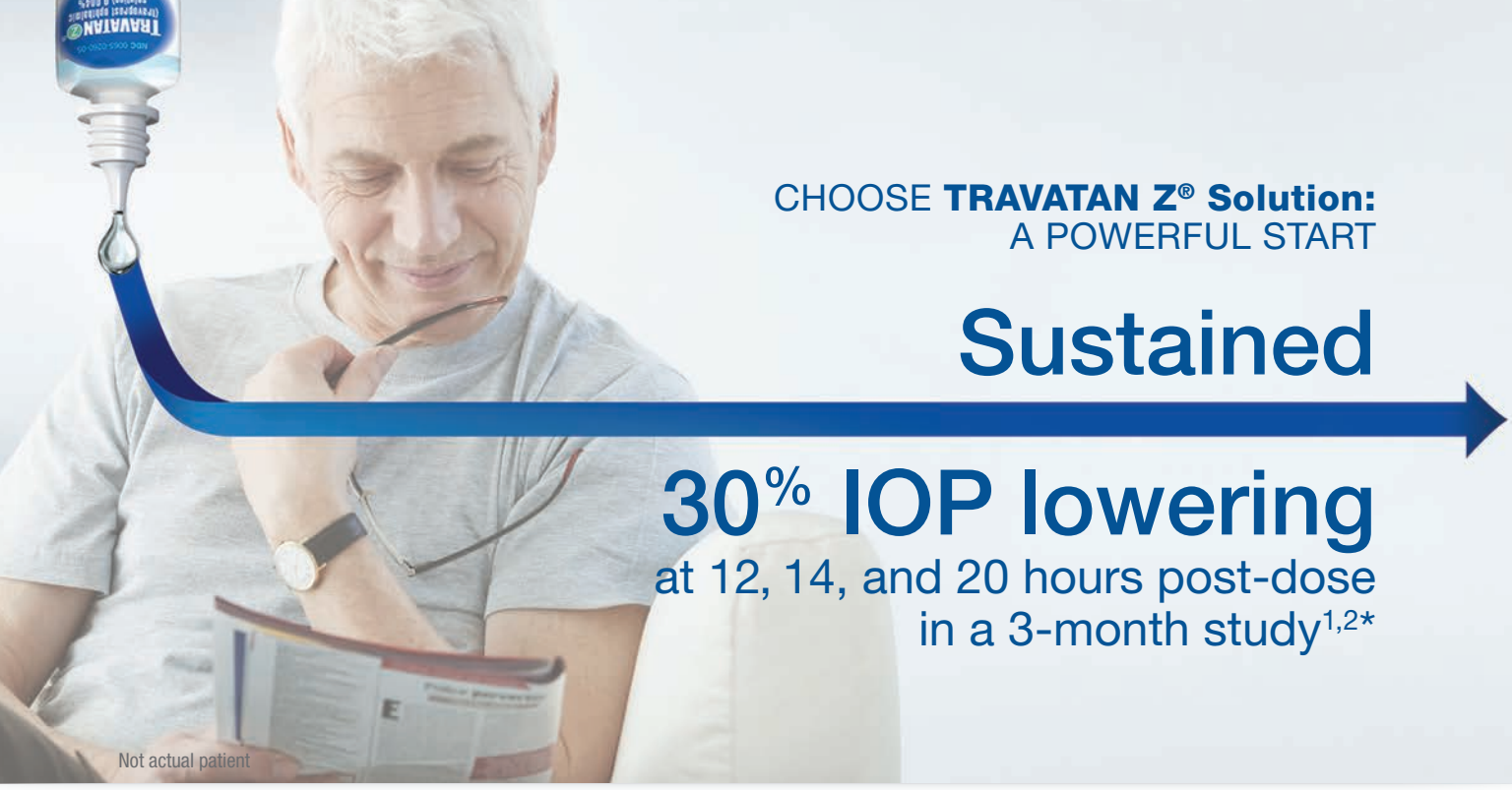

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INDICATIONS AND USAGE

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

Dosage and Administration

The recommended dosage is 1 drop in the affected eye(s) once daily in the evening. TRAVATAN Z® Solution should not be administered more than once daily since it has been shown that more frequent administration of prostaglandin analogs may decrease the IOP-lowering effect.

TRAVATAN Z® Solution may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than 1 topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

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

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

Adverse Reactions

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

Use in Specific Populations

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

For additional information about TRAVATAN Z® Solution, please see the brief summary of Prescribing Information on the adjacent page.

*__Study Design:__ Double-masked, randomized, parallel-group, multicenter non-inferiority comparison of the efficacy and safety of travoprost 0.004% preserved with benzalkonium chloride (BAK) to TRAVATAN Z® Solution after 3 months of treatment in patients with open-angle glaucoma or ocular hypertension. Baseline IOPs were 27.0 mm Hg (n=322), 25.5 mm Hg (n=322), and 24.8 mm Hg (n=322) at 8 AM, 10 AM, and 4 PM for TRAVATAN Z® Solution. At the end of Month 3, the TRAVATAN Z® Solution group had mean IOPs (95% CI) of 18.7 mm Hg (-0.4, 0.5), 17.7 mm Hg (-0.4, 0.6), and 17.4 mm Hg (-0.2, 0.8) at 8 AM, 10 AM, and 4 PM, respectively. Statistical equivalent reductions in IOP (95% confidence interval about the treatment differences were entirely within ±1.5 mm Hg) were demonstrated between the treatments at all study visits during the 3 months of treatment.

References: 1. Data on file, 2013. **2.** Lewis RA, Katz GJ, Weiss MJ, et al. Travoprost 0.004% with and without benzalkonium chloride: a comparison of safety and efficacy. *J Glaucoma.* 2007;16(1):98-103.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

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

CONTRAINDICATIONS
None

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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of the Medicare contractors have a form on their website for completion to accompany the refund check. Some other third party payers may not have an organized mechanism for accepting repayments, even though you are legally obligated to provide them. Do not send money to any payer until you are told exactly where to send it. It is advisable to send refunds via registered mail, return receipt requested or some other method that tracks delivery and signature; keep a copy of all related correspondence.

Q What information should be sent along with the refund check?

A Medicare, and likely other payers as well, need to know:

1. why the voluntary refund was made;
2. how it was identified;
3. what sampling techniques were employed;
4. what steps were taken to assure that the issue leading to the overpayment was corrected;
5. the dates the corrective action was in place;
6. specific claims involved in the inappropriate payments;
7. the methodology used to arrive at the amount of the refund; and
8. whether a full assessment was performed to determine the extent of the refund.

Q If I make a voluntary refund, will this prompt the payer to conduct an audit?

A Not necessarily. Sending a check with a clear explanation of the overpayment issue should not lead to further review. However, there is a legitimate concern that reporting a sizeable overpayment might trigger an audit.

Q Is refunding an overpayment sufficient to address the problem?

A No, it is only the beginning. The practice or facility should investigate to determine whether the overpayment is part of a larger problem and then educate staff and physicians about the proper way to obtain reimbursement so that the overpayment does not reoccur. New policies may need to be put in place to prevent a recurrence.

Q Is there a way to prevent overpayments?

A An effective compliance program is the best way to prevent these problems. It includes:

- a clear commitment to compliance;
- appointment of a compliance officer;
- effective training and education programs;
- auditing and monitoring;
- a communication system such as a hotline;
- internal investigations and enforcement; and
- response to identified offenses and application of corrective action initiatives.

Q Can an overpayment be treated as fraud?

A Yes, but only if it satisfies the definition of fraud. Fraud is an intentional deception or misrepresentation made for personal gain. It is both a crime and a civil law violation. In some cases, the False Claims Act can be implicated. REVIEW

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

(continued from page 6)

said Moshe Rogosnitzky, director of the Center for Drug Repurposing, who discovered the treatment. "Until now, the only known treatment for pterygium has been surgical removal, which involves a high recurrence rate. In addition, patients are often given topical steroids to treat their symptoms, but this can result in glaucoma. Now we have a promising potential treatment for this very difficult-to-treat disorder, and it appears to be not only effective, but entails only a small amount of a very safe medicine. This treatment possibility offers distinct advantages over the existing treatment."

Aaron Frenkel, research coordinator for MedInsight, added that studies are currently being planned at medical centers in Israel, Europe, Turkey and India. "This drug does not yet have commercial sponsorship, so studies are taking longer to initiate since research funds are dependent on donors. We are hopeful that clinical trials will begin later this year," he said.

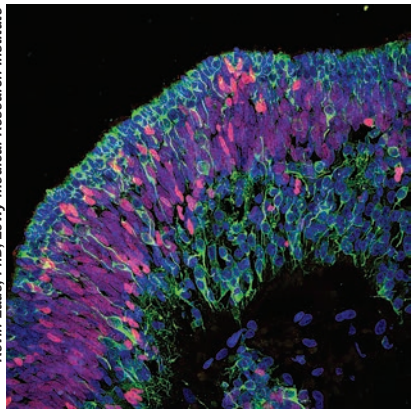
Patents Issued for Micropulse Laser

Iridex Corp. announced two new patent approvals covering key elements of its MicroPulse technology and improving the delivery of its subthreshold treatment for patients with glaucoma and retinal diseases. The patents cover Iridex's TxCell Scanning Laser Delivery System, which is a platform that allows MicroPulse laser therapy to be planned and delivered in a grid pattern, allowing the procedure to be completed with greater efficiency and confidence than older "singlespot" delivery strategies. Expanding on the core MicroPulse technology, these new patents cover automatic laser delivery with multispot pattern scanning for efficient retinal photocoagulation that is tissue-sparing and enables faster treatment procedures. REVIEW

Stem Cells: The Future Looks Bright

Christopher Kent, Senior Editor

New ideas and discoveries are leading to new possibilities for stem cell use.



Kevin Eade, PhD, Lowy Medical Research Institute

A cross section showing mature human retinal neurons (green) derived from retinal progenitor cells (red) layered in an 18 week retinal cup.

For many people, the use of stem cells to address disease represents high-tech medicine at its most promising. Being able to generate brand new cells that might replace sick cells—or even entire organs—seems like science fiction made real. Not surprisingly, however, the path to such possibilities is turning out to be full of unexpected twists and turns.

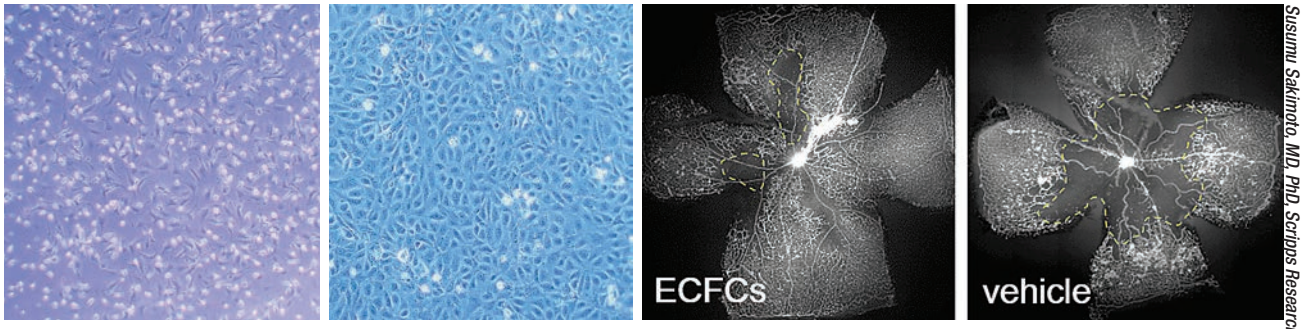
Current developments that are impacting the field include new ways to coax adult cells to return to a pluripotent stem-cell state; new ideas about using stem cells as a support network rather than replacements for diseased cells; and new insights regarding how to prevent unwanted side effects such as tumors. Here, three researchers share their latest work and discuss the state of stem cell research in general; where it may be in five years; and the potential benefits it holds for the field of ophthalmology.

Breaking New Ground

Martin Friedlander, MD, PhD, professor in the Department of Cell and Molecular Biology at the Scripps Research Institute in La Jolla, Calif., and chief of retina services in the division of ophthalmology at Scripps Clinic, along with members of his laboratory, have been at the forefront of several research projects that are shedding new light on a number of issues tied to stem cell use. One part of Dr. Friedlander's work that could have a lasting effect on the field is the development of new ways to coax adult human cells into becoming induced pluripotent stem cells (iPS)—which can then be directed to become other types of cells—without using retroviruses.

The most significant advantage of using iPS cells instead of an alternative such as embryonic stem cells is that this method avoids the introduction of foreign cells into the recipient's body, cells that the immune system might attack and reject. iPS cells have traditionally been generated from specialized adult cells via the introduction of retroviruses. Retroviruses, however, are believed to be the possible cause of developments such as tumor formation following the implantation of iPS cells. Dr. Friedlander's group has found a potential way around this problem by getting specialized adult cells to become stem cells using small molecules instead of retroviruses.

"By using small molecules instead of retroviruses to get the cells to change, we avoid some of the potential oncogenes that can trigger tumor formation," Dr. Friedlander explains. "We've been able to program the resulting stem cells to become retinal



Susumu Sakimoto, MD, PhD, Scripps Research Insti.

Endothelial progenitor cells can be isolated from human cord blood and placed in xenofree culture media to grow as endothelial colony forming cells (far left). These cells, under appropriate conditions, will differentiate into endothelial cells (second from left) and can be used to normalize vascular defects observed in a rodent model of ischemic eye disease (right images).

pigment epithelium cells, which we put into a rat model of RPE degeneration; the result was very good anatomic and functional rescue. That was exciting, not only because this method avoids a potential source of risk for the patient, but because the RPE cells that resulted were very similar to human fetal RPE cells. They shared a lot of characteristics both functionally and anatomically. We published a paper describing this work in 2012."[1]

"In a more recent paper we asked the question, if you put these cells into the eye, how long do they remain effective?" he continues. "And are there any long-term potential downsides? To determine that, we've followed the progress of a number of the animals from the first experiment. At five years, the rescue effect had worn off, but there had been no adverse effects; the animals appeared to be perfectly fine and the grafts were still viable. In fact, we can recover the transplanted cells from the rats' eyes after as long as four years."[2]

Challenging Assumptions

Some of the work done by Dr. Friedlander's team is calling into question common assumptions that underlie the hope that stem cells will provide simple and effective treatments. One discovery his team has made suggests that developing iPS cells from the patient's own tissue may not always guarantee that the body will accept tissues developed from those cells.

"There's a widespread belief that if you take autologous grafts such as skin or blood from the patient and derive iPS stem cells from those and then generate spare parts for the patient, such as RPE or heart or other organs, implanting them will not generate an immune response," he says. "It makes intuitive sense that those parts, generated from the patient's own cells, wouldn't face the potential rejection issues that we may be facing with embryonic stem cell-derived spare parts, made from someone else's cells. However, our work suggests that this may not always be true.

"Working with Yang Xu, PhD, a colleague at the University of California, San Diego, we humanized a mouse's immune system by destroying its bone marrow and replacing it with human marrow, thus giving the mouse the human's immune system," he explains. "Then we asked, if we derived different tissue types from that patient's iPS cells and put them into a mouse that now has the same immune system because of the bone marrow transplant, would all the grafts be accepted without any rejection issues?

"It turned out that some cell types still did elicit an immune response," he says. "Apparently, not all iPS-generated cells are created equal. Muscle tissue grafts, for example, triggered an immune response. However, the RPE cells that we generated did not.[3] This suggests that generating a graft of some types of tissue from a patient's own cells may not guarantee avoidance of rejection. On the other hand, it also provides good evidence that generating RPE cells in this way is likely to work." Dr. Friedlander notes that this doesn't have anything to do with the idea of the eye being immune-privileged. "A graft of RPE cells placed outside of the eye didn't elicit an immune response either," he says.

Another assumption Dr. Friedlander's work is challenging is that all of the cells developed from a patient's tissue will be identical. "If you want to recreate a patient's disease in a dish using these cells as a way to test for disease manifestation, genetic abnormalities, functional abnormalities, response to drugs and so forth, it's important that the cells not be different from the patient's original cells," he notes. "So, in collaboration with Kristin Baldwin's lab here at Scripps, we ran an experiment involving what we call 'sister clones.' We used a patient's blood or bone marrow to generate iPS cells and develop six different clones. We took one of those clones and used it to make subclones; we got six 'daughter' cell lines from that one clone. Then we checked to see whether all of the cells we derived were identical to one another. We found that the answer depended on the circumstances. Under some conditions they were identi-

Regenerating the Crystalline Lens from Endogenous Stem Cells

One of the concepts gaining traction in stem cell research is the idea of activating existing stem cells *in vivo,* either by stimulating them to greater activity or by removing obstacles to their activation. The latter approach is epitomized by work being done at Sun Yat-sen University in Guangzhou, China. Researchers there announced in early March that they have been able to get naturally occurring stem cells inside the lens bag to regrow a crystalline lens in human babies, following the removal of a diseased lens. (The study appeared in the March 2016 online edition of *Nature.*[4])

Varying degrees of disorganized lens tissue regrowth have been observed after congenital cataract removal in infants; the researchers realized that the way the diseased lens is typically removed could be preventing a full lens regeneration. Currently, surgeons make a large 6-mm diameter capsulorhexis in the center of the anterior capsule to remove the lens, which prolongs recovery time and increases inflammation while eliminating most of the anterior subcapsular lens epithelial cells—including those needed for lens regeneration. In addition, abnormal proliferation of the remaining LECs commonly causes postoperative visual axis opacity that has to be addressed via posterior laser capsulotomy or capsulorhexis and anterior vitrectomy. All of this makes lens regeneration highly unlikely.

To prevent such significant destruction of stem cells, the researchers developed a new way to perform the capsulorhexis. They created an opening 1 to 1.5 mm in diameter (about 4 percent of the size of a traditional capsulorhexis opening), and they made the opening in the periphery of the bag instead of the center. This reduced the incidence of inflammation, increased the speed of healing, improved postoperative visual axis transparency and preserved a nearly intact transparent lens capsule and layer of LECs.

A study involving 24 eyes of 12 pediatric cataract patients, with a control group of 25 pediatric patients, found that the capsular openings healed within one month of surgery. At three months, a regenerated, transparent, biconvex lens structure of relatively uniform density had formed, and all eyes regained visual function. (No lenses formed in the group treated with the standard technique.) At eight months, the average central thickness of the new lens was comparable to a native lens. No significant visual axis opacity or other complications were observed at six months.

The study authors note that lens epithelial cells in adult human eyes also show the potential for regeneration, although the regenerative capacity in adult eyes is undoubtedly diminished. In addition, phacoemulsification to remove hard cataracts in adult eyes could damage the cells, and tissue consistency and capsular thickness and elasticity issues may pose challenges as well.

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cal; under other conditions they were not. In general, we did find that RPE derived from any of the clones looked virtually identical, if we gave them enough time to fully differentiate.

"The point is that generating tissue from the patient's cells and then using that to help the patient is not as simple as it may sound," he says. "So while I remain extraordinarily enthusiastic about the possibility of using autologous grafts—that is, tissues derived from a patient's own blood or bone marrow or skin—I think we have a long way to go in terms of learning about how best to use these cells."

Despite these issues, Dr. Friedlander says he still favors using the patient's own iPS cells. "It makes sense because you don't have to worry as much—at least in the case of RPE cells—about an immune response," he says. "However, we also have to consider the cost. It's obviously going to be a lot more expensive to do individual cell-based therapies using the patient's own cells than it will be to take an embryonic stem cell line and derive one RPE cell line that will fit many, many patients. But biologically, clinically and scientifically, the idea of individualized autologous cell therapy is a lot more appealing. Besides, many current therapies are even more expensive. Some people pay $50,000 for a year of treatment with Lucentis. Suppose you could tell a patient, 'We're going to use your tissue to make iPS cells and derive RPE cells from them and treat your Stargardt's disease with one transplant every 10 or 20 years.' Even if you charge $50,000 or $100,000, it's still going to be cost-effective in comparison."

Stem Cells from the RPE

One of the most interesting stem-cell-related developments in the past decade has been the realization that different organs contain cells that are partly specialized for use exclusively in that tissue, but still qualify as stem cells because their final cell type is not yet determined. Following that premise, researchers are now working with stem cells that are found in the RPE, as well as stem cells taken from the central nervous system, both of which are showing unique promise.

Researchers at the Neural Stem Cell Institute in Rensselaer, N.Y., have been working with the stem cells found in the retina. These cells are innately programmed to produce RPE cells (although they sometimes do produce other cells, possibly accounting for certain retinal disease conditions). Sally Temple, PhD, co-founder and scientific director of the institute, and president-elect of the International Society for Stem Cell Research, heads the group. They are currently culturing human RPE stem cells and transplanting them into diseased retinas in

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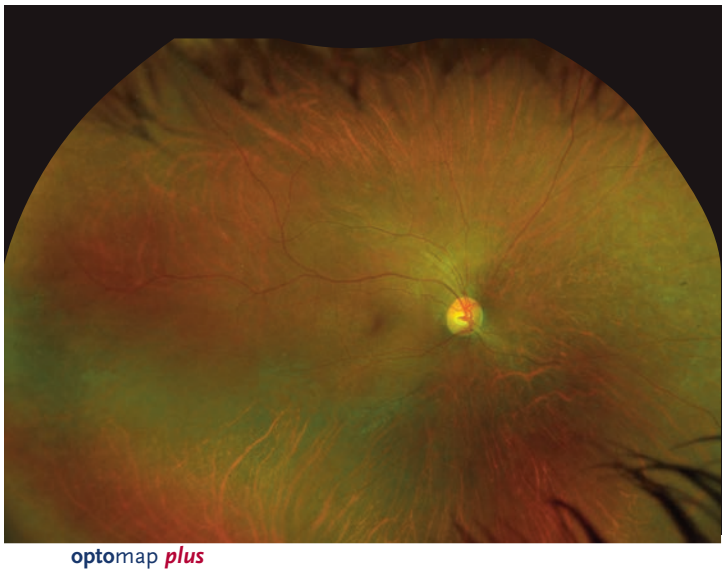

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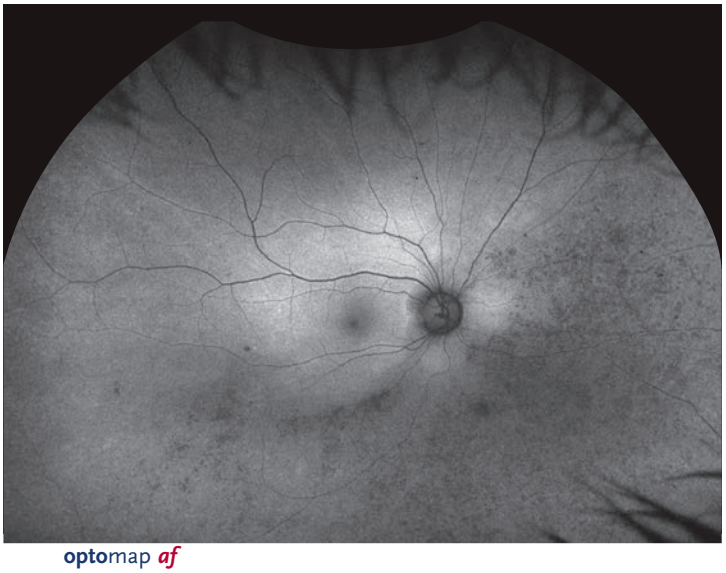

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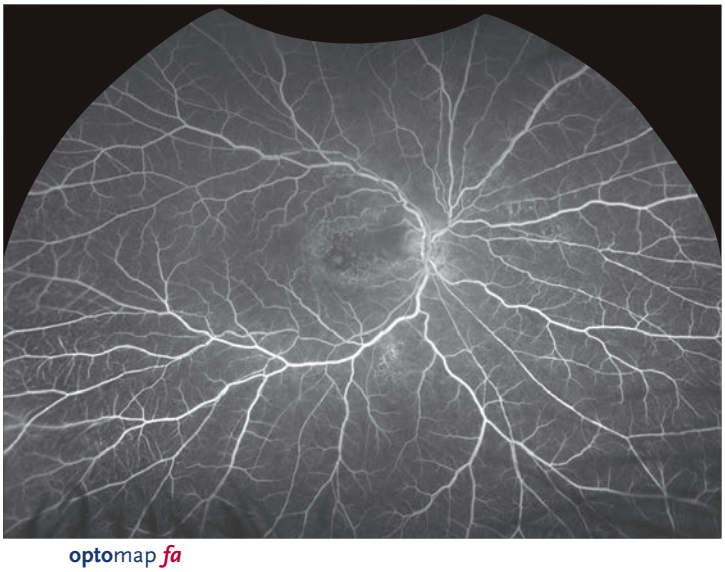

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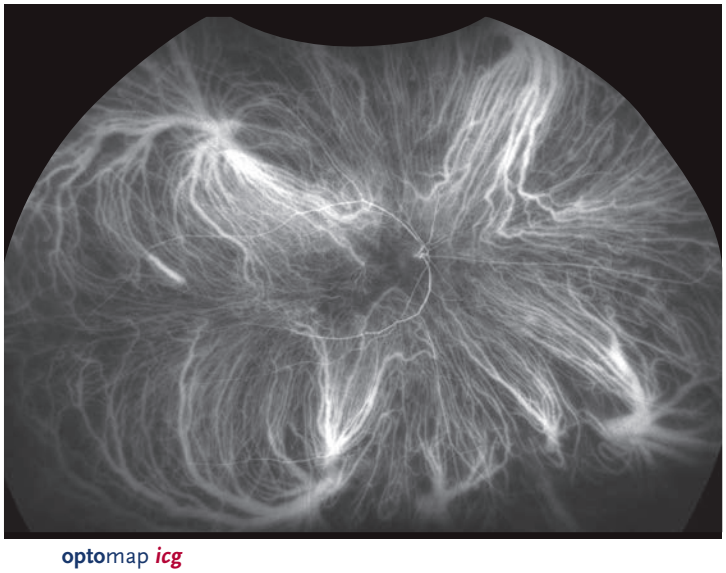

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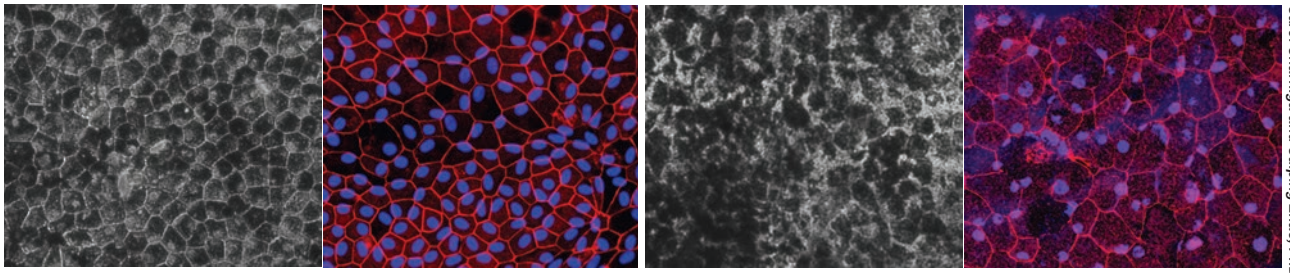


Carol Charniga and Cuiping Zhao, PhD

Left to right: 1) New human retinal pigment epithelium cells made from RPE stem cells in a culture dish; 2) the same cells stained to show ZO1 (a protein in the tight junctions between cells) and with DAPI, which reveals DNA in a cell nucleus; 3) RPE from an aged human eye; 4) the aged-eye cells, stained. The aged RPE cells are not as beautiful, which may be due to the age of the eye.

an attempt to produce anatomic and visual rescue.

"We now have really strong efficacy data for this procedure in an animal model using the Royal College of Surgeons rat," says Dr. Temple. "In that model the RPE is dysfunctional and the photoreceptors die. We've shown that we can rescue photoreceptors and vision in that animal by implanting adult RPE stem cells. We've followed these animals for six months to date, and the effect is ongoing; the treated animals are continuing to see while the untreated controls are going blind."

Dr. Temple says the cells are now being produced in a good-manufacturing-practice facility at the University of Rochester in New York. "We should have plenty for conducting future clinical trials," she says. "We've done preliminary safety studies of our procedure, and they look good—there's no evidence of abnormal growths or other problems. We're now doing definitive efficacy studies, which will go into our IND application. A definitive safety study is planned for this year as well."

One of the things Dr. Temple's team discovered several years ago is that RPE stem cells sometimes turn into mesenchymal cells like those you would find in bone marrow—cartilage, fat and bone-forming cells. "That happens in some retinal disease states, such as epiretinal membrane formation, leading to retinal detachment and potential loss of vision," she notes. "We've figured out some of the things that stimulate these stem cells to make that transformation, and we've also discovered some things that inhibit it. These discoveries are suggesting pathways and targets we can use to prevent this from occurring in the RPE cells we, or others, are transplanting. Perhaps even more important, they may help us prevent retinal problems like epiretinal membrane formation.

"This illustrates how stem cells are useful not only as a potential replacement for cells, but for disease-in-a-dish modeling," she continues. "This approach will help us understand disease mechanisms and identify therapeutic agents. For example, we've shown that if we stress a culture of these stem cells in a dish using oxidation, we can detect drusen proteins—the kind of abnormal buildup of protein and lipid mixtures found in macular degeneration. So I think these cells will be useful for modeling that disease as well."

Dr. Temple says her group is also working on finding ways to activate the endogenous stem cells already in the retina, which would have obvious advantages. "These cells are already in the eye," she says. "If they can be activated *in situ*, then we would be able to avoid transplantation; we could simply revitalize those cells and have them regenerate and repair the RPE layer. That's the next thing in the pipeline for us."

Stem Cells from the CNS

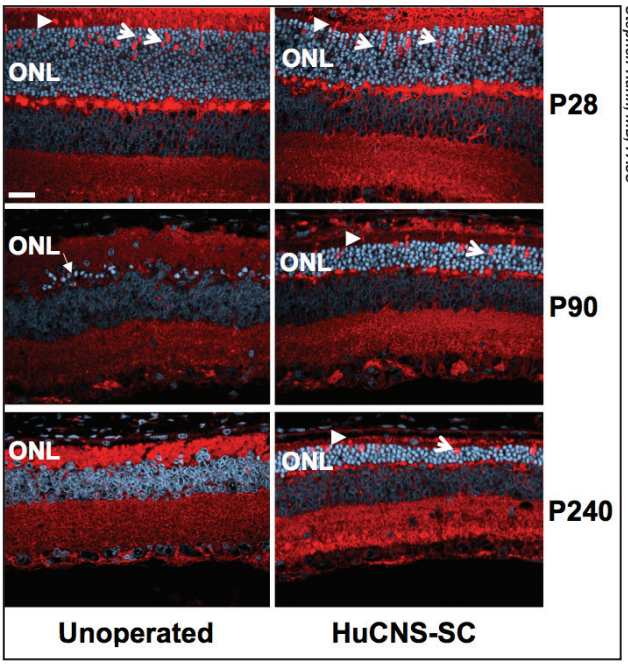
Another company pursuing the use of stem cells to support existing cells—rather than replacing diseased cells—is StemCells Inc. in Newark, Calif. The company is particularly interested in the potential of neural stem cells—unique cells found in the central nervous system that can differentiate into the building blocks of the central nervous system: astrocytes; neurons; and oligodendrocytes. Studies are indicating that an injection of these cells may slow the rate of progression of dry macular degeneration, and may even improve vision. (Banks of these cells, originally obtained from donated brain tissue, are now cryopreserved; they can be stored for years, and a small quantity can provide doses to a large number of subjects.) A unique advantage of this approach is that nothing needs to be done to change these cells; they can be harvested, grown and used without further alteration.

"Even though our cells are referred to as stem cells, they are not pluripotent," explains Stephen Huhn, MD, FACS, a neurosurgeon by training, who is vice president and chief medical officer at StemCells Inc. "They can only become nervous system cells, so they don't form tumors, which a pluripotent stem cell could do. In fact, that's a risk that comes with transplanting a culture of RPE cells created from pluripotent stem cells, with the intention of replacing diseased cells. If you don't transplant a pure population of RPE cells—if you have some embryonic or iPS cells mixed in—then you carry the risk of tumor formation. By injecting neural stem cells that we

have not altered, we avoid this problem."

Dr. Huhn says the company has performed a Phase I/II study involving patients with severe geographic atrophy. "We studied 15 subjects for a year," he says. "We compared the treated eye to the fellow eye. What we found was first and foremost, safety; the patients tolerated both the procedure and a few months of mild immunosuppression that we used postoperatively. From an efficacy standpoint we saw some intriguing outcomes. Best-corrected visual acuity remained stable or improved slightly, and nine of the 15 patients had a noticeable improvement in contrast sensitivity from baseline. Other findings included that macular volume and foveal thickness, measured using optical coherence tomography, improved in the study eye compared to the fellow eye. Also, the progression of geographic atrophy was slower in the study eye in select patients.

"The data was good enough to warrant a Phase II trial, which we started last year," he says. "However, we are a small biotech company, and financial concerns forced us to suspend the trial partway into the enrollment phase. We're currently looking for a partner who can help us develop this potential treatment for dry macular degeneration. In the future, we hope to complete a controlled study that will demonstrate that this is a viable way to treat macular degeneration."



Stephen Huhn, MD, FACS

Photoreceptor survival in the outer nuclear layer in a rat model of retinal degeneration, with transplanted human CNS stem cells (right column) compared to no transplant (left column), at days 28, 90 and 240 of the life cycle. The stem cells were transplanted at day 21, preserving the ONL layer out to more than seven months post-transplant. Arrows point to preserved cone photoreceptors. In the unoperated animals the ONL layer disappears to a few bright blue cells at Day 90 and is essentially absent at Day 240.

Replacing or Protecting?

One of the key issues this work has raised is what the stem cells are actually doing once they've been transplanted. "Over the years we've collected preclinical data relating to a number of neurological and neurodegenerative disorders, not just in the eye," says Dr. Huhn. "One of the themes that we've seen in our preclinical data is the concept of neuroprotection. Rather than replacing diseased cells, the donor neural stem cells exhibit properties that support, rescue or protect neuronal populations. This could be the result of the stem cells releasing trophic factors, or other biological properties of the cells.

"Given that photoreceptors are sensory neurons, we wondered whether we could use our cells to protect the photoreceptors and stabilize vision in someone who was suffering a retinal degenerative disorder," he continues. "Our studies produced very compelling animal data in a rat model showing that the neural stem cells would migrate within the subretinal space, graft to the retina and rescue vision out to seven months when we looked at two different visual-function measures. It was very robust data."

Dr. Huhn says the company is also working to discover what the neural stem cells are actually doing that produces the positive effect. "One of the things we recognized in the animal study was that the debris field in the subretinal space was cleared in the areas where the cells engrafted," he says. "Right away, that made us think that the neural stem cells may be taking over the phagocytosis activity that was formerly supported by the RPE, and we did find some evidence of that. The story is probably more complicated, however; I suspect some of the trophic factors and cytokines produced by the neural stem cells are exerting a neuroprotective effect on the photoreceptors as well. So even though we're not replacing diseased cells, this treatment may stabilize them and possibly even improve their function."

Dr. Huhn confirms that the neural stem cells do not appear to be turning into RPE cells. "We've seen migration of the cells into the inner retina, but we have not seen any cells that look like they're becoming RPE cells in the animal models, even many months post-transplant," he says. "We don't see any shared RPE markers. The implanted cells tend to remain in the neural stem cell state, probably because the subretinal space doesn't have the physiological signals that might direct the cells to grow into RPE cells."

Dr. Huhn notes that there's nothing wrong with the alternate strategy of trying to replace the diseased

Steering Clear of Untested Treatments

Because the public is aware of stem cell research and the occasional advances that are reported in the media, individuals hoping for respite from a given condition may seek out stem cell treatment. Unfortunately, this has provided an opportunity for some people to offer treatments that are untested and perhaps even fraudulent. For a patient, the result can range from disappointment to serious health problems, on top of a potentially significant financial loss.

Some reports have noted that this is going on in other countries, but Sally Temple, PhD, co-founder and scientific director of the Neural Stem Cell Institute in Rensselaer, N.Y., says it's happening in the United States as well. "One of the challenges in the field right now is that some clinics are providing unproven therapies that claim to cure patients of all manner of diseases, including blindness or diabetes," she says. "These clinics are charging people a lot of money for very questionable procedures. As a result, it's important to get the word out about the right places to go for help, and what questions people should ask to be well-informed and protected from unproven or dangerous treatments."

Dr. Temple says that the International Society for Stem Cell Research has created a website called "A Closer Look at Stem Cells" (closerlookatstemcells.org) designed to help educate anyone interested in pursuing treatment. The website features downloadable resources such as the *Patient Handbook on Stem Cell Therapies* (available in 12 different languages); a booklet of facts about stem cells; a stem cell glossary; and a list of questions patients need to ask before proceeding with a stem cell treatment, among many other resources. "Prospective patients can visit this site and look at the questions they should be asking and learn how to investigate whether or not a purported stem cell therapy is really a good therapy," Dr. Temple says. "This is one way the society hopes to protect patients from untested, expensive and potentially harmful treatments."

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cells. "The problem is that replacing photoreceptors involves overcoming a whole set of really complicated biological hurdles," he says. "You have to transplant a significant number of cells in a semi-mature, if not mature, differentiated state. Those cells don't usually like to be transported, and they won't migrate. Even after they're in the right location they still have to integrate with the host circuitry of the retina. Our idea was that you might not need to do all those things to achieve a therapeutic benefit. If you can stabilize the vision of someone who has dry AMD with a one-time treatment, particularly early in the course of the disease, and have the protective effect last for years, then you can achieve a therapeutic result without the burden and complexity of replacing RPE cells or photoreceptors.

"Given that this treatment works by supporting the existing cells rather than replacing them, once we've shown that it can work for macular degeneration, there are many other eye disorders it might also help to treat," he adds. "We believe this mechanism of action, in particular, will lend itself to multiple indications."

A Cellular Support System

In line with Dr. Huhn's current thinking, Dr. Friedlander's team wondered whether the improvement in vision seen after transplantation was caused by the transplanted RPE cells taking over the function of damaged or dead cells—i.e., replacing them—or by the new cells providing some kind of support for the existing cells. "We had reason to think the transplanted cells might be causing a trophic effect, because of the work we'd done with bone marrow and cord blood-derived progenitor cells," he says. "We used a technology called targeted metabolomics, a cutting-edge version of mass spectrometry, to evaluate millions of molecules present in retinal samples taken from a rat with severe degeneration after a period of time with the stem cells in the eye.

"We worked with one of the world's foremost authorities on metabolomic analysis, Gary Siuzdak here at Scripps," he continues. "With his help we compared the metabolites in retinas from normal rats, rats with severe retinal degeneration and rats that had achieved vision rescue after being treated with our iPS-derived RPE cells. It turns out the most severely disregulated class of metabolites we could detect were fatty acid amides, which act as signals during normal metabolic activity. In particular, one specific fatty acid amide called erucamide was severely disregulated. Normal rats had high levels of erucamide, while rats with retinal degeneration had dramatically lower levels of erucamide. In the rats who had been rescued by the iPS-derived RPE cells, the levels of fatty acid amides and erucamide had been restored.

"Given this result, we wondered whether just injecting erucamide might have the same rescue effect," he says. "In fact, we found that injecting erucamide did produce the same rescue effect. That's the idea of trophic action. You put the stem cells in and they know what to do—they upregulate, or modulate the expression of many different molecules, some of which have very profound vascular and neurotrophic effects. I think a lot of the effect we see from people injecting stem cells is not because the stem cells are replacing the damaged tissue directly, but because the cells

Down, Boy.

Help Tame Postoperative Ocular Inflammation and Pain With LOTEMAX® GEL

Indication

LOTEMAX® GEL (loteprednol etabonate ophthalmic gel) 0.5% is indicated for the treatment of post-operative inflammation and pain following ocular surgery.

Important Safety Information about LOTEMAX® GEL

- LOTEMAX® GEL 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.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- Use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation and occurrence of perforations in those with diseases causing corneal and scleral thinning. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, and where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infection. In acute purulent conditions, steroids may mask infection or enhance existing infection.
- Use of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- 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.
- Patients should not wear contact lenses when using LOTEMAX® GEL.
- The most common ocular adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%) and foreign body sensation (2%).

Please see brief summary of Prescribing Information on adjacent page.

LOTEMAX® GEL
loteprednol etabonate
ophthalmic gel 0.5%

BAUSCH + LOMB

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to prescribe Lotemax Gel safely and effectively. See full prescribing information for Lotemax Gel.

Lotemax (loteprednol etabonate ophthalmic gel) 0.5%

Rx only
Initial Rx Approval: 1998

INDICATIONS AND USAGE

LOTEMAX is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery.

DOSAGE AND ADMINISTRATION

Invert closed bottle and shake once to fill tip before instilling drops.

Apply one to two drops of LOTEMAX into the conjunctival sac of the affected eye four times daily beginning the day after surgery and continuing throughout the first 2 weeks of the post-operative period.

CONTRAINDICATIONS

LOTEMAX, 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.

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order 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.

Bacterial Infections

Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, steroids may mask infection or enhance existing infection.

Viral Infections

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

Fungal Infections

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.

Contact Lens Wear

Patients should not wear contact lenses during their course of therapy with LOTEMAX.

ADVERSE REACTIONS

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

The most common adverse drug reactions reported were anterior chamber inflammation (5%), eye pain (2%), and foreign body sensation (2%).

USE IN SPECIFIC POPULATIONS

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 (35 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 (6 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 post-implantation 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 (6 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. LOTEMAX 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 LOTEMAX is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

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, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration

Invert closed bottle and shake once to fill tip before instilling drops.

Risk of Contamination

Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the gel.

Contact Lens Wear

Patients should be advised not to wear contact lenses when using LOTEMAX.

Risk of Secondary Infection

If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician.

Bausch & Lomb Incorporated
Tampa, Florida 33637 USA

US Patent No. 5,800,807

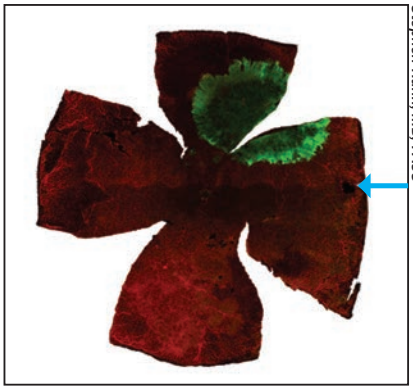
US/LGX/15/0042
Based on 9269100-9269200 Revised: 9/2012

are providing a very profound trophic rescue effect because of their ability to upregulate molecules that are important for maintaining normal homeostasis."

Dr. Friedlander notes that this supports the idea that early intervention is better. "If you put these cells in and they restore homeostasis before the retina is severely damaged, the outcome is likely to be a lot better," he says. "That's what I call 'restoration rather than resurrection.' "

Dr. Friedlander says they've seen similar evidence in studies they've done involving macular telangiectasia. "Groups that have access to adaptive optics, like Austin Roorda's group at UC Berkeley, Jacque Duncan's group at UCSF and Joe Carroll and Alf Dubra at the Medical College of Wisconsin, have now shown that in patients where the photoreceptors appeared to be completely gone—because you couldn't see them even with adaptive optics—the photoreceptors weren't really dead and gone. Actually, the rods and cones had just lost their outer segments, while the inner segments remained. That means if you can figure out how to get those cells to re-sprout their outer segments, they could theoretically become functional again. That's an absolute game-changer in terms of what we have to do to bring back vision in patients who have retinal degenerative diseases. We need to restore the cells rather than replace them. And that may be exactly what stem cells are doing."

Asked whether the transplanted RPE stem cells her team is using are replacing diseased cells or simply providing support, Dr. Temple says in some cases they may be doing both. "There are cells in clinical trials now that we know cannot turn into RPE cells, such as umbilical cord cells," she says. "In that case, when we see a positive result we know that the stem cells are not replacing the diseased cells per se, but are probably releasing trophic factors that are beneficial. In other cases, such as our research, or in the case of iPS-derived or embryonic-stem-cell-derived RPE, you're generating new RPE cells, so they at least have the opportunity to replace some of the lost or damaged cells, in addition to releasing trophic factors."



Stephen Huhn, MD, FACS

A radial pattern of human CNS stem cell migration (green) in a rat retina at day 90 after transplantation. The blue arrow marks the spot at which the cells were injected.

Managing Immunosuppression

Since many approaches to implanting stem cells involve cells that did not originate with the recipient, use of some immunosuppression is common. Naturally, this raises concerns with many doctors.

The technique being used by StemCells Inc. involves a short course of low-level immunosuppression. "There are many schools of thought about this," says Dr. Huhn. "Some believe that we shouldn't need any immunosuppression at all. We don't agree, because the blood-retinal barrier is disrupted for a period of time after you do the retinotomy and the vitrectomy. We have patients take an oral agent for a period of three months, and in our experience, patients tolerate this very well if they are generally healthy. In fact, our data indicate that after a period of immunosuppression is applied and then stopped, cell engraftment lasts at least six years.

"I think our approach to immunosuppression will become much more sophisticated and informed as the field evolves," he adds. "But at this early stage, we think it's better to include some course of immunosuppression as long as there are no safety concerns."

Dr. Huhn admits that it might be possible to derive a neural stem cell from an iPS cell made from the patient's own cells, possibly avoiding the need for immunosuppression. "However, that involves a lot of time and effort and expense," he says. "Hopefully, that will not turn out to be necessary."

Dr. Temple notes that because the RPE stem cells used in their protocol are not from the individual being treated, their current treatment protocol also includes a short period of immunosuppression. "When you cause bleeding during the surgery, you have blood cells invading that space," she explains. "This could set off an immune reaction. Most current stem cell trials that use cells not taken from the patient are having the subjects undergo at least a short period of immunosuppression. The hope is that patients will only need to do this for a few months, until the effects of the surgery have healed. Hopefully, by then the blood-retina barrier will have recovered and the cells will not be rejected. Of course, we have to see if this is what actually happens."

The Road Ahead

Dr. Huhn notes that the field of stem cell research is still largely in what might be called a "Phase I" stage of development. "I think the field has been largely focused on showing safety and tolerability up until now, and that may continue for a little while longer," he says. "But people are beginning to think about trial designs for the more mature studies, so we're kind of emerging from that phase now.

(continued on page 97)

The Future of Gene Therapy

Walter Bethke, Managing Editor

Experts in the vanguard of retinal gene therapy share their visions of the future.

Ironically, the gene mutations responsible for the suffering of patients with blinding diseases such as retinitis pigmentosa and Leber congenital amaurosis may also hold the key to their treatment. This is the idea behind gene therapy, a cutting-edge approach to treatment that uses genes to either replace genes that are missing in a patient's eye or to produce therapeutic proteins over an extended period of time. In this article, researchers on the forefront of gene therapy provide a glimpse of what gene therapy might look like five years from now, and what hurdles will need to be cleared before we can realize that vision.

Potential Diseases

Currently, gene therapy operates by injecting the eye with a virus, called a vector, that carries either a healthy gene that will replace the gene that's missing in a certain eye disease, or which enters retinal cells and turns them into "biofactories" that produce a protein that helps treat a disease. Though these approaches are being tried in different ailments, experts say that there are certain diseases that are likely candidates to have the first approved gene therapies in the United States in the next few years.

"I think the one that's most likely to be approved is gene augmentation therapy for the RPE65 form of Leber congenital amaurosis, or for other conditions caused by RPE65 deficiency," says Jean Bennett, MD, PhD, the F.M. Kirby professor of ophthalmology at the Perelman School of Medicine at the University of Pennsylvania, and one of the first researchers to use viral vector-based gene therapy to reverse blindness. She currently is the scientific director of the Phase III human trial of gene therapy for LCA. "I think others will follow, though it's hard to predict the one that will be next because they're all still in Phase I trials. However, I am excited about the data for the treatment of choroidal neovascular complications of age-related macular degeneration using sFlt-1, the receptor for VEGF. And I'm very interested in the studies that are ongoing for Leber hereditary optic neuropathy, and optogenetic therapy. Perhaps therapy for choroideremia would be the second one approved, since that research seems to be moving quickly now." Spark Therapeutics (Philadelphia) is sponsoring the LCA and the choroideremia trials working with the RPE65 gene.

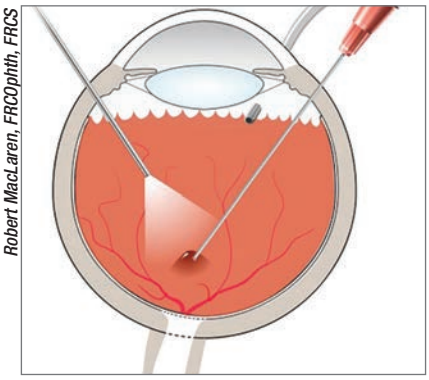
Robert MacLaren, FRCOphth, FRCS, professor of ophthalmology at

the University of Oxford in the United Kingdom, says certain types of retinal disease are more amenable to current gene therapy approaches than others, and that might hold true for the next five years. "First, the diseases that are due to deficiencies of genes are probably easier to treat than those in which the genes are causing detrimental effects," he says. "This is because we know a little bit more about gene replacement than gene knockout. Second, a gene that has such a severe effect on the eye that it affects the development of the retina and the normal structure of the eye at birth, such as in Norrie disease, is difficult to treat. This is because the retinas in such diseases can be beyond the point of repair on the day of birth. The only way around that would be to use prenatal genetic screening and begin gene therapy *in utero*."

Better Vectors?

Though there are a lot of moving parts to account for in gene therapy, one of the key elements is the vector that's used to transport the gene to the desired location. The vector that's currently used in the overwhelming majority of gene therapy studies is adeno-associated virus-2, though researchers say future vectors might bring different benefits that AAV-2 can't.

To hear it described by Prof. Elizabeth Rakoczy, PhD, director of the molecular ophthalmology department at the University of Western Australia/Lions Eye Institute, the characteristics of AAV-2 make it almost perfectly suited for gene therapy: "At the moment, there are about five different eye diseases being studied in clinical trials by approximately 10 groups, and all of them use a vector that's recombinant AAV-2, a general vector that enters into all the eye's cell types," she says. "The reason for this is that AAV-2 is naturally occurring, is non-toxic in humans—at most causing mild flu-like symptoms—and 80 percent of humans are carriers of it already. Using a virus like this as the basis for your vector is very reassuring, because it has obvious safety benefits." Prof. Rakoczy is also the inventor of Avalanche Biotechnologies' gene therapy agent AVA-101 for wet AMD.



Robert MacLaren, FRCOphth, FRCS

A subretinal gene therapy injection requires the creation of a small detachment.

Despite AAV-2's popularity, Prof. Rakoczy says she envisions a future where better vectors emerge. "We need more efficient promoters," she says, referring to the mechanism of the vector that regulates how much of the desired protein is produced in gene therapy. "Many of the present gene therapy approaches fall short of producing sufficient amounts of biologically active proteins. In many cases, we don't see the desired improvement in the patient because even though the protein is produced, it's not in a high enough concentration. That's why the promoter is essential.

"If you really want to look into the future, ideally we'd like to have vectors that are taken up by the target diseased cell with high efficiency and specificity, and switch on automatically when the target protein drops below normal," Prof. Rakoczy adds. "These vectors, in combination with the right promoter, would provide the most proficient biofactory tool set against genetically inherited and complex diseases."

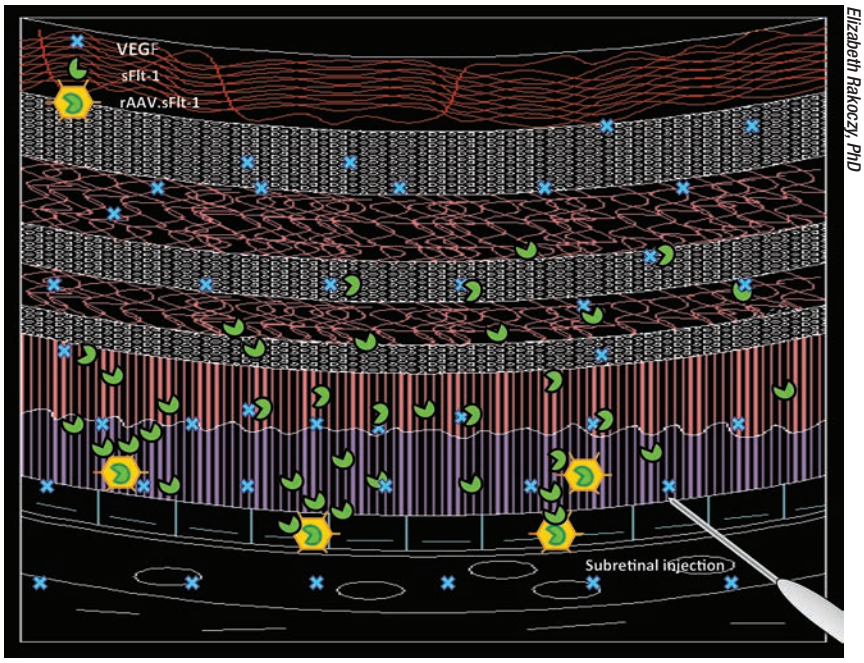
Dr. MacLaren sees vectors as one of the keys to improving gene therapy in the coming couple of years. "There are new variants of the AAV being developed that can be even more efficacious than current ones," he says. "A more efficient virus, for example, means that you can reduce the dose of the virus and still get the same therapeutic effect, and you really need to get those below a certain threshold to deliver the virus without any immune problems or other issues. In the past few years we've actually achieved that goal and now have very efficient viral vectors. We also understand more about the production process, so it's possible to scale up the AAV to good manufacturing process level—or commercial-grade production levels so it can be made for FDA approval. It's all well and good making a virus in your lab and using it for research, but to get it approved for general use in patients you need to have a reproducible GMP that's acceptable to the FDA. We're now able to achieve that."

Dr. Bennett says the development of new viral vectors is one of the areas of gene therapy that's moving quickly. "Researchers are continually modifying the toolkit," she says. "They're adding additional attractive features to the vectors by engineering the viral capsids themselves and by taking advantage of evolutionary approaches to evolve these capsids to have attractive features." The last approach, known as directed evolution, sounds almost like science fiction: Researchers create viruses in a lab in a way that maximizes their diversity, and then promote the evolution of viruses that have the traits that they want through a sort of artificial natural selection. One team of researchers was able to engineer a variety of AAV that delivered its gene cargo in a widespread fashion to the outer retina and rescue disease phenotypes of X-linked

retinoschisis and LCA in mice. It also enabled transduction of primate photoreceptors from the vitreous.[1]

Researchers say one area in which vectors will need to improve in the coming years is very basic, yet very important: their size. "Currently, one of the biggest limitations is the size of the gene that can be packaged within an AAV," Dr. Bennett says. "I think it would be great if there were further developments that allowed these capsids to package larger amounts of cargo. For instance, if we could double the size of what could be packaged inside an AAV, that would be wonderful. There are either large genes that you just can't fit into the vectors, or regulatory sequences that we can't use in the vector to limit the expression of specific cell types because those regulatory sequences are too large to fit inside the vector.

"This size constraint limits the treatment in Stargardt's, for example," Dr. Bennett adds. "Stargardt's therapy is being approached using a virus called lentivirus. Lentivirus barely fits that transgene, but doesn't allow the inclusion of the extended regulatory sequence that could potentially provide even better results. And, in some circumstances, lentivirus isn't the best for targeting photoreceptors because it doesn't target them that efficiently."



Elizabeth Rakoczy, PhD

In one iteration of gene therapy for treating wet age-related macular degeneration, rAAV.sFlt-1 is injected beneath the retina, turning cells into biofactories that produce the antiangiogenic agent sFLT-1 to reestablish the normal balance between angiogenic (vascular endothelial growth factor) and antiangiogenic (sFLT-1) factors in the retina.

Delivery Approaches

In the coming years, surgeons will solidify their route of delivery of the vectors. They now have two approaches to work with—intravitreal and subretinal—each with its own pros and cons.

The main benefit of intravitreal delivery is that it's technically easier to do: The surgeon injects the dosage of vector right into the vitreous. The drawback is that it may not get the vectors to the site the surgeon wants. Subretinal delivery is more challenging, since it involves injecting into the subretinal space and inducing a small detachment, but it gets the vectors right to their site of action. "I'm a little more skeptical of intravitreal delivery than some other people," says Dr. Bennett. "I think it could theoretically be used to treat the fovea, but not much more than that. Maybe diseases that cause distinct foveal problems, such as achromotopsia, could be targeted most efficiently with it. The other challenge with an intravitreal route is that in order to get to the site you need high doses. Those high doses can cause inflammation, which would limit the benefit one might get if one were to use them. That's my main concern: the toxicity vs. efficacy trade-off."

Prof. Rakoczy thinks this inflammation is a key issue. "If I were to look into the future of gene therapy, I believe subretinal delivery would remain the delivery method of choice," she says. "It's been proven that with intravitreal delivery you activate the immune system, so there might be an immune reaction that removes the vector. With subretinal injection, however, you're injecting into an immune-privileged space, and it seems that this fact is much more powerful than we think. It's been shown by Jean Bennett's work that, following a subretinal injection, you can freely inject into the second eye without rejection. In our own work, we've found that when you inject into the subretinal space, patients who already had been exposed to AAV2 and have neutralizing antibodies present in their blood actually responded better to the treatment than the average patient."

Dr. Bennett says, however, that it's possible intravitreal injection might be useful for the so-called generic gene therapy approaches, where the clinician can treat multiple diseases with the same reagent. "Intravitreal delivery might be useful for the delivery of secretable proteins such as neurotrophic factors or antioxidative

stress factors to generate a generic strategy for treating retinal diseases," Dr. Bennett says, "Delivering neurotrophic factor would make the cells healthier and keep them alive longer. That would be beneficial in many diseases because many are slowly progressive. If you could slow down cell death and allow those cells to live 10 years longer than they normally would have, that would be very meaningful. The same rationale would extend to using antioxidative stress approaches, because there's a huge amount of oxygen exposure in the outer retina because it's both exposed to light and has one of the highest blood-flow rates in the body. Finally, one of the more recent findings is that some retinal cells may die in these diseases because they're not getting enough metabolic support—in other words, they're not getting fed enough. Researchers are exploring approaches that may provide more nutrients, sugar and energy to these cells to allow them to function better. This could potentially be delivered in a generic approach."

Another generic option, highlighted by Dr. MacLaren, is the field known as optogenetics, or using gene therapy to switch on a gene that makes a cell light-sensitive, no matter what the genetic cause of the blindness. "It has nothing to do with replacing a normal gene," he explains, "but is quite often explored with abnormal genes that are present in other life forms that have a light-sensitive protein. It might have application in AMD to make the macula more light-sensitive."

Prof. Rakoczy thinks there may be improved instrumentation for the injection in five years, as well, assuming a gene therapy approach is approved. "In the lab, we do subretinal injections in the eyes of mice, which are much smaller than the human eye at 2 mm in diameter," she explains. "To do this, we use a stereotactic system, which means it doesn't depend so much on the ability of the person doing the injection." A stereotactic system is a partially automated system that uses computer-generated, three-dimensional coordinates to locate the area in the eye that needs to be injected. The needle's drive mechanism is fixed to the operating table. When the surgeon activates the mechanism, the needle is mechanically driven into the eye using a screw system while monitoring the depth of penetration on the microscope. "Based on this simple approach, I foresee a more automated system such as this being used, since it's less dependent on the manual handling of the needle by the surgeon, though some would not agree that it's better," Prof. Rakoczy says. "Some might argue that, since in humans the injection is performed under local anesthesia, the surgeon doesn't have the ability to correct for movement with a stereotactic system as a surgeon might."

Genetic Testing

Experts say that, though it doesn't treat disease in the way gene therapy does, genetic testing will evolve in parallel with treatment, since most gene therapy is targeted at a specific gene mutation or other genetic issue.

"For successful gene therapy in the future, we'll need better genetic testing so that we can test the genes in patients with retinitis pigmentosa or any inherited disease," says Dr. MacLaren. "Then, we'll find mutations and know exactly where they are, because you can't plan a gene therapy program without knowing which gene it is you're going to create. Going back 10 years, we had only diagnosed a fraction of the genes that cause RP in our patients. Now, with next-gen sequencing, we're getting 70 to 80 percent of the genes. So, immediately, the pool of potential patients is orders of magnitude higher than it was in previous years." Dr. MacLaren envisions a future where, as more diseases are diagnosed, physicians can add more mutations to a computerized database so that they're caught even while looking for something else. "For instance, a patient may go to his cardiologist and get gene testing," he says. "The heart doctor might look at the test results and say, 'Hang on, you've got an RP gene here,' and then refer him to us. We can then initiate a treatment possibly 10 years before he would even have been aware of the disease."

Though Prof. Rakoczy notes that there will be challenges with gene therapy, she's sure that it will come to fruition, and it will be a blockbuster. "The change in the pharmaceutical industry is coming," she says. "Within five years, we will see one of the vectors now in trial on the market. The appearance of vector-based 'biofactories' will require a new business model for the pharmaceutical industry. This is because now the drug makers get money from every single pill you put in your mouth. But, when you use gene therapy vectors for treatment, once the biofactory is delivered into the body it takes over treating the patient. Thus, at least in theory, they can only sell the product once for every patient. On the other hand, the cost to develop the system is huge, so even though it will be beneficial to patients and cheaper for the government/health-care system, we don't have a model of how to fund it. Even so, in the future gene therapy will be used more widely for complex diseases such as cancer, heart disease, diabetes and retinal disease. That's what's making patients and governments so excited." REVIEW

Dr. Bennett is the scientific cofounder of and advisor to Spark Therapeutics. Dr. Rakoczy is a consultant to Avalanche. Dr. MacLaren is the academic founder of NightstaRx, a company developing gene therapy treatments.

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.

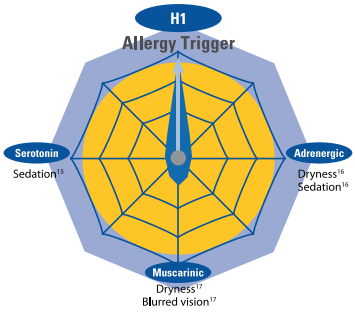
Patients can have a variety of signs, such as injection, chemosis, conjunctival chalasis, lid droop, and red, thickened lids. There is a wealth of information on examination of the everted upper tarsus: conjunctival hyperemia, papillae in the acute phase, follicles in the chronic phase, conjunctival 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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17. Crismon ML, Dorson PG. Schizophrenia. In: Dipiro T, ed. *Pharmacotherapy: A Pathophysiologic Approach*. Stamford, CT: Appleton & Lange; 1997:1367-1394.
18. Data on file. Bepreve® Integrated Summary of Safety. NDA 22-288. ISTA Pharmaceuticals, Inc. October 18, 2008.

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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*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.

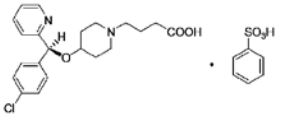
8.3 Nursing Mothers
Following a single 3 mg/kg oral dose of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection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

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

US/BEP/13/0028 4/13

Better Options Emerging In Ocular Oncology

Michelle Stephenson, Contributing Editor

Current treatments are saving eyes and lives.

Advances in the treatment of ocular cancer are allowing patients to avoid enucleation and preserve vision. There are several forms of eye cancer, but the most common primary cancers of the eye are retinoblastoma in children and uveal melanoma in adults.

Retinoblastoma

Representing 6.1 percent of all cancer in children younger than 5 years of age, retinoblastoma is the most common primary intraocular cancer in children. It primarily affects young children, with approximately 90 percent of cases occurring in children younger than 3 years of age. It is a highly malignant tumor that results in death in one to two years if left untreated. Worldwide, half of the children who are diagnosed with retinoblastoma present with extraocular manifestations that suggest advanced disease. This contributes to high mortality rates in developing countries (39 percent in Asia and 70 percent in Africa). Retinoblastoma confined to the globe, which is typical of cases diagnosed in the developed world, has survival rates as high as 96 percent to 100 percent. Treatment options include enucleation, external-beam radiation therapy, chemotherapy and focal therapies such as cryotherapy, laser therapy and brachytherapy.[1]

David Abramson, MD, says that in 90 percent of children with retinoblastoma, the disease is detected by a family member, usually their mother. They notice leukocoria or a whiteness or a glow in the eye, which is actually the cancer itself.

Two innovative treatments have caused a remarkable transformation in the treatment of retinoblastoma and have changed patients' lives. "These are the use of intra-arterial chemotherapy and the use of intravitreal chemotherapy," says Dr. Abramson, who is the chief of the ophthalmic oncology service at Memorial Sloan Kettering Cancer Center and a professor of ophthalmology at Weill-Cornell Medical School. "Historically, virtually all eyes in unilateral patients were enucleated as treatment. It is a good treatment in the sense that it removes the cancer, and more than 95 percent of the children survive, but it is a terrible treatment in the sense that you are removing a human eye, some of which have vision and others that may have the ability to regain vision after eye-salvaging therapy."

Systemic chemotherapy has been used for retinoblastoma since 1953.

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SL-5000h Handheld Slit Lamp	~~$3,150~~	$2,380
VC-170 17" LED Vision Chart	~~$2,500~~	$1,500
AB-6100 A/B Ultrasonic Scan	~~$12,000~~	$8,000
CL-1000eva Specular Attachment	~~$14,500~~	$13,500

*Basic Exam Lane Package including: HAI SL-5000bx, HAI VC-170 LED Vision Chart, S4OPTIK CB-1800 Chair/Stand Combo and SL-Y100 Refractor

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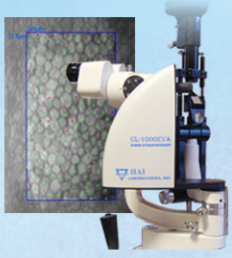
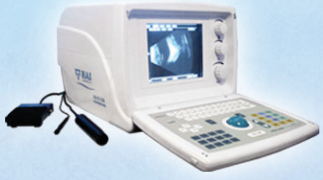


HAI CL-1000eva Endothelium Viewing Attachment

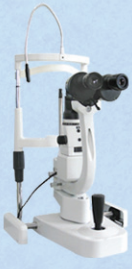


HAI AB-6100 A/B Ultrasonic Scan

VC-170 LED Vision Chart

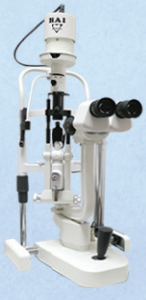
HAI SL-5000 Digital Video Slit Lamp

HAI SL-5000h Hanheld Slit Lamp



HAI SL-5000bx Basic Slit Lamp

HAI SL-5000s Standard Slit Lamp



HAI SL-5000p Plus Slit Lamp

HAI SL-5000e Elevate Slit Lamp

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HAI 20 YEARS ANNIVERSARY

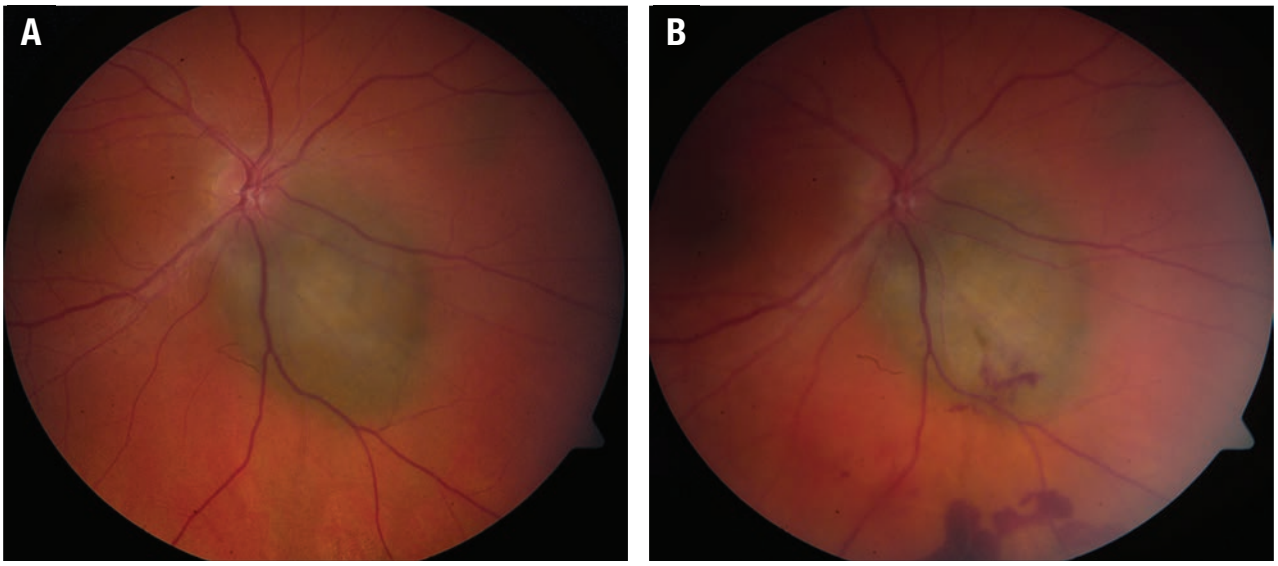

Figure 1. A) Small choroidal melanoma. B) Appearance one week after transvitreal fine-needle aspiration biopsy using a 25-ga. needle.

"It is not new, and chemotherapy for intraocular disease has always caused a nice response, but it has never cured the tumors or prevented them from recurring," says Dr. Abramson. "We've abandoned the use of systemic chemotherapy, which was never effective for the advanced eyes anyway. We've also abandoned radiation, which has many complications long term, especially second cancers; so there has truly been a transformation in management worldwide.

"In the past 10 years, since the introduction of intra-arterial chemotherapy, which Pierre Gobin, MD, and I did for the first time in May 2006, we've gone from a time when 95 percent of all children with unilateral retinoblastoma lost an eye, to a time when we are saving the eye in 95 percent of children with unilateral retinoblastoma. And, this has been accomplished without sacrificing life, which is important."

Dr. Abramson and colleagues recently published a study demonstrating this.[2] The study included 156 eyes of 156 retinoblastoma patients and showed that primary enucleation rates have progressively decreased from a rate of more than 95 percent before intra-arterial chemotherapy to 66.7 percent in the first year of intra-arterial chemotherapy treatment to the current rate of 7.4 percent. Additionally, the percentage of patients receiving intra-arterial chemotherapy has progressively increased from 33.3 percent in 2006 to 92.6 percent in 2014. And, there have been no cases of death from disease metastasis in those receiving intra-arterial chemotherapy, while two patients treated with primary enucleation died of metastatic disease.

Intra-arterial chemotherapy is administered by catheterizing a femoral artery, with the catheter passing from the abdominal aorta through the thoracic aorta through the internal carotid and then directly into the ophthalmic artery. Only a few ccs of chemotherapy are needed because the concentration in the eye is so high that it is very effective at destroying retinoblastoma. "An advantage is that the total dose is so low that the children don't get sick or lose their hair," says Dr. Abramson. "It is an outpatient procedure that takes an hour. The average child has it done either three or four times. Only about 1 percent of children develop fever or neutropenia or require blood transfusions. Half of the countries in the world that are using it are developing countries. That's critical because, last year, half of the children in the world who developed retinoblastoma died. The main reason they died is that, in much of the world, when a family is told that the eye has to come out, they refuse and never go back to medical care. This is true throughout much of Asia and Africa, which is a large part of the world's population. Children are not dying because the doctors don't know how to treat it. It's because the treatment, which does work, is unacceptable socially and culturally."

Dr. Abramson and his colleagues recently conducted another study comparing enucleation with intra-arterial chemotherapy, and they found that there were more orbital recurrences of retinoblastoma in eyes primarily treated with enucleation. The study, which included 140 eyes in 135 patients with advanced retinoblastoma, found that treatment with intra-arterial chemotherapy did not increase the chance of orbital recurrence, metastatic disease or death compared with primary enucleation in these patients.[3]

The main reason that eyes have

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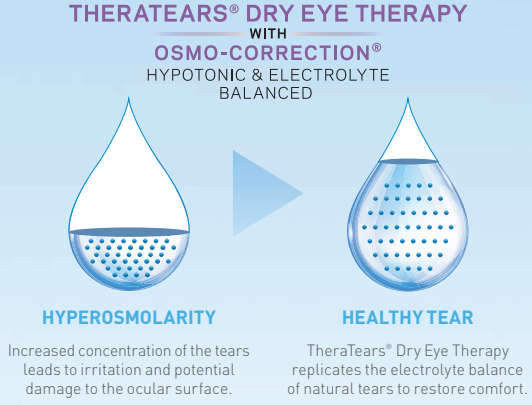

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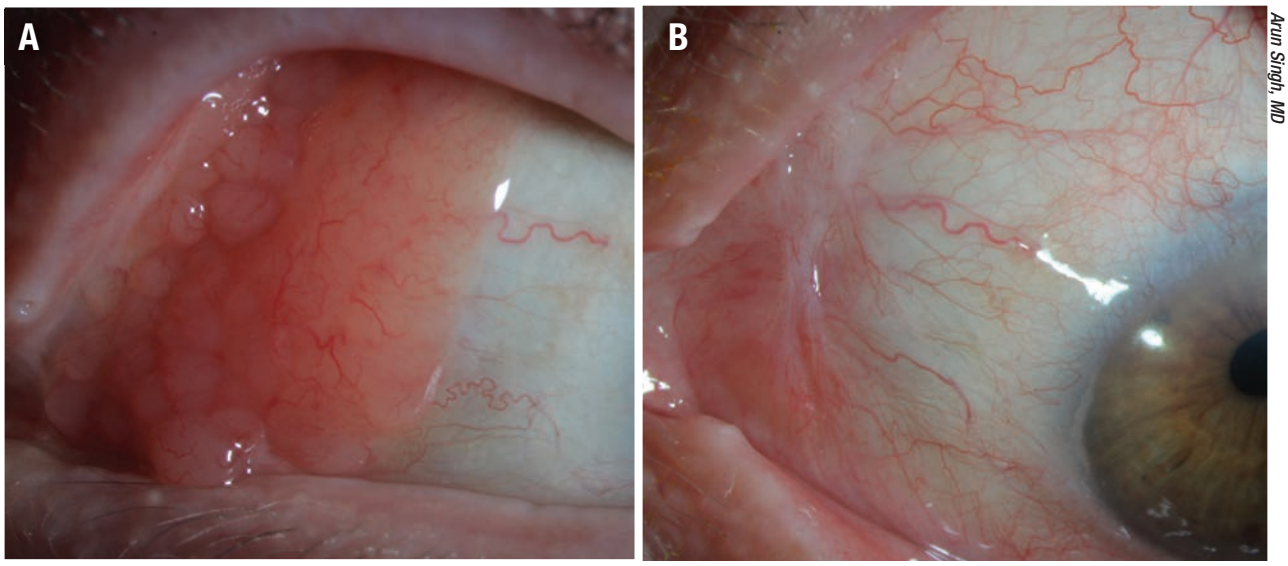

Figure 2. Ocular adnexal lymphoma (extranodal marginal zone type) A). Three months following treatment with 25 Gy external radiation. B) There is total regression of lymphoma without any surface secondary effects.

been removed for retinoblastoma is that retinoblastoma breaks off into little pieces called seeds, and the seeds have no blood supply and don't divide very often, so they have always been resistant to chemotherapy and to radiation. "For eyes with advanced seeds, less than 25 percent could ever be saved with radiation," Dr. Abramson says. "With systemic chemotherapy, almost none of them can be saved. Intra-arterial chemotherapy brought us from under 20 percent to about a 70 percent success rate. Then, Francis Munier, MD, in Switzerland introduced a modification of a technique that has also been around for 50 years. He introduced what we hope is a safe technique for injecting chemotherapy directly in the eye. It has increased the chance of saving eyes with vitreous seeds from near 0 percent to close to 90 percent. It does have some toxicity. You don't get away without any complications."

This new technique (intravitreous chemotherapy) and dosage achieved an unprecedented success rate of tumor control in the presence of vitreous seeding, and none of the treated eyes required external beam irradiation to control the vitreous seeding.[4]

This study included 23 eyes with active vitreous seeding that were eligible for intravitreous chemotherapy. These eyes received 122 intravitreal injections of melphalan (20 to 30 µg) given every seven to 10 days. All patients are alive and without evidence of extraocular spread. Eighty-seven percent of eyes achieved globe retention, and all retained eyes were in complete remission after a median follow-up period of 22 months. A localized peripheral salt-and-pepper retinopathy was observed at the injection site in 10 eyes.

Uveal Melanoma

Melanoma of the uveal tract is rare, but it is the most common primary intraocular malignancy in adults. It typically occurs in older adults, and a number of factors influence prognosis. These include cell type, tumor size, location of the anterior margin of the tumor, degree of ciliary body involvement and extraocular extension. The most commonly used predictor of outcome after enucleation is cell type, with spindle-A cell melanomas having the best prognosis and epithelioid cell melanomas having the worst prognosis.

"The majority of uveal melanomas are treated with a special type of radiation, delivered from a point source, known as brachytherapy. In contrast, if someone has a spread of cancer to their eye, such as from the lung or breast, it is generally treated with external beam radiation, as these tumors are more radiosensitive," says William F. Mieler, MD, who is from the Department of Ophthalmology and Visual Sciences at the University of Illinois at Chicago.

According to Dr. Mieler, success rates of uveal melanoma treatment are quite good, as brachytherapy treatment offers approximately an 80 to 90 percent success rate in terms of tumor containment. "Uveal melanoma presentation ranges extensively from visual blurriness, to visual field defect, to no symptoms at all," he says. "It depends on where the tumor is located inside the eye. Many tumors are found during a routine screening examination, especially if it is not involving the central region of the eye. When treating these patients, there are two main goals—keeping the patient alive, healthy and

free of metastatic disease, and preserving vision, whenever possible."

A recent study found that ruthenium-106 brachytherapy is useful for controlling uveal melanoma tumors, preserving the eye and preserving visual function.[5] The study included 143 eyes, and the median follow-up was 37.9 months. Estimated local tumor recurrence rate was 3 percent at 12 months, 8.4 percent at 24 months and 14.7 percent at 48 months after irradiation. Likelihood of eye preservation was 97.7 percent, 94.7 percent and 91.8 percent at 12, 24 and 48 months respectively after irradiation.

The key to treating uveal melanoma is to prevent it from metastasizing, because after the development of metastatic disease, the rates of survival are the same for treated and untreated patients. "After prognostication, fine-needle aspiration and biopsy, patients with uveal melanoma are classified with regard to their risk for metastasis," says Arun D. Singh, MD, director of the department of ophthalmic oncology at the Cole Eye Institute at the Cleveland Clinic. "The most significant change in how we practice and treat melanoma patients is incorporation of adjuvant therapy trials into our clinical practice."

Currently, no adjuvant therapy regimen has shown promising results. Existing cytotoxic and immunotherapeutic regimens are being used in patients who have been identified as high-risk by tumor genetic criteria. Additionally, several novel cytotoxic, immune modulatory and targeted compounds that may potentially be used in the adjuvant setting are being studied in the metastatic setting. Preclinical studies have shown that methods that stimulate uveal melanoma cellular differentiation and/or dormancy are promising.[6]

"The diagnostic accuracy for melanomas is better than 99 percent, and while treatment is generally successful, work is ongoing to better identify patients who may be at higher risk for development of metastatic disease," Dr. Mieler says. "Tissue analysis and genetic markers are allowing ophthalmologists to better assess patients regarding systemic risk. It's not foolproof, but it is a major advance that is rapidly evolving."

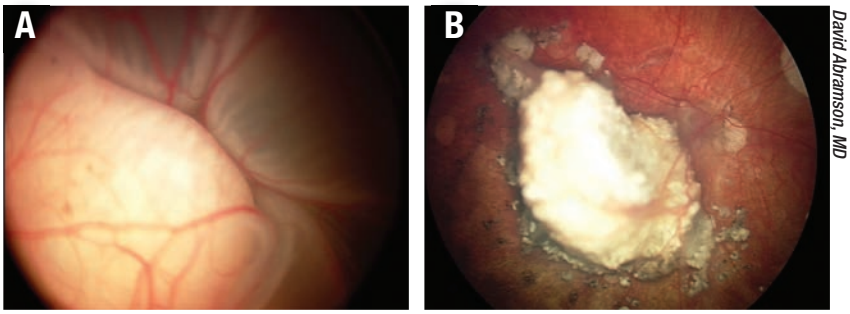

Figure 3. A) Before and B) after successful intra-arterial chemotherapy treatment of retinoblastoma. The eye was blind at diagnosis and now has useful vision.

Ocular Adnexal Lymphoma

Another form of cancer is ocular adnexal lymphoma, which is a rare, primarily B-cell, non-Hodgkin's lymphoma. Most are low-grade extranodal marginal zone (EMZL)/mucosa-associated lymphoid tissue (MALT) subtype. Before choosing a treatment approach, it is important to perform a thorough initial characterization of the disease extent and to follow staging procedures. Biopsy is the gold standard for diagnostic confirmation.[7]

Ocular adnexal lymphoma can involve the eyelids, conjunctiva, lacrimal apparatus, extraocular muscles and the orbit; however, most cases involve the orbit/lacrimal gland. A number of treatment options are available, and these include radiation, surgery, cryotherapy, chemotherapy, immunotherapy and antibiotic therapy. The standard primary therapy for ocular adnexal lymphoma is external-beam radiation therapy. EBRT has a high rate of success when used to treat ocular adnexal lymphoma without systemic involvement. Surgery is typically reserved for cases of isolated, highly focal conjunctival disease. Cryotherapy has also had limited success in eliminating disease, so it should be reserved for patients who cannot be treated any other way. With the exception of high-grade, aggressive, diffuse, large B-cell lymphoma, most cases of ocular adnexal lymphoma are localized; therefore, chemotherapy is not typically used. Recently, immunotherapy has been used as primary treatment, and rituximab, either alone or in combination with chemotherapy and/or radiation has shown promise for treating both bilateral ocular and systemic cases.[7]

"For lymphoma of the adnexa (marginal zone type), there are good data to indicate that radiation treatment is very effective and gives us very high control rates (more than 95 percent)," Dr. Singh adds. REVIEW

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Confessions of a New Chairman on Recruiting

Frederick W. Fraunfelder, MD, MBA, Columbia, Mo.

In practice or in building an academic department, here are eight major obstacles to successful recruiting. (And their solutions.)

It has been two years since I took the mantle at the University of Missouri in Columbia, and during that time our faculty roster only has four of the original clinical faculty I inherited from a starting 11. Faculty left for a myriad of reasons including: spousal job opportunities; death; claims of discrimination; disgruntled they didn't get the chair; wanting to be closer to extended family; and the chair's preference that the department move ahead without them. It is difficult to accept faculty reasons for leaving, especially when you were hoping they would stay. However, it also provides an opportunity to create a department with the strengths a good academic department should have, covering all subspecialties within ophthalmology.

Dr. Fraunfelder is adding gray hairs at a rate of about 10 per month.

As of July 2016, we will have 22 clinical faculty and 31 total faculty including PhDs. From the Association of University Professors of Ophthalmology Compensation Survey last published in December 2012, this puts our department at about an average size for all academic ophthalmology departments in the United States (The 50th percentile is 24 clinical faculty and 29 total faculty).

It has been an eye-opening two years; however, I am an old soul in regards to academic medicine. I have been going out to recruiting lunches, dinners and fund-raising activities since I was in junior high school. ***The*** Dr. Fraunfelder in many circles is my father, who was chair at the University of Arkansas straight out of fellowship in 1970 and then became chair at Oregon Health & Science University a decade later. One of his enduring legacies is the Casey Eye Institute in Portland, Ore., which now boasts almost 70 faculty and is in the top five nationally in NIH funding. What I learned from him during my formative years got me started on this quest to build a center of excel-

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lence in mid-Missouri to serve this region with some of the best eye care in the land.

I wish I could take all the credit for the rapid growth of the Mason Eye Institute here in Columbia. The truth is more complex and could not happen without support from the leadership, especially the medical school dean and the hospital CEO/COO. Investment in ophthalmology growth is not always a priority for many health systems because, at best, we may only represent 2 percent of a total health-system budget. Internal medicine and General Surgery make a much larger financial impact.

What ophthalmology can offer, however, is a large footprint in outpatient care. Because we see so many patients during the day, it is not unusual for an eye department to see more patients than family medicine and internal medicine combined. This leads to internal referrals and development of narrow networks that make the whole health-care enterprise stronger. The offshoot benefit is a key reason why eye departments are so important to academic centers and why satellite hospitals of academic centers frequently include an eye clinic as a service for patients.

From a start date of July 1, 2014, I have interviewed and recruited upwards of 50 candidates across all subspecialties of ophthalmology. The success rate in landing candidates we really want is around 40 percent. They come from all regions of the United States, and the reasons for success and failure are legion. Maybe the candidate loves the beach; perhaps their significant other loves to ski; perchance one of the Kardashians sneezed or the Oprah Winfrey Network went out of business. Sometimes you just can't tell what makes one person rock and another roll. Still, some overarching truths remain that I have learned through trial and error. From new-chair conferences sponsored by the American Association of Medical Colleges (AAMC) and the AUPO, I knew some of these things. Some issues, though, are a unique knowledge that can only be acquired through spending time, money and effort on recruiting on a daily basis. Times are different now and with time, once-universal truths that are taught in MBA schools and new-chair seminars no longer apply. Here, I want to attempt to share with chairs, faculty, recruits and trainees what is in store for us over the next few years, and to impart whatever shred of wisdom is gained through the experience of being a professional recruiter for ophthalmic faculty.

'The Hateful Eight'

I have identified eight key elements about recruiting that profoundly affect success and failure. Some may be obvious but others reflect the health-care environment that is shifting underneath our feet with health-care reform, political upheaval and scope-of-practice threats. They are in no particular order, and these are not the only factors. These are simply the most important ones from my point of view:

1. Spouses
2. Loyalty
3. Base salaries
4. Location and extended family
5. Ambition
6. Optometry
7. Search firms
8. Curriculum vitae

1. Spouses

When I first started, I knew the significant other/spouse was a key person in recruiting. But lip service and stating this out loud is not enough. This is the number-one issue for failure in recruiting, and I have failed in this area frequently despite my best efforts. The problem is that I cannot find the spouse a job. There is no such thing as a power couple. One could argue the Clintons, but I am sure there could be a debate on that. My experience is that one person is usually a much better candidate and much more qualified for an academic position than his or her significant other.

I've failed twice in obtaining a psychiatry residency for spouses, once in pediatrics, once in the music school, and could not get an interventional radiology appointment for the spouse of a pediatric ophthalmologist. I am particularly frustrated in not finding a position within psychiatry because there are eight spots at our medical school, and many of the candidates are not competitive for residencies in other specialties. My worst experience was working with the chair of music, who would not take a previously tenured music professor from another institution on the violin for free (the university would cover a spousal accommodation for two years under a special program).

A stay-at-home spouse, who is caring for the kids, frequently puts his or her foot down at a certain point and says, "I've been following your training for four to six years and now I'm going to decide where we live." Even if the candidate loves the department, sees an excellent future and believes in the leadership, there is no way to overcome a spousal trump card.

• ***Recruiting pearl:*** Create a separate agenda and visit itinerary for the spouses during the visit. Set up interviews in town in their chosen profession and have them tour the city with a realtor before the couple tours together. Have the spouses meet the principals of the schools; take them to the sports facilities in the areas that their kids excel in; show them the performing arts center for children; have your own spouse visit

There's no beach in sight of the Mason Eye Institute, but Columbia's low cost of living and other enticements have helped fuel the center's substantial growth in the past two years .

with their spouse when appropriate. Husbands and wives of department chairs can have a profound influence on whether or not a candidate wants to come to your department and stay in your department. Also, personally take them out to coffee and get to know them. A chaperone in the form of your department administrator or executive assistant is a good idea. In my experience, the spouse can be the key driver and is equally important to the candidate in a successful recruitment. It helps if the spouse is an easily employed superstar, but this is as rare as rocking horse manure.

2. Loyalty

The point here is that there is no loyalty. This was a difficult concept to comprehend, and it took some time to understand: Just because I spend a few thousand dollars on the recruitment, have a wonderful dinner, spend hours of my faculty time interviewing, campaign on their behalf with other physicians, and take the risk of trusting them with a job offer, doesn't mean they are going to reciprocate.

One particularly painful anecdote was the recruitment of a plastics specialist who called me the day after we overnighted an offer and he/she said they are considering going elsewhere (which means it was already decided). I had made sure that ENT, plastic surgery, the emergency department, and our current plastics specialist would allow for things he/she wanted to do and had shared a rough draft offer after verbal commitment to our department. A chair loses a lot of reputation points when he puts that much time and effort and public relations into a candidate who says no thank you without preamble. Everyone in the department felt the betrayal.

What I found over the next two years is that this experience is not uncommon. Fellows whom we supported, candidates that we went out of our way for, friends, former trainees and alumni children frequently feel no loyalty to your department. I have seen candidates come and go that we really wanted who didn't even send us a thank you note or even give the courtesy of returning a phone call.

• ***Recruiting pearl***: Grace is not present in all people. Are you born with it? Can you learn it? I don't know these answers; however, I've learned not to take it personally. It is not a reflection on me or my department. The way to deal with this is to be careful in your expectations and do not give a rough-draft offer without serious vetting of a candidate and his intentions. Candidates frequently use your offer letter as ammunition for the job they really want.

3. Base Salaries

It has become a bidding war for the best candidates. Talent has a price and we are not yet at an egalitarian state of health-care training where one corneal surgeon is as good as another. Some specialties are especially hard to recruit, as well. Pediatric ophthalmology, as of this writing, has no fewer than eight academic postings on the AUPO website (aupo.org).

According to the AUPO Compensation Study of December 2012, the average base salary for a pediatric ophthalmologist just out of fellowship is $160,000. An established academic pediatric ophthalmologist can expect to make on average around $264,000 in total compensation. If I want to attract a pediatric ophthalmologist or any top-of-their-profession subspecialist, I will need to meet and exceed the average base salaries that our forefathers offered. This is one of the great paradoxes of medicine occurring right now. Health-care reimbursements are falling but physician salaries are increasing. The challenge for department chairs going forward is not to hamstring your department with bloated base salaries and allow faculty to earn based on productivity.

• ***Recruiting pearl:*** Incentivize faculty based on research productivity, teaching acumen, clinical productivity, community service and administrative contributions. Paying incentive on top of base salary is the answer, not large base salaries.

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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.

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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

If the candidates you are recruiting are who you think they are, there should be no issue in being productive enough to earn benchmark salaries and more. Faculty are motivated to eat what they kill. Allow them that freedom but hold them accountable with a conservative base.

4. Location & Extended Family

This is a battle you cannot win. Sometimes it is the priority of the candidate and sometimes the priority of the spouse. One wonders why they are visiting your department if they are sure they want to live in southern California. Perhaps they are just reinforcing their already-held notion that there is no place like home and Aunt Betty is a must-see weekly. Missouri has a 20-percent lower cost-of-living than New York or California. The homes are more affordable, and the commodities at grocery stores cost less. The property tax is low, and the sales tax is negligible. None of this information matters if you have to see the ocean.

I recently was unable to convince a retina/cornea spouse team to come to our program. I'm sure the cornea specialist wanted to come and the retina specialist didn't. They were not a power couple and the cornea physician was much preferred. For reasons only known to them and the supernatural, they wanted to move to the rural northwest. It is not satisfying to hear after the fact that they regret their decision. There is no going back and there is no second chance. The decision to enter an academic program is a watershed moment in a candidate's life. If you turn your back on the offer, it is uncommon to get an opportunity again.

• ***Recruiting pearl*** Listen, be empathetic, try to reason and, ultimately, don't expect a win if location or extended family is the driver. All candidates have one or two drivers in their decision process and if this is one of them, there is no arguing. Changing a person's thought process in a couple days is unusual, if not impossible.

Times are different now and with time, once-universal truths that are taught in MBA schools and new-chair seminars no longer apply.

5. Ambition

This noun reminds me of the "greed is good" speech Gordon Gecko made in the movie, "Wall Street." In my view, ambition is good. Ambition trumps location. Ambition can supersede extended family and spouse. Ambition can even overcome salary expectations. Academic medicine frequently attracts those who aspire to train the next generation, discover cures to eye disease, innovate new treatments and collaborate with clinician scientists across the medical spectrum to improve the care of our population. Many recruits are looking for a career instead of a job. They want their career to be extraordinary. When I meet a candidate who wants to be involved in directing the residency program, lead a service, travel abroad and create a new clinic, or negotiate lots of lab space and protected time for research, I rejoice inside. These are candidates who speak an academic chair's language. Chairs can control space, funds, protected time and academic appointments. We have less influence on spouses, and we can't help our location.

• ***Recruiting pearl:*** Recruit for what your department needs. If you need a productive glaucoma surgeon, make sure you vet a productive glaucoma surgeon. Great teachers and lecturers are plentiful within our profession, but they know they are great. Appeal to their ambition to be even greater during the recruitment phase, and your department will benefit. Likewise, if you need an NIH-funded PhD researcher, these candidates are obtainable and will speak a language of space and funding that a chair can comprehend. From my perspective, ambition is the most joyous trait a candidate can have.

6. Optometry

Optometry schools have a glut of providers nationwide. As our eye residencies have remained static, optometry schools have increased and graduates are looking for a job. According to the ophthalmology fellowship match, about 70 percent of graduating ophthalmology residents will obtain a fellowship. This indicates that the general ophthalmologist is a shrinking breed and primary eye-care is increasingly becoming the purview of the optometrist. In addition, scope of practice by ODs is a constant issue and depending on the state you live in, they may already be performing procedures that used to be the privilege of only ophthalmologists.

The implications for an academic eye department is that optometrists will play a key role in primary eye-care going forward. I have found during my recruiting that optometry is an asset in our department and I need to employ at least four ODs to help sustain our primary-care enterprise. Ophthalmologists frequently do not want to see patients outside their subspecialty and even our

general ophthalmology faculty resist things at which ODs excel. These include contact lenses, refractions, low vision, pediatric care for amblyopia, diabetic eye exams and general eye exams.

• ***Recruiting pearl:*** Optometry will be a key component of general eye care going forward, therefore recruitment of the best ODs to academic centers is of paramount importance. The creation of OD residencies and OD student rotations within academic centers will help ophthalmology and optometry train excellent providers for the patients we care for. Scope-of-practice issues will not go away, but only by working together can we solve the problems that divide us. There is a place for both types of eye-care providers and the optometrists within academic centers are only too happy to refer the surgical and complicated eye diseases to the ophthalmologist most qualified to care for them.

7. Search Firms

I have been underwhelmed by the help provided by head-hunters or search firms. The professionals at these organizations simply do not know as many people as faculty within an academic department do. They are not networking as much as we do and there is no way a search firm could find a candidate for an academic department as well as a department chair could. The candidates suggested to me by the most reputable search firms are almost always not competitive in the areas that a clinician scientist would be competitive in. In addition, medical professionals speak a language and embrace a culture that is understood between medical personnel. A business like a search firm does not speak this language or understand a medical school culture.

• ***Recruiting pearl:*** Do not bother hiring a search firm. There are great job-listing sites with the American Academy of Ophthalmology, AUPO, the Association for Research in Vision and Ophthalmology and many of the subspecialty Listservs. In addition, discussing vacancies with colleagues across the nation will provide you the information you need in a much better fashion and in a language you understand apart from a search firm.

To paraphrase "Jerry Maguire," recruiting can be an "up-at-dawn, pride-swallowing siege."

8. Curriculum Vitae

Candidates are not their CVs. Unfortunately, they are usually much less than their CVs. Of course, there are surprises where the CV is average and the candidate is remarkably talented, but the inverse is usually true. In fact, the more impressive the CV sometimes the less impressive the candidate. Beware of the MD/PhD with grants, multiple publications, local awards, an MBA and considering getting a law degree. Some candidates over-train and this doesn't show a focus on success but more of a focus on being a professional student. Perhaps this is an instance where ambition turns in on itself and eats the host.

Academic departments look for triple threats; teachers; researchers; and clinicians. Triple threats may have an MD or PhD but what is important is how they work within a team; how candidates interact with patients; how they collaborate with faculty and staff. This data cannot be ascertained on a CV alone.

• ***Recruiting pearl:*** Spend hours of faculty time interviewing a candidate over more than just one day. Call the chair of the department where the candidate trained and talk directly to faculty and co-residents/fellows who trained with this candidate. You will be surprised what can be uncovered.

After talking to the residency director of a promising candidate, I learned the candidate had to repeat a year and was just not very good at surgery. After talking to a department chair at another program, I learned a candidate was considered a charlatan and a self-promoter. One cannot garner this information on paper. Information is power; learn everything you can about a candidate. One disruptive faculty member can ruin the morale of an entire department.

Our Legacy

To quote the movie, "Jerry Maguire," recruiting can be an "up-at-dawn, pride-swallowing siege." There are many disappointments that will occur during the process but the payoff in the end is to know we are all working together to improve eye care in our community. This is our legacy as ophthalmologists. Recruiting and retaining the smartest, most talented, compassionate and collaborative clinician-scientists leads to this reward.

It has only been two years and I think I've added some gray hair at a ratio of about 10 grays per month. With these recruiting pearls in my pocket, however, I believe I will be able to set my expectations at the appropriate level. It is my hope the reader, no matter what stage you are in, will also take these pearls into account as they will help ease the transition from recruit to faculty member. An efficient recruitment allows you to seamlessly start to do what we all want the most. That is to provide the best eye care, discover the cures to ocular disease, and teach the next generation of eye physicians and surgeons. REVIEW

Classic beta blocker adjunctive therapy for the right patient at the right time[3]

The concomitant use of two topical beta-adrenergic blocking agents is not recommended[4,5]

Indications and Usage

ISTALOL® (timolol maleate ophthalmic solution) is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma. It may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

Important Safety Information for Istalol® and Timoptic® in Ocudose®

- Both ISTALOL® (timolol maleate ophthalmic solution) and TIMOPTIC® (timolol maleate ophthalmic solution) in OCUDOSE® (dispenser) are contraindicated in patients with: bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease; sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure; cardiogenic shock; hypersensitivity to any component of the product.
- **The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. Severe respiratory reactions and cardiac reaction, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate.**
- Patients with a history of atopy or severe anaphylactic reactions to a variety of allergens may be unresponsive to the usual doses of epinephrine used to treat anaphylactic reactions.
- Timolol has been reported rarely to increase muscle weakness in some patients with myasthenia gravis or myasthenic symptoms.
- Beta-adrenergic blocking agents may mask signs and symptoms of acute hypoglycemia or certain clinical signs of hyperthyroidism. Patients subject to spontaneous hypoglycemia, or diabetic patients receiving either insulin or oral hypoglycemic agents, or patients suspected of developing thyrotoxicosis, should be managed carefully, with caution.
- In patients undergoing elective surgery, some authorities recommend gradual withdrawal of beta adrenergic receptor blocking agents because these agents impair the ability of the heart to respond to beta-adrenergically mediated reflex stimuli.
- The most frequently reported adverse reactions have been burning and stinging upon instillation. This was seen in 38% of patients treated with ISTALOL and in approximately one in eight patients treated with TIMOPTIC in OCUDOSE. Additional reactions reported with ISTALOL at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity.

Please see Brief Summary of Prescribing Information for ISTALOL and TIMOPTIC in OCUDOSE on the following pages.

For the patients who need incremental IOP reduction in a preservative free form[6]

Preservative-Free

TIMOPTIC® in OCUDOSE®
(TIMOLOL MALEATE 0.5% OPHTHALMIC SOLUTION) (DISPENSER)

For the patients who need incremental IOP reduction in a once a day form[6]

Istalol®
(timolol maleate ophthalmic solution) 0.5%

References: 1. Alm A, Stjernschantz J. Effects on Intraocular Pressure and Side Effects of 0.005% Latanoprost Applied Once Daily, Evening or Morning. *Ophthalmology*. 1995;102:1743-1752. **2.** Brubaker R. Flow of Aqueous Humor in Humans. *IOVS*. 1991;32:(13)3145-3166. **3.** Obstbaum S, Cioffi GA, Krieglstein GK, et al. Gold Standard Medical Therapy for Glaucoma: Defining the Criteria Identifying Measures for an Evidence-Based Analysis. *Clin Ther.* 2004;26(12)2102-2119. **4.** Istalol [package insert]. Bridgewater, NJ: Bausch & Lomb Incorporated; 2013. **5.** Timoptic in Ocudose [package insert]. Lawrenceville, NJ: Aton Pharma; 2009. **6.** Stewart W, Day DG, Sharpe ED. Efficacy and Safety of Timolol Solution Once Daily vs Timolol Gel Added to Latanoprost. *Am J Ophthalmol*. 1999;128(6)692-696.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use TIMOPTIC® 0.25% AND 0.5% (timolol maleate ophthalmic solution) in OCUDOSE® (DISPENSER) safely and effectively. See full prescribing information for TIMOPTIC in OCUDOSE.

PRESERVATIVE-FREE STERILE OPHTHALMIC SOLUTION
in a Sterile Ophthalmic Unit Dose Dispenser

TIMOPTIC® 0.25% AND 0.5% (TIMOLOL MALEATE OPHTHALMIC SOLUTION)

in OCUDOSE® (DISPENSER)

INDICATIONS AND USAGE

Preservative-free TIMOPTIC in OCUDOSE is indicated in the treatment of elevated intraocular pressure in patients with ocular hypertension or open-angle glaucoma.

Preservative-free TIMOPTIC in OCUDOSE may be used when a patient is sensitive to the preservative in TIMOPTIC (timolol maleate ophthalmic solution), benzalkonium chloride, or when use of a preservative-free topical medication is advisable.

CONTRAINDICATIONS

Preservative-free TIMOPTIC in OCUDOSE is contraindicated in patients with (1) bronchial asthma; (2) a history of bronchial asthma; (3) severe chronic obstructive pulmonary disease (see WARNINGS); (4) sinus bradycardia; (5) second or third degree atrioventricular block; (6) overt cardiac failure (see WARNINGS); (7) cardiogenic shock; or (8) hypersensitivity to any component of this product.

WARNINGS

As with many topically applied ophthalmic drugs, this drug is absorbed systemically.

The same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions, including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see CONTRAINDICATIONS).

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

In Patients Without a History of Cardiac Failure continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Preservative-free TIMOPTIC in OCUDOSE should be discontinued.

Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease (other than bronchial asthma or a history of bronchial asthma, in which TIMOPTIC in OCUDOSE is contraindicated [see CONTRAINDICATIONS]) should, in general, not receive beta-blockers, including Preservativefree TIMOPTIC in OCUDOSE.

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

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

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

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

PRECAUTIONS

General: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Preservative-free TIMOPTIC in OCUDOSE, alternative therapy should be considered.

Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

Angle-closure glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This requires constricting the pupil. Timolol maleate has little or no effect on the pupil. TIMOPTIC in OCUDOSE should not be used alone in the treatment of angle-closure glaucoma.

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

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

Information for Patients: Patients should be instructed about the use of Preservative-free TIMOPTIC in OCUDOSE.

Since sterility cannot be maintained after the individual unit is opened, patients should be instructed to use the product immediately after opening, and to discard the individual unit and any remaining contents immediately after use.

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (See CONTRAINDICATIONS.)

Drug Interactions: Although TIMOPTIC (timolol maleate ophthalmic solution) used alone has little or no effect on pupil size, mydriasis resulting from concomitant therapy with TIMOPTIC (timolol maleate ophthalmic solution) and epinephrine has been reported occasionally.

Beta-adrenergic blocking agents: Patients who are receiving a beta-adrenergic blocking agent orally and Preservative-free TIMOPTIC in OCUDOSE should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

Calcium antagonists: Caution should be used in the coadministration of beta-adrenergic blocking agents, such as Preservative-free TIMOPTIC in OCUDOSE, and oral or intravenous calcium antagonists, because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, coadministration should be avoided.

Catecholamine-depleting drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

Digitalis and calcium antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

CYP2D6 inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate, depression) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine, SSRIs) and timolol.

Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

Injectable epinephrine: (See PRECAUTIONS, *General, Anaphylaxis*)

Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year oral study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose.

In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000 times, respectively, the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day.

The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin.

Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test.

Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

Pregnancy: *Teratogenic Effects* — Pregnancy Category C. Teratogenicity studies with timolol in mice, rats and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity.

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

Nursing Mothers: Timolol maleate has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from timolol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

ADVERSE REACTIONS

The most frequently reported adverse experiences have been burning and stinging upon instillation (approximately one in eight patients).

The following additional adverse experiences have been reported less frequently with ocular administration of this or other timolol maleate formulations:

BODY AS A WHOLE: Headache, asthenia/fatigue, and chest pain.
CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.
DIGESTIVE: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.
IMMUNOLOGIC: Systemic lupus erythematosus.
NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.
SKIN: Alopecia and psoriasiform rash or exacerbation of psoriasis.
HYPERSENSITIVITY: Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localized and generalized rash.
RESPIRATORY: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.
ENDOCRINE: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).
SPECIAL SENSES: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, *General*); and tinnitus.
UROGENITAL: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta blocking agents, and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura; agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium, and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

OVERDOSAGE

There have been reports of inadvertent overdosage with Ophthalmic Solution TIMOPTIC (timolol maleate ophthalmic solution) resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest (see also ADVERSE REACTIONS).

Overdosage has been reported with Tablets BLOCADREN* (timolol maleate tablets). A 30 year old female ingested 650 mg of BLOCADREN (maximum recommended oral daily dose is 60 mg) and experienced second and third degree heart block. She recovered without treatment but approximately two months later developed irregular heartbeat, hypertension, dizziness, tinnitus, faintness, increased pulse rate, and borderline first degree heart block.

An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

DOSAGE AND ADMINISTRATION

Preservative-free TIMOPTIC in OCUDOSE is a sterile solution that does not contain a preservative. The solution from one individual unit is to be used immediately after opening for administration to one or both eyes. Since sterility cannot be guaranteed after the individual unit is opened, the remaining contents should be discarded immediately after administration.

Preservative-free TIMOPTIC in OCUDOSE is available in concentrations of 0.25 and 0.5 percent. The usual starting dose is one drop of 0.25 percent Preservative-free TIMOPTIC in OCUDOSE in the affected eye(s) administered twice a day. Apply enough gentle pressure on the individual container to obtain a single drop of solution. If the clinical response is not adequate, the dosage may be changed to one drop of 0.5 percent solution in the affected eye(s) administered twice a day.

Since in some patients the pressure-lowering response to Preservative-free TIMOPTIC in OCUDOSE may require a few weeks to stabilize, evaluation should include a determination of intraocular pressure after approximately 4 weeks of treatment with Preservative-free TIMOPTIC in OCUDOSE.

If the intraocular pressure is maintained at satisfactory levels, the dosage schedule may be changed to one drop once a day in the affected eye(s). Because of diurnal variations in intraocular pressure, satisfactory response to the once-a-day dose is best determined by measuring the intraocular pressure at different times during the day.

Dosages above one drop of 0.5 percent TIMOPTIC (timolol maleate ophthalmic solution) twice a day generally have not been shown to produce further reduction in intraocular pressure. If the patient's intraocular pressure is still not at a satisfactory level on this regimen, concomitant therapy with other agent(s) for lowering intraocular pressure can be instituted taking into consideration that the preparation(s) used concomitantly may contain one or more preservatives. The concomitant use of two topical beta-adrenergic blocking agents is not recommended. (See PRECAUTIONS, *Drug Interactions, Beta-adrenergic blocking agents.*)

Manuf. for:
ATON PHARMA
Lawrenceville
NJ 08648
USA

By: Laboratories Merck Sharp & Dohme-Chibret
63963 Clermont-Ferrand Cedex 9, France

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use ISTALOL® (timolol maleate ophthalmic solution) 0.5% safely and effectively. See full prescribing information for ISTALOL.

Istalol® (timolol maleate ophthalmic solution) 0.5%

Initial U.S. Approval: 1978

STERILE

INDICATIONS AND USAGE

Istalol (timolol maleate ophthalmic solution) 0.5% is a non-selective beta-adrenergic receptor blocking agent indicated in the treatment of elevated intraocular pressure (IOP) in patients with ocular hypertension or open-angle glaucoma.

CONTRAINDICATIONS

4.1 Asthma, COPD: Istalol is contraindicated in patients with bronchial asthma; a history of bronchial asthma; severe chronic obstructive pulmonary disease (see **WARNINGS AND PRECAUTIONS, 5.1, 5.3**).

4.2 Sinus Bradycardia, AV Block, Cardiac Failure, Cardiogenic Shock: Istalol is contraindicated in patients with sinus bradycardia; second or third degree atrioventricular block; overt cardiac failure (see **WARNINGS AND PRECAUTIONS, 5.2**); cardiogenic shock.

4.3 Hypersensitivity Reactions: Istalol is contraindicated in patients who have exhibited a hypersensitivity reaction to any component of this product in the past.

WARNINGS AND PRECAUTIONS

5.1 Potentiation of Respiratory Reactions Including Asthma: Istalol contains timolol maleate; and although administered topically, it can be absorbed systemically. Therefore, the same adverse reactions found with systemic administration of beta-adrenergic blocking agents may occur with topical administration. For example, severe respiratory reactions and cardiac reactions including death due to bronchospasm in patients with asthma, and rarely death in association with cardiac failure, have been reported following systemic or ophthalmic administration of timolol maleate (see **CONTRAINDICATIONS, 4.1**).

5.2 Cardiac Failure: Sympathetic stimulation may be essential for support of the circulation in individuals with diminished myocardial contractility, and its inhibition of beta-adrenergic receptor blockade may precipitate more severe failure. In patients without a history of cardiac failure, continued depression of the myocardium with beta-blocking agents over a period of time can, in some cases, lead to cardiac failure. At the first sign or symptom of cardiac failure, Istalol should be discontinued (see also **CONTRAINDICATIONS, 4.2**).

5.3 Obstructive Pulmonary Disease: Patients with chronic obstructive pulmonary disease (e.g., chronic bronchitis, emphysema) of mild or moderate severity, bronchospastic disease, or a history of bronchospastic disease [other than bronchial asthma or a history of bronchial asthma in which Istalol is contraindicated (see **CONTRAINDICATIONS, 4.2**)] should, in general, not receive beta-blocking agents, including Istalol.

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

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

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

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

5.8 Contamination of Topical Ophthalmic Products After Use: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers had been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface (see **PATIENT COUNSELING INFORMATION, 17**).

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

5.10 Angle-Closure Glaucoma: In patients with angle-closure glaucoma, the immediate objective of treatment is to reopen the angle. This may require constricting the pupil. Timolol maleate has little or no effect on the pupil. Istalol should not be used alone in the treatment of angle-closure glaucoma.

5.11 Cerebrovascular Insufficiency: Because of potential effects of beta-adrenergic blocking agents on blood pressure and pulse, these agents should be used with caution in patients with cerebrovascular insufficiency. If signs or symptoms suggesting reduced cerebral blood flow develop following initiation of therapy with Istalol, alternative therapy should be considered.

5.12 Choroidal Detachment: Choroidal detachment after filtration procedures has been reported with the administration of aqueous suppressant therapy (e.g. timolol).

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 practice.

The most frequently reported adverse reactions have been burning and stinging upon instillation in 38% of patients treated with Istalol. Additional reactions reported with Istalol at a frequency of 4 to 10% include: blurred vision, cataract, conjunctival injection, headache, hypertension, infection, itching and decreased visual acuity. The following additional adverse reactions have been reported less frequently with ocular administration of this or other timolol maleate formulations.

Timolol (Ocular Administration): *Body as a whole:* Asthenia/fatigue and chest pain; *Cardiovascular:* Bradycardia, arrhythmia, hypotension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon and cold hands and feet; *Digestive:* Nausea, diarrhea, dyspepsia, anorexia, and dry mouth; *Immunologic:* Systemic lupus erythematosus; *Nervous System/Psychiatric:* Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness and memory loss; *Skin:* Alopecia and psoriasiform rash or exacerbation of psoriasis; *Hypersensitivity:* Signs and symptoms of systemic allergic reactions, including angioedema, urticaria, and localized and generalized rash; *Respiratory:* Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections; *Endocrine:* Masked symptoms of hypoglycemia in diabetic patients (see **WARNINGS AND PRECAUTIONS, 5.6**); *Special Senses:* Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis, decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see **WARNINGS AND PRECAUTIONS, 5.12**); *Urogenital:* Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

6.2 Postmarketing Experience

Oral Timolol/Oral Beta-blockers: The following additional adverse effects have been reported in clinical experience with ORAL timolol maleate or other ORAL beta-blocking agents and may be considered potential effects of ophthalmic timolol maleate: *Allergic:* Erythematous rash, fever combined with aching and sore throat, laryngospasm with respiratory distress; *Body as a Whole:* Extremity pain, decreased exercise tolerance, weight loss; *Cardiovascular:* Worsening of arterial insufficiency, vasodilatation; *Digestive:* Gastrointestinal pain, hepatomegaly, vomiting, mesenteric arterial thrombosis, ischemic colitis; *Hematologic:* Nonthrombocytopenic purpura; thrombocytopenic purpura, agranulocytosis; *Endocrine:* Hyperglycemia, hypoglycemia; *Skin:* Pruritus, skin irritation, increased pigmentation, sweating; *Musculoskeletal:* Arthralgia; *Nervous System/Psychiatric:* Vertigo, local weakness, diminished concentration, reversible mental depression progressing to catatonia, an acute reversible syndrome characterized by disorientation for time and place, emotional lability, slightly clouded sensorium and decreased performance on neuropsychometrics; *Respiratory:* Rales, bronchial obstruction; *Urogenital:* Urination difficulties.

DRUG INTERACTIONS

7.1 Beta-Adrenergic Blocking Agents: Patients who are receiving a beta-adrenergic blocking agent orally and Istalol® should be observed for potential additive effects of beta-blockade, both systemic and on intraocular pressure. The concomitant use of two topical beta-adrenergic blocking agents is not recommended.

7.2 Calcium Antagonists: Caution should be used in the co-administration of beta-adrenergic blocking agents, such as Istalol, and oral or intravenous calcium antagonists because of possible atrioventricular conduction disturbances, left ventricular failure, and hypotension. In patients with impaired cardiac function, co-administration should be avoided.

7.3 Catecholamine-Depleting Drugs: Close observation of the patient is recommended when a beta blocker is administered to patients receiving catecholamine-depleting drugs such as reserpine, because of possible additive effects and the production of hypotension and/or marked bradycardia, which may result in vertigo, syncope, or postural hypotension.

7.4 Digitalis and Calcium Antagonists: The concomitant use of beta-adrenergic blocking agents with digitalis and calcium antagonists may have additive effects in prolonging atrioventricular conduction time.

7.5 CYP2D6 Inhibitors: Potentiated systemic beta-blockade (e.g., decreased heart rate) has been reported during combined treatment with CYP2D6 inhibitors (e.g., quinidine) and timolol.

7.6 Clonidine: Oral beta-adrenergic blocking agents may exacerbate the rebound hypertension which can follow the withdrawal of clonidine. There have been no reports of exacerbation of rebound hypertension with ophthalmic timolol maleate.

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category C: Teratogenicity studies have been performed in animals. Teratogenicity studies with timolol in mice, rats, and rabbits at oral doses up to 50 mg/kg/day (7,000 times the systemic exposure following the maximum recommended human ophthalmic dose) demonstrated no evidence of fetal malformations. Although delayed fetal ossification was observed at this dose in rats, there were no adverse effects on postnatal development of offspring. Doses of 1000 mg/kg/day (142,000 times the systemic exposure following the maximum recommended human ophthalmic dose) were maternotoxic in mice and resulted in an increased number of fetal resorptions. Increased fetal resorptions were also seen in rabbits at doses of 14,000 times the systemic exposure following the maximum recommended human ophthalmic dose, in this case without apparent maternotoxicity. There are no adequate and well-controlled studies in pregnant women. Istalol should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers: Timolol has been detected in human milk following oral and ophthalmic drug administration. Because of the potential for serious adverse reactions from Istalol in nursing infants, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

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

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

OVERDOSAGE

There have been reports of inadvertent overdosage with Istalol resulting in systemic effects similar to those seen with systemic beta-adrenergic blocking agents such as dizziness, headache, shortness of breath, bradycardia, bronchospasm, and cardiac arrest. An *in vitro* hemodialysis study, using ^{14}C timolol added to human plasma or whole blood, showed that timolol was readily dialyzed from these fluids; however, a study of patients with renal failure showed that timolol did not dialyze readily.

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: In a two-year study of timolol maleate administered orally to rats, there was a statistically significant increase in the incidence of adrenal pheochromocytomas in male rats administered 300 mg/kg/day (approximately 42,000 times the systemic exposure following the maximum recommended human ophthalmic dose). Similar differences were not observed in rats administered oral doses equivalent to approximately 14,000 times the maximum recommended human ophthalmic dose. In a lifetime oral study in mice, there were statistically significant increases in the incidence of benign and malignant pulmonary tumors, benign uterine polyps and mammary adenocarcinomas in female mice at 500 mg/kg/day, (approximately 71,000 times the systemic exposure following the maximum recommended human ophthalmic dose), but not at 5 or 50 mg/kg/day (approximately 700 or 7,000, respectively, times the systemic exposure following the maximum recommended human ophthalmic dose). In a subsequent study in female mice, in which post-mortem examinations were limited to the uterus and the lungs, a statistically significant increase in the incidence of pulmonary tumors was again observed at 500 mg/kg/day. The increased occurrence of mammary adenocarcinomas was associated with elevations in serum prolactin which occurred in female mice administered oral timolol at 500 mg/kg/day, but not at doses of 5 or 50 mg/kg/day. An increased incidence of mammary adenocarcinomas in rodents has been associated with administration of several other therapeutic agents that elevate serum prolactin, but no correlation between serum prolactin levels and mammary tumors has been established in humans. Furthermore, in adult human female subjects who received oral dosages of up to 60 mg of timolol maleate (the maximum recommended human oral dosage), there were no clinically meaningful changes in serum prolactin. Timolol maleate was devoid of mutagenic potential when tested *in vivo* (mouse) in the micronucleus test and cytogenetic assay (doses up to 800 mg/kg) and *in vitro* in a neoplastic cell transformation assay (up to 100 mcg/mL). In Ames tests the highest concentrations of timolol employed, 5,000 or 10,000 mcg/plate, were associated with statistically significant elevations of revertants observed with tester strain TA100 (in seven replicate assays), but not in the remaining three strains. In the assays with tester strain TA100, no consistent dose response relationship was observed, and the ratio of test to control revertants did not reach 2. A ratio of 2 is usually considered the criterion for a positive Ames test. Reproduction and fertility studies in rats demonstrated no adverse effect on male or female fertility at doses up to 21,000 times the systemic exposure following the maximum recommended human ophthalmic dose.

PATIENT COUNSELING INFORMATION

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (see **CONTRAINDICATIONS, 4.1, 4.2**) Patients should also be instructed 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 5.8**) Patients should also be advised 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. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart. Patients should be advised that Istalol® contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following Istalol® administration.

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Is There Room for God in the Exam Room?

William C. Stewart, MD, Lindsay A. Nelson, and Jeanette A. Stewart, RN, Charleston, S.C.

There's substantial literature on whether and how religion and prayer impact medical care. Still, there is little consensus.

Physicians are trained to make treatment decisions based on the scientific literature and their medical training. Many patients express, at some level, a dependence on God to help heal their disease, as well as provide happiness in life and hope for the future.[1,2] This may prove awkward for the physician, whose basis for bedside interaction may be primarily clinical, and who may have little spiritual training and know little about spiritual assessment or care.[3,4]

Further, physicians often think it is inappropriate to mention God or offer prayer to patients.[5,6] However, clinical studies show that patients often want the physician to speak with them about their religion.[7,24] Further, there is increasing demand for spiritual-care training and a competency-based spiritual-care curriculum among health-care professionals.[8,9]

The purpose of this article is to discuss the benefit of religion, shown in the medical literature in recent years, in a patient's life and how it might influence the relationship with his ophthalmologist and the treatment course. We'll look

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what the literature has revealed through a series of questions about patient attitudes and beliefs, and the potential benefit of prayer. We also will discuss methods for physicians to approach religious conversations with patients.

What the Studies Show

• ***Do patients really use religion as medical care?*** Peer-reviewed articles demonstrate that religious faith is important to many patients, particularly those with serious disease, and that they depend upon it as a positive coping mechanism and treatment method. Idethia Harvey, DrPH, and Lawanda Cook identified four categories of spirituality that influenced self-management in patients with chronic illnesses: God's involvement; prayer; spirituality; as well as a combination of conventional and spiritual practices.[10] The most frequently used spiritual practices included prayer and reading the Bible.

Gina Maygar-Russell, PhD, and coworkers found in ophthalmic patients that 82 percent believed prayer was important for their well-being.[11] Further, Justine R. Smith, PhD, and associates found in patients with inflammatory eye disease that prayer was their most commonly used alternative treatment (18 percent), greater than vitamins or herbal medicines.[12]

• ***Can religion really influence clinical outcomes?*** This issue is most often discussed in terms of prayer, and its impact on the course of a disease appears inconsistent. This is especially true with cardiovascular disease and systemic hypertension, in which prayer was associated with a positive effect (n=three articles) about as often as no impact (n=five articles).[13-20] A 2001 study at the Mayo Clinic noted no effect of prayer on cardiovascular disease outcomes after hospitalization in the coronary care unit.[13] In addition, Herbert Benson, MD, and associates at Harvard Medical School showed that prayer had no impact on the complication rate (52 percent), compared to no prayer (51 percent) following coronary bypass surgery.[14]

There is increasing demand for spiritual-care training and a competency-based spiritual-care curriculum among health-care professionals.

In contrast, prayer is associated generally with positive clinical outcomes in non-cardiovascular diseases including: rheumatoid arthritis; head injuries; inflammation; and infection. Prassad Vannemreddy, MD, and coworkers analyzed severe head injuries and found that patients who received prayer demonstrated lower death rates, fewer long-term vegetative states and improved state of consciousness.[21] Additionally, in a 2001 study at the Cha Hospital, in Seoul, South Korea, patients in that largely Christian country who underwent *in vitro* fertilization and received intercessory prayer, demonstrated a 50-percent pregnancy rate versus 25 percent in the non-prayer group.[22]

The reason for the inconsistency in prayer and religious factors is not known. Medically related reasons perhaps derived from differences in clinical measures between disease states that might influence the results.

Several religious factors also might influence study results such as: the content of the prayer; the attitude of the supplicant; and to whom the prayer is directed. These factors were not controlled generally in prayer-related studies. Spiritual aspects of healing are difficult to study because, if there is a God, he might have a "say so" in which prayers are answered and how!

However, other religious factors beyond prayer might influence clinical results. For example, Eliezer Schnall, PhD, and associates showed that religious affiliation or frequent religious service attendance did not reduce cardiovascular mortality or morbidity, but they were associated with decreased all-cause mortality.[23] Further, another group at the University of North Carolina at Chapel Hill observed that church-based interventions were successful in helping weight loss, diabetes and cardiovascular disease.[24]

• ***Do patients really want me to discuss religion with them?*** Maybe. Many patients, but not all, react positively to a physician's spiritual discussion with them. One group of researchers found that in patients with any systemic disease, 33 percent wanted to be asked, and 67 percent felt their physician should know about their religious beliefs.[25] Further, patient agreement with physician spiritual interaction increased with severity of illness (19 percent at a clinic visit, 29 percent during hospitalization, and 50 percent at near death).

Be careful, however. The authors found that the patient's desire for spiritual interaction with the physician decreased with greater intensity of the intervention: 33 percent would discuss spiritual issues; 28 percent assented to silent prayer; and 19 percent desired spoken

prayer. The authors concluded that the physician should be aware that a substantial minority of patients wants spiritual interaction, even at an office visit, and the desire for this interaction increases with severity of the illness.[25]

For eye doctors, Michael Siatkowski, MD, and coworkers found that before surgery 90 percent of the Christians studied thought praying with their doctor was positive in an ophthalmological setting.[26]

• ***Can religion make my patients happy?*** Generally, studies have found a positive relationship between religious practice, the seriousness of this practice, and quality of life in patients.

Harold Koenig, MD, of Duke University, found in older patients that most had religious beliefs and practices that were associated with positive social, psychological and physical-health outcomes.[27] Further, in 40 percent, their belief was the most important factor to help them cope with physical illness and major life stresses. In a separate study, Dr. Koenig and coworkers found that positive aspects of religious worship—believing God is benevolent, seeking a connection with God, and asking support from clergy—were related to better mental health.[28]

In addition, our own group found that glaucoma patients who practiced their Christian faith and who had at least some knowledge about their religion had a more positive attitude towards their glaucoma; better disease-coping; and a belief that God was concerned about their glaucoma and helped with their treatment.[29] In a separate study in which we collaborated, we found similar findings in ocular diabetic patients.[30] These results may indicate that the more serious the practice of religion, the greater sense of well-being derived in relationship to their glaucoma disease and treatment.

... glaucoma patients who practiced their Christian faith ... had a more positive attitude towards their glaucoma; better disease-coping; and a belief that God was concerned about their glaucoma and helped with their treatment.

• ***Can religion make my patients unhappy?*** It seems, yes, depending on the nature of a patient's relationship with God. Dr. Koenig and associates showed negative experiences, such as dealing with God's vengeance, punishment, demonic forces and spiritual discontent, were associated with poorer health outcomes.[27] Further, Kenneth Pargament, PhD, and coworkers noted patients' struggles related to perceived anger from God or being unloved by God, were associated with poorer health outcomes.[31] No clear explanations were provided by these negative interactions by the authors.

• ***Can religion make my patients take their medicine?*** Religious belief may be associated with greater treatment adherence. Gerard Silvestri, MD, and coworkers noted that lung cancer patients ranked the doctor's recommendations first and faith in God second when evaluating treatment options.[32] James Park, MD, and Sharon Nachman, MD, studying AIDS patients aged 14 to 22, found that excellent treatment adherence was associated with greater religious beliefs.[33]

In addition, several studies have noted that greater spirituality is generally associated with more knowledge about a patient's disease. Ramesh Ve Sathyamangalam and associates found, in an urban glaucoma population, that greater knowledge about this disease was associated with: practice of religion; female gender; higher education levels; older age; and family history of glaucoma.[34] In a rural health clinic, Padmaja Rani and coworkers observed that Christians and people from social economic upper strata knew the most about diabetes and retinopathy.[35]

The reasons for the benefits associated with adherence are not completely understood. However, they might potentially result from the effect of religion in the patients' lives, which generally encourages them to maintain a positive attitude and be respectful of medical staff and their treatment decisions, and provides a comforting hope regarding either a potential cure or their eternal future. Additionally, the structure of religious practice itself may provide the necessary discipline to encourage the patient to learn about his disease and adhere to treatment.

How Do I Use This?

Research studies have shown that religion generally plays a positive role in patients' lives, enabling them to draw encouragement from their relationship with God and helping them cope with their disease. Religious patients also show improved adherence to treatment and greater knowledge about their disease. The physician might use religion in certain cases as a resource to assist a

struggling patient.

How then should you approach the issue of religious faith? There are no set rules, and it depends on the preferences of the individual doctor. In general, a physician might choose one of three directions in interacting with a patient's faith.

First, a secular approach. A physician might assume that God does not interact with a patient and his or her disease or treatment. However, the physician could use the positive aspects of a patient's faith to further encourage her knowledge about the disease, about adherence to treatment, and about the use of faith as a coping mechanism.

In one sense this is the easiest choice, because it allows the physician to contain religious-based interactions with the patient within the framework of the scientific literature. However, such an approach might be perceived by the patient as impersonal, or as lacking respect for her religion.

Second, a humanistic approach. The physician might assume that a loving God exists and interacts equally among adherents in all faith groups. This approach allows the physician to be positive towards all religions, and limits the need to learn specifics about each.

However, it does have a disadvantage—the lack of knowledge about a patient's individual religion may limit the doctor's ability to counsel because the approach may appear uninformed or insincere. In reality, there are vast differences between religions and how God is perceived to interact with humankind that might have psychological consequences for the patient.

Third, a religion-specific approach. A doctor might assume that if God exists, then the Deity would manifest certain characteristics consistent with the religious literature (i.e., Judeo-Christian God, Mus-

lim God or Hindu pantheon, etc.). Therefore, the religion-specific approach has the advantage of providing better counsel to patients in a more sensitive and knowledgeable way.

For example, in Christianity, by far the most common religion in the United States, a patient struggling over guilt or fear of punishment by God—which has been linked to negative disease outcomes—or fear of death and the afterlife might receive encouragement from a physician who is knowledgeable in Christian tenets. Since Christianity bases acceptance by God solely on faith and not upon a system of works, the patient could be counseled in the proper precepts of this religion.[36] This might assist the patient to derive comfort and reduced anxiety, and raise hope from the conversation. Further, a referral by the doctor to a local church also might benefit the patient's socialization. Finding a support group and ultimately a better sense of well-being might conceivably improve patients'adherence and knowledge of their disease.

In summary, our short journey through religion suggests that patients frequently interact with God about their disease state. This spiritual interaction may benefit the patient by providing better well-being, a disease-coping mechanism and increased treatment adherence.

Many research avenues remain open regarding religion and disease, including controlled longitudinal studies investigating the impact of religion on a patient's quality of life and disease, as well as research that evaluates how physicians can best interact with patients' religious beliefs and encourage them to use their religion to cope with their disease.

Further, the great majority of available research about religious practices and medicine is derived from the United States, primarily in self-identified Christians. Importantly, cultures differ across the world and dogma differs across religions. Therefore, the results in this review might not reflect research performed in other countries or in religions with beliefs differing from Christianity. REVIEW

Dr. and Mrs. Stewart are co-founders of PRN Pharmaceutical Research Network, LLC, and PRN PharmaFarm. They also founded and direct Teleios, Inc, a private foundation dedicated to studying religion in medicine. Ms. Nelson is the research coordinator for Teleios. For information, teleiosresearch.com.

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Caring for the Eye's Gatekeepers

A look at the etiology, signs and symptoms of blepharitis, as well as strategies for treatment.

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

Tolstoy once wrote: "… he knew his soul, it was dear to him, and he guarded it as the eyelid guards the eye, and never let anyone enter his heart without the key of love." If eyes are the windows to the soul, then perhaps it's not too much of a stretch to say that the eyelids, as Tolstoy wrote, are its gatekeepers. As such, they must be tended to, cared for and nourished. In this and next month's columns, we will drill down on two related and often confused lid conditions: blepharitis and meibomian gland dysfunction. Blepharitis is one of the most common, chronic ocular surface diseases seen in the ophthalmologist's clinic, affecting more than 20 million individuals worldwide.[1,2] Its etiology is multifactorial and includes inflammation of the eyelid margin; it often involves dysfunction of the eyelashes, the muco-cutaneous junction and meibomian glands, rendering effective treatment choices difficult at best.

In 1946, ophthalmologist Phillips Thygeson described blepharitis as a chronic inflammation of the lid border and, oddly enough, identified the condition as one of the most common causes of disability observed in military air crew personnel. Patients can present with a range of signs and symptoms that include swelling and crusting of the eyelid and palpebral conjunctiva; superficial keratitis; dry eye; itching; burning; photophobia; incomplete blinks; vision loss and asthenopia.[1,3]

In this article, we'll examine the classification and prevalence of blepharitis, look at its presentation and diagnosis, describe some associated conditions, and then discuss current and promising new treatment modalities for controlling symptoms and minimizing complications.

The Scope of the Problem

Blepharitis, defined simply as inflammation of the eyelids, can affect all age and ethnic groups.[4,5] In a survey of U.S. ophthalmologists and optometrists, 37 to 47 percent of their patients had signs of blepharitis.[4] However, there is very little reliable data on the true prevalence of blepharitis and the manner in which clinicians manage the condition. One single-center study of 90 patients with chronic blepharitis found that the mean age of patients was 50 years.[6] In a case-control study, staphylococcal blepharitis occurred more commonly in women and had an average age of onset of approximately 42 years.[7,8] In the same study, the mean age of participants with seborrheic blepharitis was about 50. There was no difference in prevalence between men and women.[7]

The etiology of blepharitis can be described in several different ways, but in the clinical setting, patients don't fall neatly into categories. Evaluations of structural and functional changes to the lid margin, ocular surface, meibomian and accessory glands, as well as measures of tear-film stability and location of inflammation may be the best approaches to properly diagnose the disease. Dr. Thygeson's early description of the etiology of blepharitis classified it into three main types: seborrheic; staphylococcic; and mixed.[3,9] Dallas ophthalmologist James McCulley updated this to include six categories: staphylococcal; pure seborrheic; seborrheic associated with a staphylococcal component; seborrheic with

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secondary meibomian seborrhea; seborrheic with secondary meibomitis; and meibomian keratoconjunctivitis.[8] Another, more recent effort created a classification system for blepharitis and dry eye that emphasized the role of meibomian gland dysfunction.[10]

These efforts to classify and categorize highlight the heterogeneity of the disease etiology and help to explain the therapeutic challenges posed by the disease. In 2006, the research group at Ora developed a structure-specific and clinically relevant photographic scale for evaluating signs and symptoms of blepharitis and meibomitis. This seven-item scale provides investigator grading for lid margin redness and bulbar and palpebral conjunctival redness on a scale of zero to 3 (corresponding to gradings of none to severe), as well as subject-reported signs and symptoms (lid swelling, itchy eyelids and gritty eyes). This grading scale is suitable for the Food and Drug Administration development process of therapeutics and has now become an accepted industry standard.

Organisms such as *Demodex* mites have also been implicated in the development of blepharitis in some cases. Infestation, characterized by cylindrical dandruff or sleeves around the eyelashes, has been found in 30 percent of patients with chronic blepharitis. These mites live in the eyelash follicles; their eggs and decomposing bodies can clog the follicles and meibomian glands and cause an inflammatory response.[11]

Colonization of the eyelid by bacteria such as staphylococcus also plays a role in blepharitis; although this and other bacterial species are resident in both healthy and blepharitic eyelids, overgrowth is common in blepharitic eyelids.[12,13] Comparisons of bacterial flora between normal eyes and those diagnosed with staphylococcal blepharitis show that only 8 percent of normal patients had cultures positive for *Staphylococcus aureus*, as compared to 46 to 51 percent of those with staphylococcal blepharitis.[14] We know that normally non-pathogenic bacteria may become virulent if their population increases sufficiently. *Staphylococcus epidermidis*, one of the types of bacteria most often found on the eyelids, can produce inflammation-mediating virulence factors known as phenol-soluble modulins. PSMs are produced at the late stage of infection, leading to the production of inflammatory cytokines and the calling of neutrophils into the tissue.[15,16]

The symptoms and causes of blepharitis can overlap with many disorders, complicating the clinician's diagnosis and treatment plan.

Presentation and Diagnosis

Unfortunately, the symptoms and causes of blepharitis often overlap with a range of disorders that can complicate diagnosis and treatment. A patient history that includes symptoms associated with systemic disease (e.g., lupus erythematosus, scleroderma), recent systemic and topical medications, and contact lens use is important in determining the diagnosis.[17] Some patients can be asymptomatic, while others experience a burning sensation, foreign body sensation, contact lens intolerance or photophobia. The patients' symptoms are usually worse in the morning, and the disease may be characterized by cycles of exacerbations and remissions.

Staphylococcal blepharitis is recognized under the slit lamp by erythema, edema and irregular eyelid margins, all of which disrupt normal blink patterns, especially with incomplete blinks, resulting in dry spots, disruption of the tear film and inferior punctate keratitis. Telangiectasia can also be seen on the eyelid.

If the condition is mild, scales at the lash line may form collarettes or cuffs of fibrin (appearing as matted, hard scales), which encircle the lash at the base. Keratinization appears as a greasy coating, and lashes may be missing or broken (madarosis), suggesting folliculitis.

In severe and long-standing cases, the lid margin may be irregular due to fibrosis and thickening of the lid, trichiasis (misdirection of eyelashes toward the eye), poliosis (depigmen-

tation of the eyelashes) and eyelid ulceration and damage to the meibomian glands.[4,9] Seborrheic blepharitis presents with less erythema, edema and telangiectasia of the lid margins than staphylococcal blepharitis, but with an increased production of sebum and crusting on the lashes.[7]

Meibomian gland dysfunction is often present in these patients, and is characterized by inflammatory changes at the eyelid margins, in the structural anatomy of the gland orifices, and in the character of the glands' lipid secretions. The opening to the meibomian glands may develop an operculum with a pouting appearance, while the orifices may become keratinized, obstructed and scarred. Due to gland dropout, secretions may diminish, giving the appearance of infection with their thickened consistency and opaque color.[18-22] Lid scarring may also be present in some patients, leading to retraction of the orifice such that secretions are not delivered where they are needed. An irregular lid margin combined with a decrease in meibomian gland secretion can alter the tear-film composition, leading to the dry-eye syndrome that so often occurs in tandem with blepharitis.[23]

Before the clinician can make a diagnosis of blepharitis, it's important to rule out conditions that mimic the lid disease's signs and symptoms. Associated conditions like dry-eye syndrome, chalazia, acne rosacea, allergic conjunctivitis, demodicosis and ocular pemphigoid should all be considered.[24]

In addition, clinicians should be on the lookout for lesser-known systemic conditions associated with blepharitis such as hormonal dysregulation, certain cardiovascular conditions, inflammatory diseases, imbalance of gastrointestinal tract flora and psychological stress. A better understanding of the pathophysiologic association between those diseases and blepharitis may help in the treatment and prevention of blepharitis.

Treatment Options

Managing blepharitis relies heavily on the patient-doctor relationship. Treatment is based on the practice of careful lid hygiene, possibly combined with the use of topical antibiotics, with or without topical steroids or topical anti-inflammatory agents. Systemic antibiotics may be appropriate in some patients.

The goal of treating inflammation in blepharitis with a topical steroid is a rapid, potent suppressive burst that will quiet the eye in a window of time that's too brief for the well-known adverse effects of steroids to develop.

Initial treatment is eyelid hygiene, which includes lid scrubs, warm compresses and lid massage. Warm compresses raise the temperature of the eyelid above the melting point for meibomian gland secretions, thus aiding in secretion.

Massage can enhance the flow of secretions from the meibomian glands. To perform it, the patient holds the lid at the outer corner with one hand while the index finger of the other hand applies pressure and sweeps from the inner corner of the lid toward the ear.

Eyelid scrubs, which involve just a gentle scrubbing of the eyelids twice daily with a wet washcloth and detergent such as baby shampoo applied with a cotton-tipped swab applicator, are performed after the warm compresses to clear away crusts (scale and debris) that have accumulated on the eyelid margin.[25] If the crusts are difficult to remove, warm compresses can be applied two to four times daily with a washcloth at 10-minute intervals to soften and loosen encrustations and warm the secretions. Blepharitis is a chronic disease, so lid hygiene must be consistent and continue even after an acute exacerbation has resolved.

If substantial inflammation is present, patients may benefit from a short course of treatment with a topical corticosteroid. The goal of treating ocular inflammation is a rapid and potent suppressive burst, an "attack-and-retreat" approach that will successfully quiet the eye in a window of time too brief for developing the well-known adverse effects of steroids.

One such therapy in development is NCX 4251 (Nicox SA; Sophia Antipolis, France) a novel nano-crystalline formulation of fluticasone propionate that utilizes a unique applicator for topical delivery to the eyelid margin. In lymphocyte proliferation assays, fluticasone propionate has been observed to have a tenfold greater immunosuppressive potency than dexamethasone and a hundredfold greater potency than prednisolone acetate, which are currently the two leading ophthalmic steroids. It's thought that a more potent steroid could effectively quiet an inflamed eye in one- or two-week bursts of therapy, allowing for cessation of the therapy before any side effects ensue.

The proposed route of delivery for this blepharitis product is topical dosing directly to the eyelid with a sterile applicator. This eyelid applicator also features a lid scrubbing movement to aid in the efficacy of the product. The drug's potency might also allow for once-daily dosing, which would

be a significant advantage over other steroid options.

Decreasing bacterial colonization of the lids can be beneficial. A topical antibiotic ointment such as erythromycin or bacitracin may be indicated in some cases; it may be applied after lid hygiene techniques once or twice daily at the base of the eyelashes, depending on the severity of the inflammation.

Patients who do not respond to lid hygiene therapies or those suffering from ocular rosacea may benefit from orally administered tetracyclines. Clinical improvement with tetracycline use may be related to inhibition of bacterial lipases in both *S. aureus* and *S. epidermidis*.[14] However, tetracyclines may cause photosensitivity and should not be used orally in pregnant or lactating women or children younger than 8 years old because of the risk of tooth enamel abnormalities.[24]

In 2011, ophthalmologist Gail Torkildsen and her colleagues evaluated the clinical efficacy and safety of a tobramycin and dexamethasone ophthalmic suspension (TobraDex ST, Alcon) compared to azithromycin ophthalmic solution 1% (Azasite, Inspire Pharmaceuticals) in the treatment of moderate to severe blepharitis/blepharoconjunctivitis.[26] The study was sponsored by Alcon. The primary outcome parameter of the study was the difference in the seven-item global score (evaluated using standardized Ora scales). This study demonstrated that TobraDex ST was faster than Azasite in controlling the signs and symptoms of acute blepharitis/blepharoconjunctivitis when administered q.i.d. for a week.

Since many blepharitis patients also have both evaporative and aqueous tear deficiency, topical lubrication with artificial tears may improve symptoms when used as an adjunct to eyelid cleansing and medications. The LipiFlow system (TearScience, Morrisville, N.C.) is a novel thermal pulsation approach that applies simultaneous heat and pressure to the eyelid tissue to express the meibomian glands. Jack Greiner, DO, PhD, of the Schepens Eye Research Institute, and his colleagues found that a single 12-minute treatment with the LipiFlow system improved both signs (based on tear breakup time, corneal fluorescein staining and meibomian gland secretion scores) and symptoms (based on Ocular Surface Disease Index and standard patient evaluation of eye dryness scores) of meibomian gland dysfunction for up to one year after the treatment.[27]

Blepharitis is a common, complex, chronic disease of the eyelids that can present with a range of signs and symptoms. It's critical that patients and their caregivers remain on the lookout for the signs of blepharitis even after a flare-up is controlled. Careful and consistent lid hygiene, with the occasional use of topical antibiotics with or without topical steroids, remain the mainstays for disease management. Going forward, improvements in technology and diagnostics will help clinicians to better understand the complex manifestations of this disease, ultimately aiding in the future development of customizable treatment plans.

With eyelids standing as the guardians of our most precious sense, encouraging sensible lid hygiene and prompt response to blepharitis outbreaks seems a small price to pay for ocular health. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School. Mr. Shapiro is vice president at Ora, where Mr. Rimmer is a medical writer. Dr. Abelson may be reached at MarkAbelsonMD@gmail.com.

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Edited by Ann P. Murchison, MD, MPH

Eyelid Lesions: Diagnosis and Treatment

A look at some of the common eyelid lesions that you may encounter in practice, their risk factors and treatment options.

James Kasenchak, MD, and Gregory Notz, DO, Danville, Pa.

Eyelid lesions are more often than not benign. Accurate diagnosis by an ophthalmologist is based on history and clinical examination. When in doubt, any suspicious lesion should undergo biopsy. Here we offer a brief review of some of the more common eyelid lesions that an ophthalmologist may encounter in a general practice.

Background, Exam

To diagnose eyelid lesions one must first understand the anatomy of the eyelid and especially the eyelid margin and its characteristics. The eyelid margin consists of the skin, muscle, fat, tarsus, conjunctiva and adnexal structures including the approximately 100 eyelashes, glands of Zeis, glands of Moll, meibomian glands and the associated vascular and lymphatic supply.

The examination of an eyelid lesion begins with history. History should include chronicity, symptoms (tenderness, change in vision, discharge), and evolution of the lesion. Other pertinent points include a history of skin cancer, immunosuppression, fair skin or radiation therapy. Physical examination should include assessment of location, the appearance of the surface of the lesion and surrounding skin including adnexal structures. The clinician should be assessing for any ulceration with crusting or bleeding, irregular pigment, loss of normal eyelid architecture, pearly edges with central ulceration, fine telangiectasia or loss of cutaneous wrinkles. Finally, a physical examination of the patient should include palpation of the edges and/or fixation to deeper tissues, and assessment of regional lymph nodes and the function of cranial nerves II-VII. A picture can be priceless for following disease progression or response to treatment.

Although experienced clinicians may feel comfortable in their diagnosis, any doubt in clinical judgment should push the clinician for a histologic examination. Reports of clinically accurate diagnoses ranged from 83.7 percent to 96.9 percent with between 2 percent and 4.6 percent thought to be clinically benign but found to be histologically malignant.[1,2]

Classification

Among tumors encountered by ophthalmologist the most common neoplasms are those of the eyelid. Benign lesions of the eyelid represent upwards of 80 percent of eyelid neoplasms, while malignant tumors account for the remaining, with basal cell cancer the most frequent malignant tumor.[3] It can be helpful to categorize eyelid lesions into inflammatory, infectious and neoplastic.

Inflammatory Lesions

• *Chalazion* presents as chronic, localized swelling of the eyelid and typically affects the meibomian glands or glands of Zeis *(See Figure 1)*. Data on the frequencies is difficult to come by, but in one recent review chalazia represented nearly half of all eyelid lesions encountered in an ophthalmology practice.[3] Conservative treatment with warm compresses or topical steroids is often sufficient. Surgical management includes transconjunctival incision and curettage. If excision is performed it is recommended that histopathologic confirmation of the excised lesion be performed every time.[1] Alternatively, management with intralesional triamcinolone can

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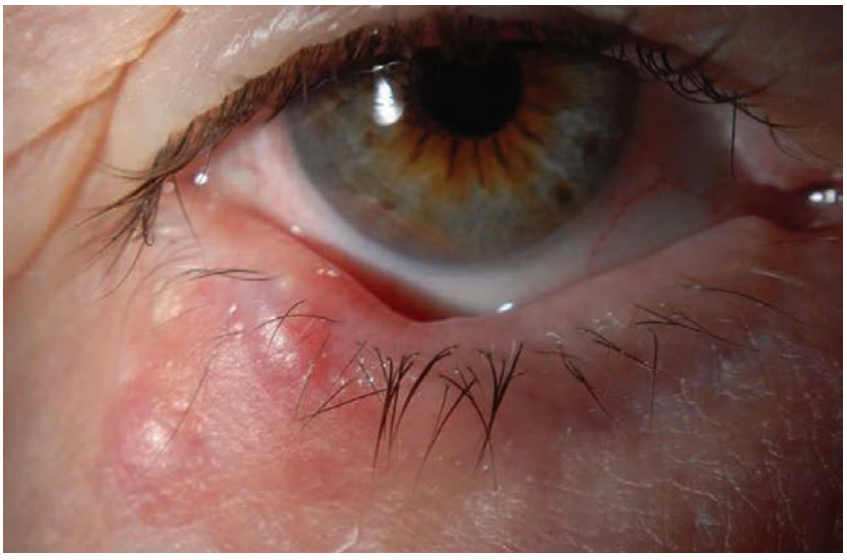

Figure 1. Multiple chalazia located in the right lower lid of a 74-year-old female. They were treated with incision and drainage, and the biopsy was consistent with chalazion.

be used although this approach carries with it complications of pigment changes or more devastating central retinal artery embolization. Intralesional dexamethasone is a safer alternative.

Infectious Lesions

• *Molluscum contagiosum* presents as pale, waxy and nodular cysts, classically with central umbilication. The patient is typically young, although there is increased incidence with more exuberant cases seen in AIDS patients due to reduced T cell count. They form secondary to infection from a DNA poxvirus and can present as a follicular conjunctivitis or lid nodules. The lid lesions may be misdiagnosed as a number of other eyelid lesions including basal cell carcinoma, papilloma, chalazion and sebaceous cyst. There is no predilection for the upper or lower eyelid and the local immune response will often be sufficient to eliminate the virus. Other treatment options include excision, cryotherapy or curettage.[4]

Neoplastic Lesions, Benign

• *Squamous cell papillomas* are formed from proliferation of epidermis and present either pedunculated, broad-based or white and hyperkeratotic lesions forming fingerlike projections.[5] Treatment is usually not required except for cosmetic removal.

• *Epidermal inclusion cysts* present as elevated, smooth and progressively growing cysts that arise from entrapment of epidermal tissue in the dermis. Rupture with release of keratin can cause an inflammatory foreign-body reaction.[6] Treatment involves excision with retention of the surrounding capsule, simply decapitating the head of the cyst allowing granulation tissue to form.

• *Acquired melanocytic nevi* are frequently molded to the eyelid margin and represent clumps of melanocytes at the epidermis and dermis. Not clinically apparent at birth, they increase in pigmentation at puberty. In the second decade they tend to present as elevated, pigmented papules. Later, the superficial pigmentation is lost, and an elevated, but amelanotic le-

Table 1. Malignant Eyelid Lesions Demographics and Risk Factors

Malignant Lesions	Age	Sex Predilection	Location	Race	Risk Factors
Basal Cell[3,12]	70	Equal	Lower, medial canthus	Caucasians of Celtic ancestry	Fair skin, sun exposure, smoking
Squamous Cell[3,12]	65	Male	Lower	Caucasians and Asians	Fair skin, sun exposure, exposure to radiation
Sebaceous Gland[3,14]	65-70	Female	Upper	Asian	Cancer syndromes and immunosuppression
Merkel Cell[3,10]	75	Female	Upper	Caucasians	Immunosuppression
Metastasis[17]	>50	Equal	Upper slightly	None	Systemic cancer
Lymphoma[17]	65	Female	No predilection	Caucasians	Systemic lymphoma
Melanoma[18]	60-80	None	Lower	Caucasians	Sun exposure

sion remains.[6] They usually require no treatment, but malignant transformation of a junctional or compound nevus can rarely occur and requires excision.

• *Seborrheic keratosis* is an acquired benign condition affecting elderly patients. Classically the lesions have a greasy and stuck-on appearance with varying degrees of pigmentation. Excision is sometimes required but recurrence is quite high.

• *Hidrocystoma*, also known as sweat ductal cysts, are caused by blockage of a sweat duct. They present as small (average of 4 mm) soft, smooth and transparent lesions.[5,7] Eccrine hidrocystoma often present as multiple cysts along the eyelids but do not involve the eyelid margin. Apocrine hidrocystomas characteristically transilluminate, involve the eyelid margin, and are associated with a hair follicle. The apocrine variety also tend to have a bluish color with yellow deposits. Cystic basal cell carcinoma is in the differential and specimens should be sent to pathology.

• *Xanthelasmas* present as yellowish plaques, usually in the medial canthal areas of either the upper or lower eyelids. The plaques are filled with lipid-laden macrophages. Patients usually have normal serum cholesterol levels but it is prudent to check lipid levels, as they can be associated with hypercholesterolemia.[6] Treatment options include superficial excision, CO2 laser ablation or topical 100% trichloroacetic acid.

Neoplastic Lesions, Premalignant

• *Actinic keratosis* presents as round, scaly, hyper-keratotic plaques that have the texture of sandpaper. They are the most common precancerous skin lesion and usually affect elderly persons with fair complexion and excessive sun exposure. Malignant transformation for a single plaque is less than 1 percent per year.[6] Observation is an option, but excisional biopsy is usually recommended to establish a diagnosis. Multiple lesions can be treated with cryotherapy, imiquimod 5% cream or other newer topical agents.

• *Keratoacanthoma* presents as flesh-colored papules usually on the lower eyelid in patients with chronic sun exposure or immunocompromised patients. This is now considered a low-grade squamous cell carcinoma in which dome-shaped hyperkeratotic lesions develop and can grow rapidly, with involution and regression at up to one year, once a keratin-filled crater develops.[8] After diagnosis with incisional biopsy has been made, current recommendations include complete surgical excision.[6]

Neoplastic Lesions—Malignant

• *Basal cell carcinoma* represents 80 to 92.2 percent of malignant neoplasms in the periocular region.[9] The localized nodular subtype is the "classic" lesion and presents most frequently on the lower lid at the medial canthus as a firm, raised, pearly nodules with fine telangiectasias *(See Figure 2)*.[11] A less common form of BCC, but more locally aggressive is the morpheaform type; these lesions lack ulceration, and appear as an indurated white to yellow plaque with indistinct margins.[8]

Patients are typically middle-aged or older and often fair-skinned, although it can occur in children and persons of African ancestry.[12] BCC in younger patients has a more aggressive growth pattern and does not demonstrate the latency period seen in older patients.[12] Treatment is primarily with Mohs' micrographic surgery followed by eyelid/facial repair with oculoplastics.

Orbital invasion occurs in less than 5 percent of BCC and most commonly the lesions are at the medial canthus.[8,12] Signs of orbital invasion include a fixed orbital mass, restrictive

strabismus and globe displacement or destruction.[9] CT or MRI is indicated to determine the extent of the disease. Once penetration reaches deep to the septum, local excision is very difficult. Nests of basal cells often hide, and this leads to more aggressive surgery (including orbital exenteration). Some cancer centers prefer external beam radiation followed by surgical removal in these advanced cases.

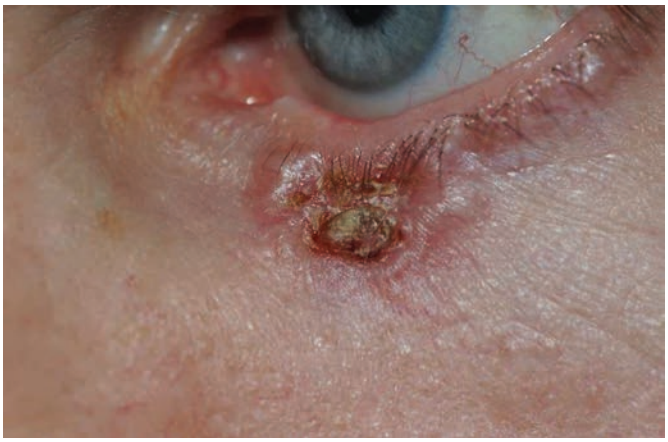

Figure 2. Basal cell carcinoma of the left lower lid in a 57-year-old male. Note the pearly edges and central scab. Initial biopsy was consistent with BCC. The condition is treated with Mohs' surgery with reconstruction with a Hughes flap by an oculoplastic specialist.

• *Squamous cell carcinoma* is the second most common eyelid malignancy, occurring in the lower lid approximately 60 percent of the time.[13] SCC lacks the pathognomonic features, which allows for differentiation from precursor lesions including actinic keratosis, Bowen's disease (squamous cell cancer *in situ*) and radiation dermatitis.[8,12] The presentation is often with a painless nodular lesion with irregular rolled edges, pearly borders, telangiectasias and central ulceration, similar to BCC.[12] The clinical diagnosis has been reported to be accurate anywhere from 51 percent to 62.7 percent of the time.[13] Patients are generally males older than 60 and often have a history of other skin lesions requiring excision.[11]

Predisposing factors include both extrinsic factors, such as ultraviolet light, exposure to arsenic/hydrocarbons/radiation, HPV infection or immunosuppressive drugs and burns; and intrinsic factors of albinism and xeroderma pigmentosa.[11,13] Metastasis of the lesions is most commonly through the lymphatic system, and early detection of lymph node involvement is essential to improve the prognosis.[9,11] SCC invades along the trigeminal, oculomotor and facial nerves and can present as asymptomatic perineural invasion detected on histologic examination or symptomatic perineural invasion. SCC with perineural invasion has a recurrence rate of up to 50 percent, and postoperative radiotherapy for all SCC with perineural invasion has been suggested.[9]

• *Sebaceous carcinoma* originates in the meibomian glands or the glands of Zeis and presents clinically as yellowish discoloration due to its lipid content; it can mimic blepharoconjunctivitis, chronic chalazia, BCC, SCC or other tumors *(See Figure 3)*.[8] The lesions most commonly affect women aged 65 to 70 in along the upper lid.[14] It can present as loss of eyelashes, destruction of Meibomian orifices or chronic unilateral blepharoconjunctivitis. SC affects all races, but Asians in particular, and represents the most common or second most common periocular malignancy in this group.[3,9]

The diagnosis can be missed on initial biopsy, and may require multiple biopsies or special stains. Superficial biopsy is often not sufficient and can miss the underlying tumor; therefore a pentagonal full-thickness excision or punch biopsy may be necessary to make the diagnosis. Biopsy specimens with intraepithelial involvement of the conjunctiva should raise the suspicion for orbital invasion.[8]

Although the etiology is not usually known, there is an association with Muir-Torre syndrome, an autosomal dominant cancer syndrome thought to be a subtype of hereditary nonpolyposis colorectal cancer. If SC is identified the patient should be evaluated for this syndrome.[11] Mortality rates within industrialized countries have fallen to 9 to 15 percent; poor prognostic factors include duration longer than six months; vascular and lymphatic involvement; orbital extension; multicentric origin; intraepithelial carcinoma

Juri Bilyk, MD

Figure 3. Sebaceous carcinoma of the left lower lid in a 52-year-old female. Patient presented with chronic unilateral blepharoconjunctivitis for 12 months, madarosis and eyelid lesion. Incisional biopsy showed sebaceous gland carcinoma. Definitive treatment should be undertaken by an experienced oculoplastic specialist or multidisciplinary team.

or pagetoid spread into the conjunctiva, cornea, or skin; upper lid location; and previous radiation.[14]

• *Merkel cell carcinoma* of the eyelid presents in elderly Caucasian women, average age of 75, with immunosuppression being a risk factor. Half of all MCCs are located in the head and neck, and between 5 and 10 percent occur in the eyelids.[10] MCC presents in the upper lid as a painless, red-purple vascularized nodule, sparing of the overlying epidermis. In 20 to 60 percent of patients, there is lymph-node positivity at presentation and distant metastases appear within two years 70 percent of the time.[15] This can be an aggressive, fatal cancer that requires judicious biopsy and systemic management by oncology.

Tumor size and metastasis at presentation are the most important prognostic factor with MCC tumors. The evaluation for tumor-lymph node-metastasis starts after the histologic diagnosis. Regarding treatment, the tumor responds well to radiation therapy, but primary treatment of the tumor is with excision and wide margins or Mohs' surgery.[10]

• *Metastasis* to the eyelid is rare and represents less than 1 percent of malignant eyelid tumors; it usually occurs in the course of widespread metastatic disease, but can be the presenting sign of systemic cancer. The features of metastasis to the eyelid are not specific and can be solitary or multiple eyelid nodules or diffuse eyelid swelling. Biopsy should always be considered. Breast and cutaneous melanoma are the most common primary carcinomas.[16]

• *Lymphomas* of the ocular adnexa are primary tumors involving the orbit. Lymphoma presenting on the eyelid is rare and usually associated with systemic disease. Lymphoma of the eyelid represents 10 percent of ocular adnexal lymphoma.[17]

• *Melanoma* of the eyelid is a relatively rare tumor, making up less than 1 percent of eyelid cancers.[5] Lesions present in a patient in the sixth to eighth decade of life as a pigmented and thickened area of pigment on the lower eyelid with irregular borders.[10,18] In any patient with a pigmented lesion, biopsy should be considered. REVIEW

Dr. Notz is a staff associate in ophthalmology at Geisinger Health System. Contact him at 100 North Academy Ave. Department of Ophthalmology, Danville, PA 17822. E-mail: gmnotz@geisinger.edu. Dr. Kasenchak is a second-year ophthalmology resident at Geisinger. E-mail: jekasenchak@geisinger.edu.

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Ultra-Widefield Retinal Imaging in Uveitis

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

Igor Kozak, MD, PhD, MAS, Riyadh, Saudi Arabia and Quan Dong Nguyen, MD, MSc, Omaha, Neb.

The diagnosis of uveitis always requires careful examination of the peripheral retina, which can harbor significant pathology in many uveitic entities. Careful clinical examination of a patient's peripheral retina with indentation along with appropriate imaging studies are of utmost importance in clinical decision making and reproducible documentation of findings. Recent advances in wide- and ultra-widefield imaging techniques have significantly contributed to better assessment of the retinal periphery. Ultra-widefield imaging is an example of such technology available to retina and uveitis specialists. Current UWF imaging modalities can help in the assessment of posterior uveitis including capturing color images, red-free images, fluorescein and indocyanine green angiography and fundus autofluorescence.[1,2]

Experience with these modern imaging devices has truly changed the way ophthalmologists evaluate the vitreous, retina and choroid and has led to more understanding of the role of the peripheral pathology in uveitis.

Technology for UWF Imaging

Standardized imaging protocols were employed in some early clinical trials and research studies. The Diabetic Retinopathy Study used a protocol consisting of seven standard 30-degree photos for acquisition of images of the retinal periphery in a systematic manner. The width of these composite images in this protocol is approximately 75 degrees. Photographs anterior to the equator can be obtained with this protocol by tilting the camera, but they will not image farther peripheral structures.[3] This protocol was extended to a nine standard-field protocol for the Longitudinal Studies of Ocular Complications of AIDS (L-SOCA) protocol to image both active and inactive peripheral cytomegalovirus retinitis. Per specifications of the Fundus Photography Reading Center at the University of Wisconsin, retinal cameras approved for this procedure had 50-degree or 60-degree magnification settings. Such photography, however, may be limited by patient alignment problems, focusing irregularities, marginal corneal astig-

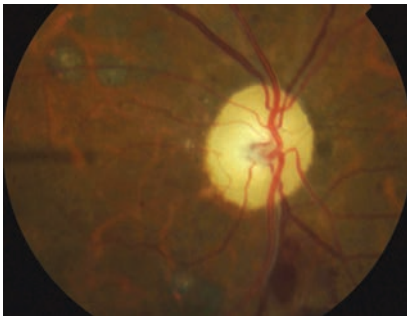

Figure 1. 20-degree field of view. Color fundus photograph of an eye post retinal laser photocoagulation due to retinal vein occlusion associated with Behçet's disease. There is optic nerve pallor, intraretinal hemorrhages and laser spots.

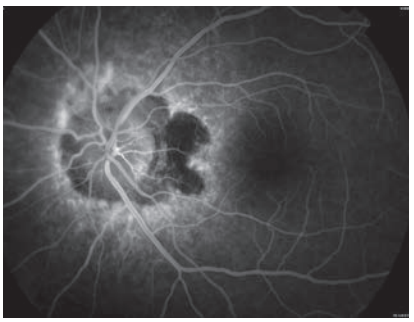

Figure 2. 35-degree field of view. Fundus fluorescein angiography showing peripapillary staining and blockage from choroidal neovascularization in an eye with presumed ocular tuberculosis.

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matism, poor fixation and light reflex artifacts.[4]

Since then, numerous advances have been made that permit visualization of the retinal periphery in a practical manner. The Retcam (Clarity Medical Systems) is a contact-based, wide-angle camera system with a 130-degree field of view.[5] The system is particularly well-suited for imaging pediatric patients because it is portable and can be placed directly just over the eyes of patients who are unable to position themselves, such as neonates and infants.

Reflection of light from interfaces in the ocular media is a major cause of artifacts with any fundus imaging. Confocal scanning laser ophthalmoscopy, which separates the illuminating and imaging beam within the eye, eliminates these reflections.[4] Giovanni Staurenghi, MD, and colleagues developed a combined contact and noncontact handheld lens system coupled with SLO. The Staurenghi lens system obtains high-resolution images with a 150-degree field.[6]

The Optos 200Tx (Optos) is a UWF imaging system that produces a 200-degree view depending on the definition of the geometric center of the retina. The Optos technology utilizes a combined SLO with an ellipsoidal mirror to obtain pictures of the peripheral retina with one capture without the need for bright illumination lighting or a contact lens, and in some patients, pupillary dilation. The system provides the ability to capture red and green reflectance imaging, as well as fundus autofluorescence and fluorescein/indocyanine green angiography.[7]

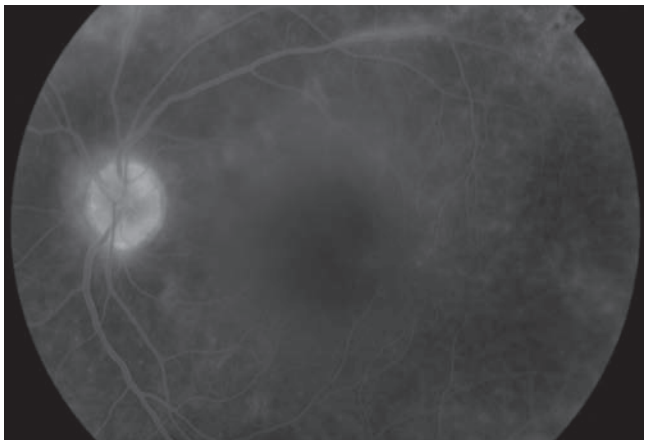

Figure 3. 50-degree field of view. Fundus fluorescein angiography showing mild optic disc and retinal pigment epithelium staining and vascular sheathing in an eye with idiopathic retinal vasculitis.

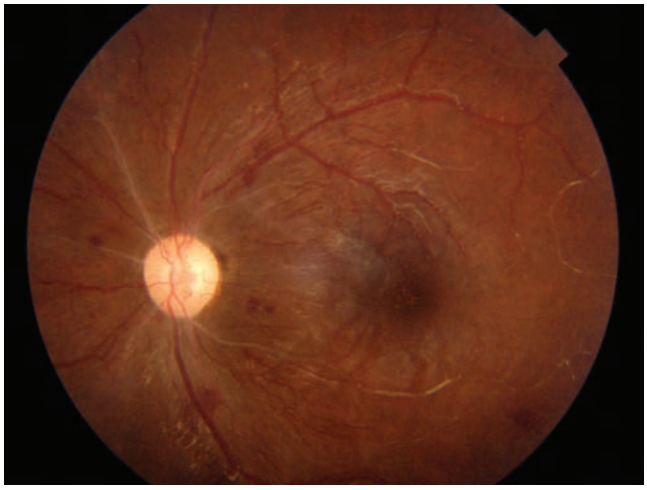

Figure 4. 80-degree field of view. Color fundus photograph of an eye with lupus retinopathy showing sclerotic retinal arteries, intraretinal hemorrhages and macular deposits. Fundus fluorescein angiography demonstrated central retinal artery occlusion.

Wide-field imaging of the vitreous is now possible with the introduction of a biomicroscopic wide-angle retinal and vitreous observation system utilizing a three CCD (charge-coupled devices) video camera and a personal computer for image display.[8] Optical coherence tomography technology is expanding toward examining wider areas of the retina. The systems have now expanded from 30 degrees to 55 degrees (Heidelberg Spectralis system, Heidelberg Engineering). With moving of the scan towards periphery, some areas can be visualized that were previously unreachable for OCT imaging.[9]

Uveitis

The diagnosis of posterior uveitis requires careful clinical examination of both the central and peripheral retina. Conventional fundus photography and fluorescein angiography are limited by their fields of view; thus, significant retinal findings are likely to be missed. Figures 1 to 7 demonstrate differences in the fields of view using different cameras and acquisition systems. UWF imaging technology detects peripheral lesions and reduces the rate of false negative findings.[10,11] Previous studies noted that the detailed images obtained with UWF technology allowed clear identification of peripheral retinal lesions and greatly enhanced objective documentation of disease activity and progression.[4,7,10] In numerous instances, the additional information provided by the UWF has altered management decisions compared with standard examination and conventional imaging. Moreover, UWF fundus autofluorescence has been proven helpful in detecting and monitoring areas of old or new foci of retinal inflammation in patients with posterior uveitis. It revealed areas of focal loss of autofluorescence that were in high concordance with visual field testing results, which showed deep scotomas.[12] Similarly, UWF imaging may allow clear detection of inflammation in non-infectious vasculi-

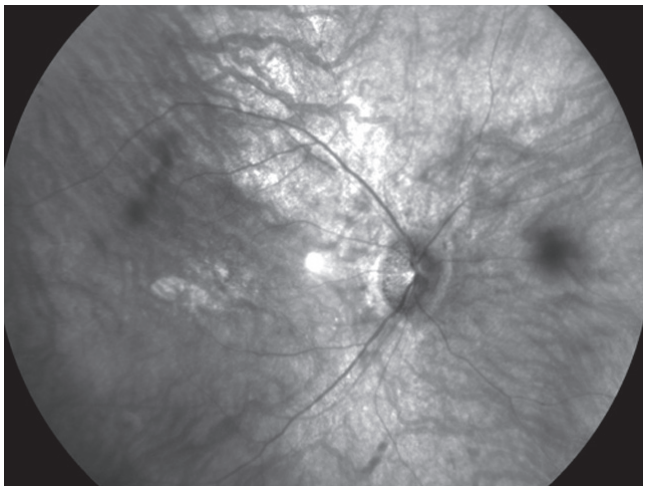

Figure 5. 100-degree field of view. Red-free fundus photograph of an eye with unknown retinal dystrophy and inflammatory reaction in the cortical vitreous.

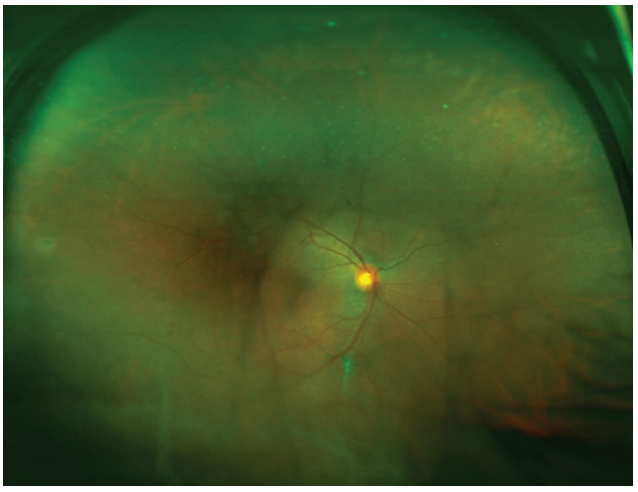

Figure 6. 150-degree field of view. Color fundus photograph of an eye with intermediate uveitis showing vitreous debris. The patient had a positive Quantiferon test for tuberculosis.

tis, which may lead to earlier treatment and perhaps better patient outcomes.[13] In some cases of retinal vasculitis, the vessels anterior to the equator may cause peripheral leakage, ischemia and neovascularization, which are difficult to detect clinically and before the process extends to the posterior pole. Accordingly, visualization of the peripheral retina could be essential to the diagnosis, monitoring and treatment of retinal vasculitis.[13]

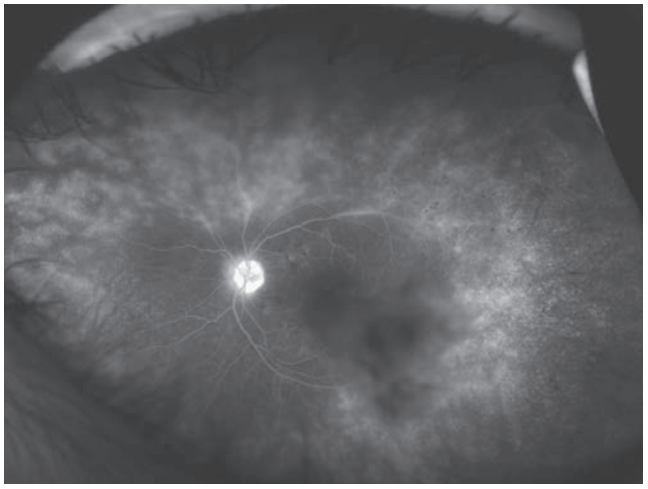

Figure 7. 200-degree field of view. Ultra-widefield fundus fluorescein angiography of an eye with idiopathic retinal vasculitis (the same eye as Figure 3). The image demonstrates mild optic disc staining, staining and stippling of the retinal pigment epithelium and vascular sheathing.

Marina Mesquida, MD, MSc, PhD, and colleagues assessed the role of UWF retinal imaging in the diagnosis and management of retinal vasculitis associated with Behçet's disease.[14] They found that UWF retinal imaging had allowed documentation of peripheral retinal lesions and greatly simplified longitudinal comparisons for disease activity and progression. In their study, peripheral vein sheathing and retinal infiltrates that denote disease activity were clearly detected with UWF pseudocolour imaging. UWF fluorescein angiography was a very helpful tool in their patients for determining whether the vasculitis had an occlusive nature and for quantifying the true extent of the capillary nonperfusion. Areas of retinal ischemia and neovascularization were easily identified in their series, aiding in the decision for targeted laser photocoagulation. Their observations also suggested that active retinal vasculitis in patients with Behçet's disease may induce retinal epithelium alterations in the retinal periphery. These abnormalities were visible with UWF fundus autofluorescence as multiple hyperfluorescent spots in the retinal periphery.[14] UWF indocyanine green angiography has been shown to produce high-resolution images of both the central and peripheral choroidal vasculature.[15] Wide-field ICG may also be invaluable in the diagnosis and monitoring of some uveitic entities.

Future Directions

There have been significant improvements in imaging the peripheral retina over the past years. UWF technology has become important clinically with regards to early diagnosis, effective treatment and monitoring of posterior uveitis. We expect that wide-field imaging will be used to extend and/or modify certain morphologic classifications of posterior uveitis phenotypes. It will be widely used in clinical research and maybe in some clinical trials. In addition,

we can expect incorporation of UWF retinal imaging in the field of telemedicine. Recently, a novel portable handheld smartphone-based retinal camera capable of capturing high-quality, widefield fundus images was developed. The use of the mobile phone platform creates a fully embedded system capable of acquisition, storage and analysis of fundus images that can be directly transmitted from the phone via wireless telecommunication system for remote evaluation.[16] A significant amount of work is going on to validate and expand the utilization of UWF imaging. We believe that UWF imaging technology will be indispensable for the routine uveitis practice in the near future. REVIEW

Dr. Kozak is a senior academic consultant in the Vitreoretinal and Uveitis Division, King Khaled Eye Specialist Hospital, Riyadh, Saudi Arabia. Dr. Nguyen is a professor and chairman at the Truhlsen Eye Institute, University of Nebraska Medical Center, Omaha, Neb. Contact Dr. Kozak at King Khaled Eye Specialist Hospital, Box 7191, Riyadh 11462 Saudi Arabia. Phone: +96614281234 ext. 3772; e-mail: ikozak@kkesh.med.sa.

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How to Eliminate Epithelial Ingrowth

Epithelial cells creeping under the LASIK flap are an annoying, though rare, complication. Here's how to address them.

Walter Bethke, Managing Editor

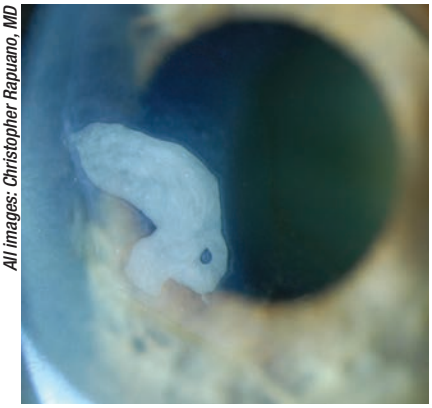
Though surgeons say the ingrowth of epithelial cells beneath the LASIK flap isn't as common as it once was, it can still occur, so it pays to be prepared for it if and when it appears. Left untreated, the cells can advance into the visual axis or compromise the integrity of the flap. Here, several surgeons with years of experience handling LASIK complications explain the best ways to manage epithelial ingrowth or, better yet, prevent it from occurring in the first place.

Patients at Risk

Surgeons say you can identify patients preoperatively who might be at increased risk for postop cells in the interface.

"Epithelial basement membrane dystrophy will increase the chance of an epithelial irregularity or a defect, and those increase the risk of ingrowth," explains Christopher Rapuano, MD, director of the cornea service at Philadelphia's Wills Eye Hospital. "Also, obviously, trauma to the flap increases the risk, whether the trauma is unintended or is caused by a flap-lift enhancement. Some surgeons will perform a diamond-burr polishing or excimer PTK several months before the LASIK in EBMD patients as a preventive measure, just in an attempt to get a healthier epithelium. However, some surgeons will just do PRK in these patients rather than LASIK. In the past, I've done the preop diamond-burr polishing technique, and it's reasonable to do if a patient really wants LASIK. However, even with the diamond burr and the PTK, the epithelium is often not cemented down; it's good enough that they don't get symptoms, but when you stress it with a LASIK flap, sometimes it still gets loose."

All images: Christopher Rapuano, MD



Epithelial ingrowth that interferes with vision needs to be addressed, say surgeons.

The flap-lift enhancement is a particular risk for ingrowth. "In my entire career, I've only had one patient who got epithelial ingrowth from a primary LASIK," says Beverly Hills, Calif., surgeon Andrew Caster. "It's almost exclusively a complication of a flap-lift enhancement. Also, when doing an enhancement, if a person has blepharitis or meibomian gland dysfunction—in other words, poor tear coverage—those are the ones more likely to get epithelial ingrowth when lifting the flap for an enhancement. If they have ocular surface issues before the flap lift, make sure to get those things quiet beforehand.

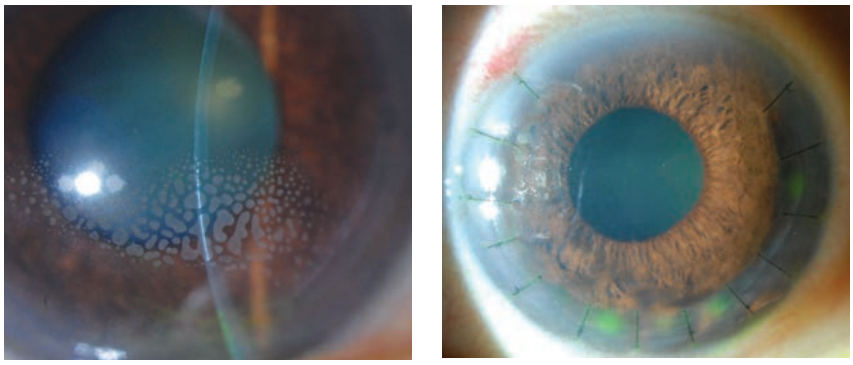
"I performed a study quite a few years ago that showed that the three-year mark after the primary LASIK procedure seems to be a dividing line," Dr. Caster continues. "I found that eyes in which the flap is lifted sooner than three years after the primary LASIK have almost no epithelial ingrowth, and eyes that are three or more years out seem to have about a 7-percent chance of ingrowth."[1] Be-

cause of this risk with later enhancements, some surgeons prefer to perform a PRK enhancement rather than relift the flap to perform a LASIK enhancement if it's been three years since the initial procedure.

Denver surgeon Michael Taravella says you can take steps to prevent ingrowth in certain cases. "I try to carefully check the edge of the flap on freshly created laser flaps, and in cases in which a flap lift is necessary for an enhancement," he says. "I'll take a Weck-Cel sponge and gently touch the edge of the flap 360 degrees around, including the hinge area, looking for and removing loose fragments of epithelium, especially on flap-lift cases." Dr. Caster will treat flap-lift enhancement patients with a longer course of steroids than his primary cases, treating them on a tapering basis for a month postop.

Though it's not been scientifically proven, a couple of surgeons feel that a hyperopic treatment increases the risk for ingrowth. "It's my clinical impression that epithelial ingrowth is more common when you're doing an enhancement that's going to involve a hyperopic treatment," Dr. Caster says. "My theory is that with these treatments, you're applying laser energy farther out, near the edge of the flap, and this may be a predisposing factor.

"There's something that's important to note," he continues. "Before you do a flap-lift enhancement, you need to discuss the risk of epithelial ingrowth with the patient. If it's been three years since the primary LASIK, I always tell him that there's a 7-percent risk of getting this problem, and that it can be completely avoided by doing a PRK, but that we're choosing to do a flap lift because it heals faster. I say we'll just have to deal with that 7-percent risk of ingrowth. Likewise, if you're doing an epithelial ingrowth removal, you should discuss with the patient the fact that the ingrowth could recur. It's important to have the patient onboard before you do these treatments."



This patient's epithelial ingrowth was removed initially, but then recurred (left). In response, the surgeon scraped out the cells and then sutured down the flap in an effort to seal down the flap edges and prevent further infiltration of epithelial cells (right).

Deciding to Treat

There are certain signs and symptoms to watch for when deciding whether it's time to intervene in a case of epithelial ingrowth, surgeons say.

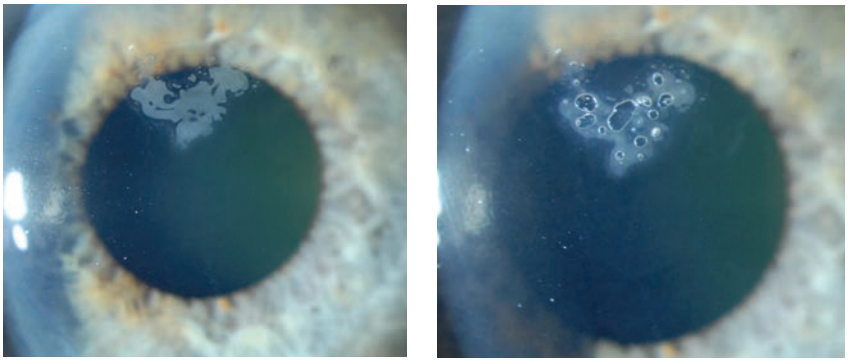
"Ingrowth affecting the health of the cornea is the number-one indication to remove it," says Dr. Rapuano. "Basically, if it's causing pain or a foreign-body sensation, that's usually because there's overlying superficial punctate keratitis or an epithelial defect—or stromal melting, which is even worse. Those are indications for removing it. The number-two indication for removal is if it's distorting the vision. Typically, distortion occurs when the ingrowth is somewhat elevated and is reaching at least a couple of millimeters away from the flap edge toward the center. Usually, if it's one or two millimeters from the edge it won't cause a big change in vision, but more than that and it often affects vision. If it's less than a millimeter away from the edge and even if there's a very little bit of melting, we won't intervene; we'll just use lubrication and observe it."

There's also the type of ingrowth that appears as an island beneath the flap, and doesn't appear connected to the flap edge. "If this island is more central, it tends to affect vision," says Dr. Rapuano. "If this is the case then you often need to treat it." Dr. Taravella says imaging can help in some cases of epithelial islands. "Topography can be a useful tool in assessing whether or not an island of epithelium is distorting the central corneal curvature," he says, "and it can also be used to follow progression, especially if tomography is available and shows thickening/increased pachymetry in the area of concern."

Edward Manche, MD, director of cornea and refractive surgery at Stanford University's Eye Laser Center, says the timing can also be a clue to the severity. "If it's less than a millimeter from the edge with no elevation, scalloping, staining, fibrosis or topographic changes, and patients are comfortable, it's something you can just watch," he says. "Usually, ingrowth will declare itself within three to four weeks after the surgery and then, if it's going to progress, it will do so after that. So, if I see any progression after that first month, I'll intervene."

How to Treat

Once you've made the decision to intervene in a case of epithelial ingrowth, surgeons say you can begin conservatively and then get more



A "semi-surgical" method some surgeons use to treat epithelial ingrowth is YAG laser. Here, a patient's progressive ingrowth, left, was treated with the YAG. The laser creates bubbles that work to remove the epithelial cells (right).

aggressive as necessary. Also, some surgeons take slightly different approaches.

"There are two main ways to treat ingrowth," says Dr. Rapuano. "First, you can lift the flap, scrape it out, and replace the flap. If the ingrowth is just in one quadrant, just lift that quadrant and carefully but aggressively scrape both the bed and the underside of the flap to get the ingrowth out. The underside of the flap is important because often there are a number of epithelial cells there. However, it's trickier scraping the underside of the flap because it can be difficult to see if there are any epithelial cells left there, and you don't want to cut or otherwise damage the flap. Some surgeons also use alcohol to make sure they kill all the cells, but, if you do that, be careful because alcohol can damage the cornea.

"The second way to remove the cells is to treat them with a YAG laser," Dr. Rapuano continues. "You pepper the ingrowth with a series of YAG spots that create air bubbles that can work to get rid of the ingrowth. Sometimes this works well—but sometimes it doesn't. It's not a perfect treatment, and it usually takes two to five laser treatments before you get rid of it all. Whichever way I choose to remove the cells, afterward I'll remove about two millimeters of peripheral epithelium outside the edge of the flap in order to create a larger epithelial defect. The reason for this is I want the flap to have more time to settle before that peripheral epithelium reaches it. Because when the epithelium reaches the flap edge, I want it to grow over the flap rather than underneath it." Dr. Caster, however, avoids creating this peripheral defect in ingrowth removal cases. "I haven't tried that method, but it seems that it might increase the inflammation," he muses. "This might be counterproductive, since you want to make sure you minimize any inflammation during the procedure and do as little manipulation as possible."

If the ingrowth recurs, surgeons get more aggressive with sealing the flap down after the cells are removed. "If it recurs, I'll lift the flap again, remove the epithelial ingrowth, and then use fibrin tissue glue to seal the edge of the flap," says Dr. Manche. "My experience with that approach has been quite good. I've done two dozen recurrent erosion cases this way and, of those, only one had another case of recurrent ingrowth. That patient, however, was someone who had epithelial ingrowth under the flap for many years after his LASIK procedure, and had three or four ingrowth removal treatments at other practices before coming to mine. In rare cases that aren't addressed well with tissue adhesive, we'll suture the flap. Suturing has been 100-percent successful in my hands."

Dr. Rapuano skips glue and sutures recurrent ingrowth cases right away. He describes his approach: "I place between six and 14 radial sutures, depending on how much of the flap I need to lift to remove the cells," he says. "I put the sutures in pretty tight. I'll take out about half of the sutures at around six weeks, and then remove the rest at 12 weeks."

Dr. Caster says he sometimes takes a novel approach to recurrent cases of small amounts of ingrowth that were causing some astigmatism. "In those cases, I decided that, rather than try to get rid of the recalcitrant epithelial ingrowth, it was better to do an astigmatic PRK to compensate for astigmatism caused by the ingrowth," he avers. "The treatment has been successful and the patients who've had it have been happy; they kept the little bit of ingrowth that I couldn't seem to get rid of, and I treated the astigmatism it was causing.

"If someone were to take this tack, however," Dr. Caster adds, "it depends entirely on the patient's best-corrected acuity. So, if the patient has epithelial ingrowth that's causing astigmatism and you can use trial glasses to get her to 20/20 and she says she likes that vision, then it's OK to do a PRK to counteract the astigmatism from the ingrowth. Also, this assumes you've been observing the patient and the ingrowth seems to be stable. If however, the ingrowth is causing a decrease in best-corrected vision, then, obviously, you need to remove it and not just treat its effects. Typically, its effect depends on how far toward the pupil margin the ingrowth extends, and how many clock hours it involves. If it's extending into the pupillary area and decreasing best-corrected vision, then you have to remove it." REVIEW

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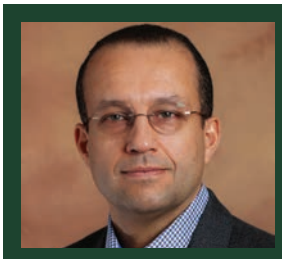
Edited by
Taliva D. Martin, MD


Sara J. Haug, MD

Air to Displace Submacular Hemorrhage



By Tamer H. Mahmoud, MD, PhD

Adding air through this simple technique can achieve **better displacement of a hemorrhage.**

I joined the retina faculty at the Kresge Eye Institute, Wayne State University in Michigan after my fellowship at Duke. After almost six years, I returned to Duke and can remember very vividly my first day back in the OR. Surgeons can be very particular about a systematic approach to pathology, instrumentation, machines used, lighting, visualization and supporting staff. Some nervousness would not be unexpected on this first day back, with a change of operating environment, and working with a first-year fellow, despite prior experience and some familiarity with the Duke operating rooms. My best consolation was Irma showing up that day to assist me. She was one of most experienced scrub nurses who used to assist Robert Machemer and Brooks McCuen.

Our patient presented with recent onset of extensive submacular hemorrhage, and I was planning to inject a combination of subretinal tPA and Avastin following pars plana vitrectomy. I felt it would be safer for me to inject while the fellow had the subretinal cannula tip in the subretinal space. I checked the line and withdrew the tPA and Avastin myself. I was planning to inject a larger volume to bathe the clot for a better displacement. The fluid went in nicely to the subretinal space but suddenly air bubbles entered the subretinal space, with rapid elevation of the macular detachment. What should I do now? I did not want to go back and try to remove the air from under the macula. I thought to leave it as is, since it's not gas and no traction existed, so it may resorb spontaneously. I could not sleep that night and felt it wasn't the best way to start back at Duke!

Next day, it was that moment of truth when I went in to see the post-ops. The fellow said: "You're not going to like this; the air is in the submacular area, which is detached!" Well! I was hoping the air would go to a different location, but what I saw amazed me. Indeed air was under the macula, but where was the blood? It was completely displaced far inferiorly. We examined the patient every day thereafter and within four days, air completely resolved, the subretinal blood stayed way inferiorly and vision recovered to the pre-bleeding level. I had never seen that much displacement away from the macula and I felt the urge to

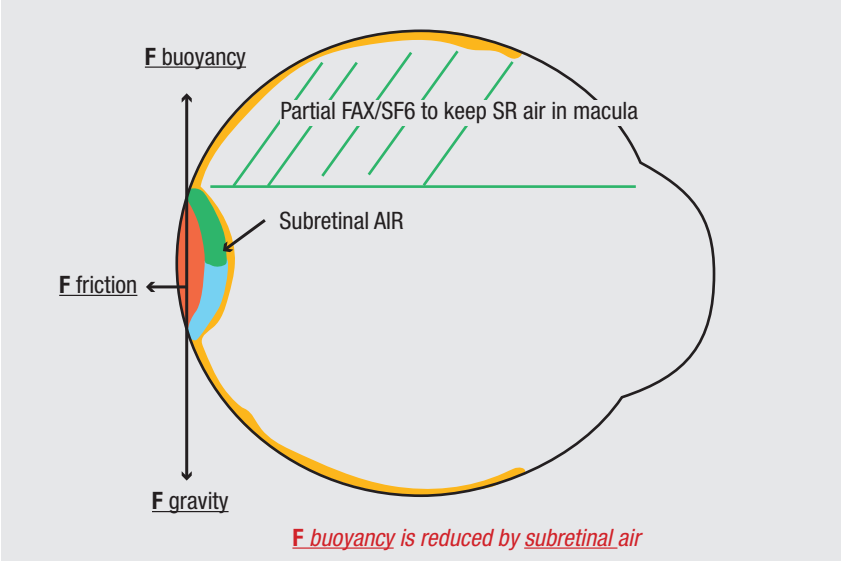


Figure 1. F forces acting on the subretinal hemorrhage in the subretinal space.

investigate this effect further.

After reviewing the forces acting on the subretinal hemorrhage from prior publications by Harvey Lincoff, it was obvious that air can change the vector for a better displacement. Think of air bubbles in a swimming pool or while scuba diving; those bubbles always move to the top of the pool; but imagine if the top is sealed and the walls are slightly distensible: Air will still move to the top and have to displace fluid underneath to the bottom and sides. After a long thought process and analysis of those forces *(See Figure 1)*, I purposely injected air in the subretinal space of subsequent cases. Displacement was again amazing, with recovery of most visual function and clearing of the macular area of any blood, also helping recovery not only of foveal function but of the central visual field *(See Figure 2)*. Fluid-air exchange and SF6 gas 20%, non-expansile, with partial fill was required to keep the submacular air in the macular region while the patient sat at the end of the procedure *(See Figure 1)*. Without gas in the vitreous cavity, air can migrate superiorly and detach the superior neurosensory retina. SMH would follow and therefore would stay in the macular area.

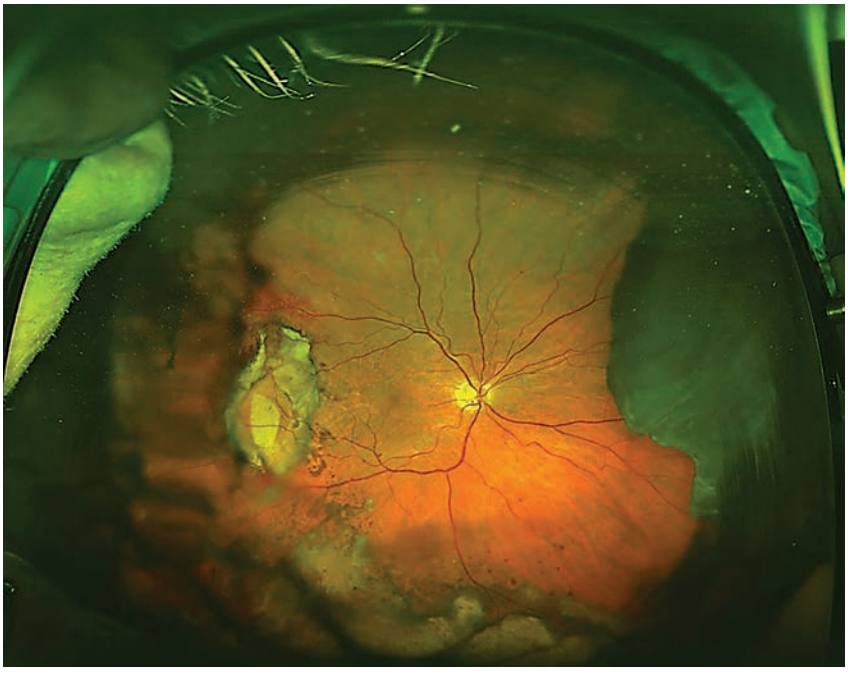


Figure 2. Wide displacement of the submacular hemorrhage away from the macular area.

We reported our initial experience for the first time at the Vail Vitrectomy meeting in 2013 and published later on that year.[1,2] Since then, many surgeons worldwide have adopted the technique. Some thought that they had accidentally injected air during their cases but never thought of researching the principles of better displacement. Japanese surgeons reported their experience with the technique more than a year later in a prospective study with 100-percent displacement and great visual outcomes.[3]

Many surgeons in the United States have adopted the technique, especially early on in North Carolina, where we have discussed it intensively at the NC Retina Club meetings. Retina surgeons in pri-

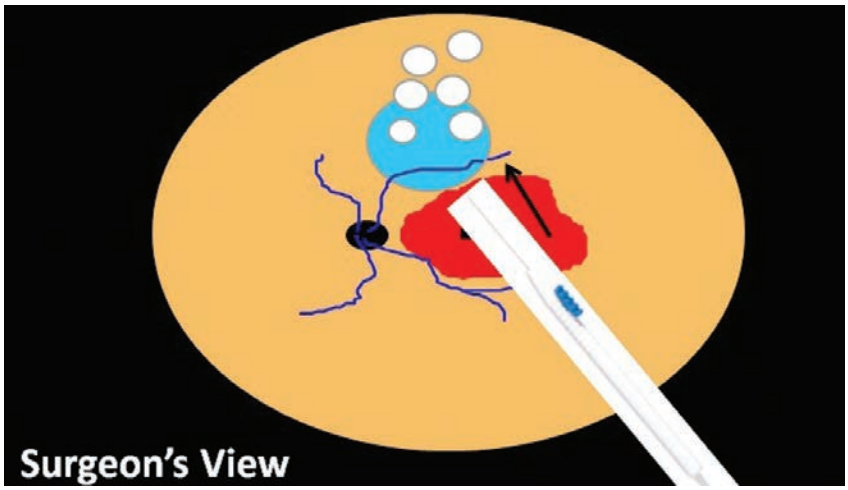


Figure 3. A Subretinal cannula inserted in the subretinal hemorrhage just inside the inferior arcade and fluid followed by air are injected.

vate practice and academics alike feel the technique is pretty simple since they have already been displacing SMH but just need to add the air. I had the pleasure of discussing with many surgeons around the world on the phone the day prior to the planned surgery and received great feedback and very encouraging results.

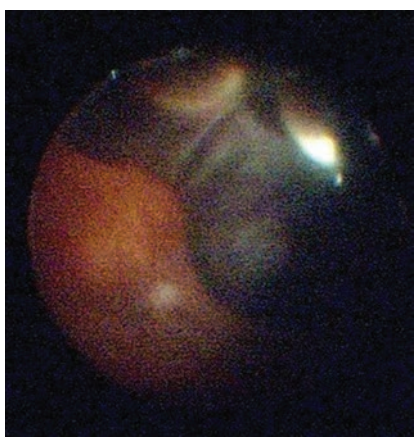


Figure 4: Surgeon's intraoperative view of air that gravitated up to the inferior ora, which is higher that the macular area, proving the concept of air dissecting its way through fluid and hemorrhage to a superior location.

Following the initial experience, the technique has evolved for the past three years. Macular holes can be very common in cases of large SMH and are easy to induce, with and without air injection. I have since changed the injection site to just inside the inferior arcade in all cases *(See Figure 3)*. With the direction of injection inferiorly, the bleb of subretinal fluid is formed of tPA and Avastin followed by the flow of air in the subretinal area. Since patients are supine during the procedure, air flows to the inferior ora *(See Figure 4)*. This prevents that initial rush into the subfoveal air, avoiding hole formation. When patients sit at the end of the procedure, air migrates up to the submacular area and is kept from moving more superiorly by the partial gas fill. Any head position between sitting up and chin down allows the subretinal air to massage the submacular area from any hemorrhage for complete displacement. The air also keeps the macular area detached for few days, allowing more time for subretinal tPA to liquefy the clot for better displacement. Air may hypothetically also provide more oxygenation to deprived photoreceptors; hence the level of improvement in visual function approaches vision prior to the hemorrhage. Patients with mainly subretinal pigment epithelial hemorrhage also have benefited from the mechanical effect of air flattening the PED with vision recovery. Many patients had recurrent bleeding and were displaced two more times with successful recovery; this is difficult to achieve just with injections.

Surgeons who have tried adding air to the subretinal mixture of fluid realize how they can achieve better displacement away from the fovea *(See Figure 2)* and have continued adopting this simple technique. We are currently working on gathering information from many surgeons with initial early experience, and those results will be shared soon with the retina community.

The culture created by Robert Machemer and Brooks McCuen still exists nowadays at Duke. Careful observation in the OR, understanding surgical concepts, and discussing techniques and complications are keys to advancing vitreoretinal surgery. REVIEW

Dr. Mahmoud is an associate professor in the Department of Ophthalmology, and program director of the vitreoretinal fellowship at Duke University Eye Center, Durham, N.C. Contact him at thmahmoud@yahoo.com.

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When a Prostaglandin Drop Isn't Enough

Many patients need more than a prostaglandin in order to reach your target IOP. Here are the pros and cons of each option.

Sanjay Asrani, MD, Durham, N.C.

Today, the first-line treatment for most glaucoma patients is a prostaglandin. These drugs are highly effective and only require once-a-day dosing, making them an ideal choice for a single-drug treatment regimen. But in many cases, one agent isn't sufficient to lower the pressure to your target. Furthermore, in some cases you'll find signs of progression even after the pressure has reached your target level. In both situations further action is required.

For example, a patient might present with advanced cupping and a pressure of 28 mmHg. My target pressure in this situation would be in the low teens with a fluctuation tolerance of less than 3 mmHg; but after using a prostaglandin the patient's pressure might only go down to 21 mmHg, meaning that additional treatment is called for. (In this particular case adding a single agent probably wouldn't suffice, so I would add a combination drug.) Or, you might find that a patient has, in fact, reached your target intraocular pressure, but in follow-up visits the patient's visual fields or optical coherence tomography scans—or both—are showing progression. In that case, you'll need to lower your target pressure and add a second-line treatment. (It's worth noting that simply switching the patient to a different prostaglandin seldom helps. If the patient is not responding adequately to one prostaglandin, there's very little chance he'll respond better to another.) Currently, about 30 percent of patients require adjunctive therapy within one year of starting prostaglandins.

The target pressures I typically aim for are based on the guidelines suggested by the Canadian Ophthalmological Society,[1] along with a few of my personal preferences. *(See table, facing page.)* Following those guidelines, in cases of severe glaucoma the target pressure should be in the low teens, with a fluctuation tolerance of less than 3 mmHg; in cases of moderate glaucoma, the pressure can be maintained in the mid-teens, with fluctuation acceptable below 4 mmHg; and in mild glaucoma cases, the pressure target can be in the high teens, with fluctuation kept to less than 5 mmHg. (Of course, these numbers may need to be adjusted based on pachymetry.)

Today, when a first-line prostaglandin is not sufficient to stop progression, multiple alternatives are available to choose as an adjunctive treatment. However, different choices will produce better results with different patients. So when deciding which second-line treatment makes the most sense for a given patient, you need to consider a number of issues, including compliance concerns, possible side effects, allergic reactions, contraindications and the need for callbacks—as well as the possibility that a non-drug alternative like selective laser trabeculoplasty might be the most efficacious option.

Adding a Single-agent Drop

Let's say you're considering adding a second single-agent drop—usually a carbonic anhydrase inhibitor, beta-blocker or alpha agonist—to the patient's regimen. Notably, any differences in the mean amount reduction in intraocular pressure you might achieve with the addition of a given agent should not be your main concern. More important con-

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siderations include the drug's side-effect profile, dosing and nocturnal pressure-lowering efficacy.

One important note: Never add a second prostaglandin! This can sometimes result in an unexpected pressure rise so extreme as to send the patient to surgery. In fact, this so-called paradoxical pressure rise can even occur if someone simply uses the first prostaglandin more than once a day.[2]

Let's take a closer look at the benefits and drawbacks of each of the other alternatives:

• ***Topical CAIs.*** These include dorzolamide and brinzolamide. On the positive side, they produce a significant lowering of IOP when combined with a prostaglandin, including significant nocturnal pressure reduction. (One study found a diurnal mean IOP-lowering of 19.8 percent when the two drug classes were combined, versus 14 percent with latanoprost alone, and a nocturnal mean IOP-lowering of 13.4 percent with the combination versus 10 percent with latanoprost alone.[3]) In addition, they have a low allergy rate, despite being related to sulfa drugs.[4]

When combined with a prostaglandin, CAIs are generally better at lowering IOP than beta-blockers. And they are preferable as a second-line therapy for low-pressure glaucoma patients because they don't cause systemic blood pressure to drop the way a beta blocker might. (If systemic blood pressure stays the same while IOP is lowered, one effect is an increase in the perfusion pressure of the eye, which is a good thing.) On the negative side, problems with CAIs include the risk of corneal endothelial toxicity. If a patient has Fuchs' corneal dystrophy, for example, topical CAI drops could trigger corneal edema.

• ***Beta-blockers.*** The advantage of adding a beta-blocker such as timolol is that it can be used once daily in the morning. That means your patient only has to manage two drops: the beta-blocker in the morning and the prostaglandin at night. In contrast, if you prescribe a drop like dorzolamide or brimonidine, your patient will have to use it at least two or three times a day, in addition to the prostaglandin. Prescribing a less-frequently dosed beta-blocker increases the likelihood of compliance.

However, if you're considering adding a beta-blocker to your prostaglandin, there are three things you should consider. First, does the patient have a history of emphysema or asthma? Beta-blockers are associated with a risk of bronchospasm, so this could be a contraindication.

Second, does the patient have a history of bradycardia or a bundle branch block (a defect of the bundle branches or fascicles in the electrical conduction system of the heart)? This can lead to trouble because beta-blockers can slow the patient's heart rate. For example, if your patient is a runner, his resting heart rate could be in the low- to mid-50s. If you start the patient on a beta blocker, that rate could drop into the 40s, prompting the patient to have a fainting attack—and maybe causing another doctor to prescribe a pacemaker. Such a mistake is not unheard of, and often neither the other doctor nor the patient makes the connection. The patient will return to you and say, "Oh, since I saw you I got a pacemaker." If you ask why, the patients may say, "Well, my heart rate dropped from 55 to 42, and we don't know why." Then you realize that this was caused by the beta-blocker that you added; it pushed the patient into bradycardia. So, if you're considering adding a beta-blocker to your patient's prostaglandin, you have to get a good idea of the patient's general systemic health, and in particular you have to investigate the patient's resting pulse rate.

Other factors to consider include that adding a beta-blocker to a prostaglandin only causes a mild-to-moderate further decrease in pressure—less than you would likely achieve with either of the other two single-drug options. Finally, it's worth remembering that tachyphylaxis may occur with beta-blockers, which means they may lose some of their effect after two to three years of use.

• ***Alpha agonists.*** Generally, this means brimonidine. There are two big problems associated with adding brimonidine to your prostaglandin: One is a very high allergy rate compared to other drugs. Nearly 28 percent of patients have an allergic reaction to alpha agonists. The second problem is its effect on systemic blood pressure. Brimonidine is a cousin of clonidine, which is an antihypertensive agent, and like clonidine it lowers systemic blood pressure.[5] That's significant because lowering systemic blood pressure can decrease ocular perfusion pressure—and lowering ocular perfusion pressure has the potential to make glaucoma worse. Although at least one clinical trial has suggested that brimonidine may be somewhat neuroprotective,[6] concerns about side effects may limit the use of this drug in some patients.

It's worth noting that a low perfusion pressure isn't just an issue with low-pressure glaucoma patients. A few years ago Christina Leske, MD, published a review of the literature showing how low diastolic perfusion

IOP Target Range*

Advanced glaucoma: Target range = low teens (least fluctuation tolerance, <3 mmHg)
Moderate glaucoma: Target range = mid teens (acceptable fluctuation <4 mmHg)
Mild glaucoma: Target range = high teens (acceptable fluctuation <5 mmHg)

*Canadian Society Guidelines and personal choice (after adjustment for pachymetry, if necessary)

pressure impacts the prevalence and incidence of OAG. The data from multiple population studies showed that when diastolic perfusion pressure is less than 55, the prevalence and incidence of OAG increases two- to sixfold.[7]

Given this correlation, it's reasonable to look for medications that might have the opposite effect—increasing perfusion pressure and hence improving the blood supply. A 2006 study by Luciano Quaranta, MD, showed the effects of various medications on ocular perfusion pressure.[8] He demonstrated that only prostaglandins and CAIs increase perfusion pressure and improved the blood supply because they lower eye pressure without decreasing blood pressure. In contrast, alpha agonists like brimonidine were associated with a significant decrease in perfusion pressure. (Perfusion pressure was unchanged with beta-blockers because the impact of the beta-blockers was negligible at night.)

Adding a Combination Drop

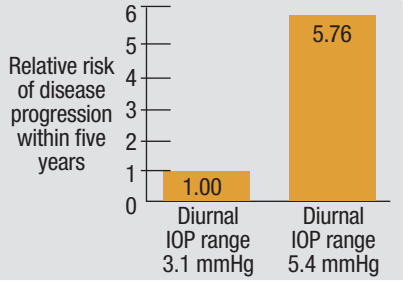
Recently, it's become more common for glaucoma patients to receive a fixed-combination product as the initial adjunctive therapy.[9] Instead of the doctor adding a CAI to the prostaglandin, and later adding timolol and eventually brimonidine, people are just going straight to the combination therapy once a prostaglandin has been deemed insufficient.

There are a number of reasons that this may be advantageous:

• ***Combination drops provide more aggressive therapy more quickly.*** As long as the combination agent has no negative side effects, this may reduce the pressure sooner and to a greater degree.

• ***Combination drops may improve treatment adherence.*** Instead of dealing with three or four bottles, the patient only has to manage two bottles. Improved adherence means more stable IOP control over time.

IOP Fluctuation & Progression



Drug options that reduce IOP fluctuation may be advantageous to the patient because reducing fluctuation has been shown to reduce the risk of glaucoma progression. One study found that the hazard ratio between the higher and lower quartiles for "range in home IOP" was 5.76, even after adjusting for factors such as age, race, level of visual field damage at onset and IOP measured in the office.[14]

• ***The more rapid and dramatic impact of combination drops makes the physician more confident and the patient more adherent to the protocol***. The dramatic IOP reduction that's usually achieved with a combination drug instills confidence in the treating physician, and that, in turn, has a positive effect on patient compliance. I've seen this many times. After adding the combination drug, the patient comes in with a significant reduction in IOP, boosting his confidence in the doctor and his motivation to continue taking the drops on a regular basis. The patient can see that the treatment is really working. In contrast, if the effect of the adjunct is not great, patients often lose enthusiasm for following the treatment regimen.

• ***Patients have fewer copays.*** Each time the doctor adds a drug the patient has to come in for an additional visit and pay another copay. Adding multiple drugs in a single drop means fewer copays for visits and drugs, and fewer pressure-check visits (unless the patient has an allergic reaction).

• ***Combination drugs may provide better pressure control because of complementary modes of action.*** The prostaglandins are great outflow-enhancing drugs. All of the combination drugs available in the United States are inflow-inhibitors, so they complement the prostaglandins. This means great diurnal control and more consistent lowering of pressure during the day.

• ***Reduced exposure to preservatives.*** If you put two drops in instead of four, you're going to reduce the amount of preservative placed on the eye.

• ***Reduced washout effect.*** The reality is that when taking multiple drops at the same time of day, very few patients wait five minutes between the drops. Thus, there is invariably a washout effect. If the multiple drugs are all in one drop, that's no longer an issue.

• ***Fewer doses for the patient to manage.*** Many of these combination drugs are still twice-a-day dosing, so the patient doesn't have to manage drops at three different times during the day.

Of course, there are a few potential downsides to adding a combination drug. One issue is that if the added drop fails to produce the pressure reduction you expected—or if the combination drop triggers an allergic reaction—you won't know which drug was responsible. That means eliminating one of the components of the combination drug to determine which is triggering the allergic reaction, and/or which drug is not working for this patient. Having to do a process of elimination removes all the benefits that come with using a combination drug. (Luckily, this doesn't happen too often. Allergic reactions will probably only occur in 5 to 10 percent of patients receiving a combination drug.)

Another potential concern is that you're exposing the patient to the

side effects of two types of drugs. However, you know the side effect profiles of each component of a combination drop, so if a problem occurs you should be able to identify the culprit immediately. (Also, less-problematic side effects would still have to be tolerated if you gave the patient the drops separately.)

One final issue has just become a concern in the past few months. Some insurance companies have begun refusing to pay for combination glaucoma drops such as generic Cosopt or Combigan—drops they covered in 2015. This is forcing us to shift patients back to multiple single-medication drops, simply because of the insurance companies' change in policy. The reason for this abrupt change in policy isn't clear, but we're getting a lot of phone calls about it. Now, patients who are stable on a combination drug have to change their routine and manage more bottles.

What About SLT?

Another option, if a first-line prostaglandin is not sufficient, is selective laser trabeculoplasty. SLT uses laser energy to cause alterations in the trabecular meshwork that result in a fairly long-lasting increase in outflow. Not surprisingly, improving outflow with a laser instead of additional drugs reduces issues with compliance, allergies, side effects and cost. When SLT is combined with a prostaglandin, the patient remains on monotherapy.

Typically, patients who benefit the most from SLT are the young and the elderly. Younger patients (in their 40s and 50s) usually have a busy life and don't understand the full import of glaucoma, and therefore don't appreciate the need for compliance. At the other end of the spectrum, patients in their 80s and 90s may have memory issues and arthritis, and their medication burden

Pros and Cons of Adjunctive Treatment Options

	Pros	*Cons*
Topical CAIs	• Significant lowering of IOP when combined with a prostaglandin. • Significant nocturnal pressure reduction. • Low allergy rate. • No effect on systemic blood pressure. With decreased IOP, this may increase ocular perfusion pressure, benefitting the optic nerve.	• Risk of corneal endothelial toxicity.
Beta-blockers	• Once-daily dosing	• Associated with risk of bronchospasm. • Can slow patient's heart rate, potentially causing problems. • Less pressure reduction with a prostaglandin than other alternatives. • May lose some effect after two or three years of use.
Alpha agonists	• Possibly neuroprotective.	• High allergic response rate (about 28 percent). • Lowers systemic blood pressure, thus lowering ocular perfusion pressure, which may increase risk of progression.
Combination drops	• More aggressive therapy more quickly. • Fewer drops means better compliance. • The greater impact on IOP increases doctor confidence and patient adherence. • Fewer copays for patients. • Complementary mechanisms of action (in association with a prostaglandin). • Reduced exposure to preservatives. • Reduced washout effect.	• If result is not ideal, more work is required to determine the reason. • Multiple potential side effects. • Some insurance companies are withdrawing coverage.
Selective laser trabeculoplasty	• No issues with compliance. • No issues with side effects or allergy. • No drug costs for the patient. • Reduces the patient's medication burden. • Reduces IOP fluctuation, associated with less risk of progression.	• Doesn't work in every patient. • Can't be done in some patients. • Some patients don't like the idea of a laser treatment. • The effect eventually wears off (but the treatment can be repeated).

may be considerable. They're often very grateful to have the number of medications they have to use reduced.

SLT can also be a good choice for adjunctive therapy in a patient with narrow angles. That's because one important side benefit of SLT is a significant reduction in IOP fluctuation—presumably as a result of avoiding compliance issues, washout issues and so forth. One study published in 2009 followed 22 patients for six to 24 months. After 360 degrees of SLT, the mean reduction in IOP was 35 percent, and 86 percent had intervisit fluctuation ≤2 mmHg.[10] Furthermore, multiple studies have shown that SLT effectively reduces pressure fluctuation in low-pressure glaucoma patients.[11-13]

Reducing the amount of fluctuation is important because pressure fluctuation has turned out to be a significant factor in glaucoma progression. For example, a glaucomatous eye with a pressure fluctuation of about 5.5 mmHg has a six-times greater risk of progression than an eye that has a fluctuation of 3 mmHg.[14] And while this factor is important in any type of glaucoma, controlling fluctuation is absolutely vital in low-pressure glaucoma. I have found that controlling fluctuation in low-pressure glaucoma patients stabilizes their disease.[11] In such patients, I typically recommend considering SLT as a second-line treatment rather than another drug, because my goal in that situation is not so much to lower the mean pressure as to control pressure fluctuation.

Given its advantages, SLT is potentially a good choice for many patients. Nevertheless, it does have several limitations. First, it doesn't work in 15 or 20 percent of the patients we try it on, for reasons we don't yet understand. Second, there are patients in whom you cannot do SLT, such as patients with uveitic glaucoma and some patients with trauma-associated glaucoma (there's a good chance it won't work if the trabecular meshwork has been injured in the past). Third, some patients simply don't like the idea of a laser being pointed into their eye. Fourth, the effect doesn't last more than two or three years. (Luckily, it can be repeated.)

Given its many advantages, I generally offer SLT as a second-line option to most patients who need an adjunctive therapy.

Despite these limitations, given its many advantages, I generally offer it as a second-line option to most patients who need an adjunctive therapy. It avoids the downsides of adding drugs and is better in terms of its impact on the patient's quality of life.

Choosing the Best Option

When choosing a second-line treatment to add to a prostaglandin, you should consider its potential side effects; the general systemic health of the patient, especially in terms of bronchial and heart issues; the patient's ability and willingness to adhere to your protocol; the cost to the patient; how the adjunct will affect the patient's IOP fluctuation; how it will affect the patient's diastolic ocular perfusion pressure; and how managing multiple medications (and possibly having to return to your office) will impact the patient's quality of life. If you choose to prescribe a second drug, you also need to be on the lookout for any allergic or systemic-health reaction.

Today, we are fortunate to have multiple second-line alternatives to choose from (with more potential options such as rho-kinase inhibitors in the pipeline). That gives us the opportunity to help our patients with the fewest possible downsides. We just have to choose wisely. REVIEW

Dr. Asrani is a professor of ophthalmology at Duke University School of Medicine and a specialist in the Glaucoma Service at Duke Eye Center in Durham, N.C.

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Patient Communication And Bottle Cap Color

A study from Wilmer Eye Institute researchers showed that physician understanding of patient topical ophthalmic medication use based solely on bottle cap color is frequently incorrect, particularly in patients with glaucoma. Errors based on communication using bottle cap color alone may be common and could lead to confusion and harm.

Patients aged ≥18 years with primary open-angle, primary angle-closure, pseudoexfoliation or pigment-dispersion glaucoma, bilateral visual acuity of ≥20/400 and no concurrent conditions that may affect color vision were included in this cross-sectional study. One hundred patients provided color descriptions of 11 distinct medication bottle caps. Color descriptors were presented to three physicians who matched each color descriptor to the medication they thought the descriptor was describing. The main outcome measure was frequency of patient-physician agreement, i.e., all three physicians accurately matched the color descriptor to the correct medication. Multivariate regression models evaluated whether patient-physician agreement decreased with degree of better-eye visual field damage, color descriptor heterogeneity or color vision deficiency, as determined by the Hardy-Rand-Rittler (HRR) score and Lanthony D15 color confusion index (D15 CCI).

Subjects had a mean age of 69 (±11) years, with VF mean deviation of -4.7 (±6.0) and -10.9 (±8.4) decibels in the better- and worse-seeing eyes, respectively. Patients produced 102 unique color descriptors to describe the colors of the 11 bottle caps. Among individual patients, the mean number of medications demonstrating agreement was 6.1/11 (55.5 percent). Agreement was <15 percent for four medications (prednisolone acetate, betaxolol HCl, brinzolamide/brimonidine and latanoprost). Lower HRR scores and higher D15 CCI, both indicating worse color vision, were associated with greater VF damage ($p<0.001$). The extent of color vision deficiency and color descriptor heterogeneity significantly predicted agreement in multivariate models (odds of agreement = 0.90 per one point decrement in HRR score, $p<0.001$; odds of agreement = 0.30 for medications exhibiting high heterogeneity [≥11 descriptors], $p=0.007$).

Ophthalmology 2015;122:2373-2379.

Dave P, Villareal G, Friedman D, Kahook M, et al.

Provider Communication Improves Eye Exam Adherence

Researchers from the Wills Eye Hospital evaluated the effect of written communication between an ophthalmologist and a primary-care physician on patient adherence to diabetic eye exam recommendations, and found that those patients with communication between providers are more likely to adhere to examinations.

In the retrospective cohort study, records of all patients with diabetes (n=1,968) and clinic visits between 2007 and 2010 were reviewed to collect: patient demographics; insurance status; hemoglobin A1C; severity of diabetic retinopathy; follow-up examinations; and written communication between a patient's ophthalmologist and primary-care physician. Statistical analyses examined the relationship between physician communication and adherence to diabetic eye exam based on the American Academy of Ophthalmology-published recommendations.

Written communication from an ophthalmologist to a primary-care physician was associated with increased adherence to follow-up eye examination recommendations (odds ratio: 1.49; 95 percent confidence interval: 1.16 to 1.92; $p=0.0018$). Communication from a primary-care physician to an ophthalmologist was also associated with increased adherence (OR: 1.94; 95 percent CI: 1.37 to 2.77; $p=0.0002$). Multivariable analysis controlling for other factors associated with examination adherence confirmed that communication both to and from an ophthalmologist was independently and significantly associated with increased follow-up adherence.

Retina 2016;36:20-27.

Storey P, Murchison A, Pizzi L, Hark L, et al.

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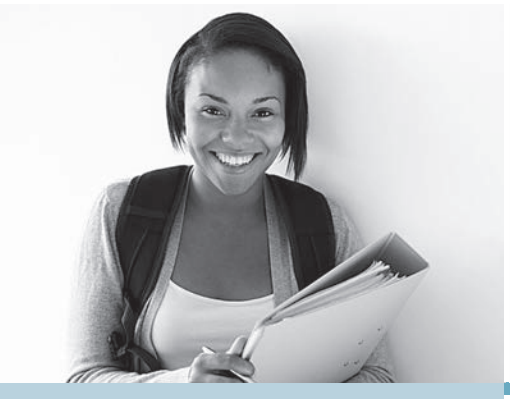

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To those who worked for him, he was a leader whose essence was based in a fierce and boundless loyalty.

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A young boy's nyctalopia and deteriorating vision over the course of a year prompts a referral to the Pediatrics and Genetics Service.

Cindy X. Zheng, MD, Wendy Shieh, MD, Brenton Finklea, MD, and Alex V. Levin, MD, MHSc

Presentation

An 8-year-old Caucasian male was referred to the Wills Eye Pediatric Ophthalmology and Ocular Genetics Service for decreased vision and nyctalopia, which had been progressively worsening over the past year. The patient had been evaluated by a referring optometrist for his subjective decrease in vision approximately one month prior to presentation. Spectral-domain optical coherence tomography at that time was notable for "retinal thinning" in both eyes, and thus he was referred for further evaluation. He did not have any prior ocular history or trauma.

Medical History

The patient was born full-term via an uneventful vaginal delivery following an uncomplicated pregnancy. Although he was physically and developmentally normal, his medical history was notable for a prior episode of a partial complex seizure two years prior to presentation. As part of his neurological workup, a CT scan and MRI of his brain were normal. He had an abnormal electroencephalogram and was started on levetiracetam. Post treatment initiation, repeat EEG was noted to be normal and he did not have any further seizure episodes. No other significant medical history or medication usage was noted. In exploring his family history, multigenerational pedigree did not reveal any pertinent findings or other affected family members.

Examination

Ocular examination revealed a best-corrected visual acuity of 20/30 in each eye. His cycloplegic refraction was +2.25 sphere in the right eye and +2.00 sphere in the left eye.

His pupils were equal, round and reactive without an afferent pupillary defect or paradoxical pupil. His extraocular motility was full and there was no nystagmus. His intraocular pressure by Goldmann applanation tonometry was 10 mmHg in both eyes. Both external examination and slit-lamp examination of the anterior segment were normal. Dilated fundus examination revealed healthy optic nerves, but demonstrated a blunted foveal reflex with a well-circumscribed area of macular pigmentary mottling that resembled a pseudo "bull's-eye" appearance *(See Figure 1)*. Additionally, wrinkling irregularities of the internal limiting membrane were noted in the macula of both eyes. In the mid-peripheral retina, there was pigmentary mottling without spicules or clumping of pigment. The retinal vessels were mildly attenuated bilaterally.

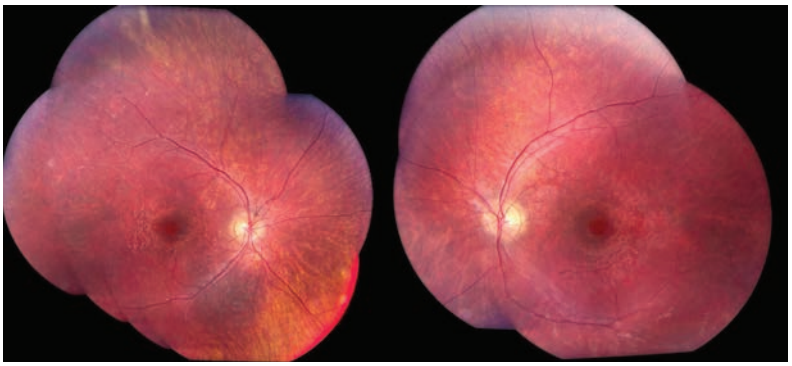

Figure 1. Montage photos of the fundus and mid-peripheral retina depicting blunted foveal reflex, a pseudo "bulls-eye" appearance of the macula, in addition to peripheral pigmentary mottling noted by the examiner.

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

Diagnosis, Workup and Treatment

Given our patient's history and exam, a differential diagnosis was directed toward retinal dystrophies that could cause decreased visual acuity and nyctalopia as well as pigmentary changes in the macula and mid-periphery. Further workup was directed at identifying the nature of his apparent retinal dystrophy. OCT showed an abnormal foveal contour with macular thinning and photoreceptor loss in both eyes *(See Figure 2)*.

Additionally, macular intraretinal cystoid spaces were noted, largely in the left eye. Both eyes showed surface gliosis. Fundus autofluorescence was notable for mottled hypofluorescent changes throughout the macula surrounding a relatively normal fovea *(See Figure 3)*. Electrophysiology testing revealed near isoelectric responses on multifocal and full-field electroretinogram of each eye. Given the aforementioned non-specific ophthalmic findings, genetic testing with a retinal dystrophy panel was performed at the initial visit. Due to the presence of intraretinal cystoid spaces, the patient was started on dorzolamide ophthalmic drops twice daily in both eyes.

At his three-month follow-up visit, fundus examination was unchanged from the previous visit. Repeat OCT showed resolution of cysts *(See Figure 4)*. Despite these findings, best-corrected visual acuity was now 20/40 in each eye and the parents reported a notable decrease in visual function. Genetic testing revealed a well-known homozygous 1.02kb deletion in exon 7 to 8 of the CLN3 gene.

Based on these examination and genetic test findings, a diagnosis of juvenile neuronal ceroid lipofuscinosis was made.

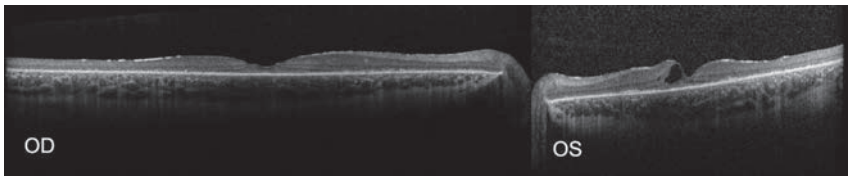

Figure 2. Spectral-domain optical coherence tomography of the right and left eyes showing an abnormal foveal contour with retinal thinning and photoreceptor loss. Large intraretinal cystic spaces were noted, mainly within the left eye.

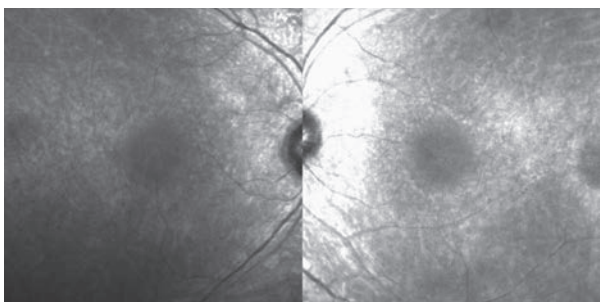
Figure 3. Fundus autofluorescence of the right and left eyes depicting mottled hypofluorescent changes throughout the macula surrounding a relatively normal fovea.

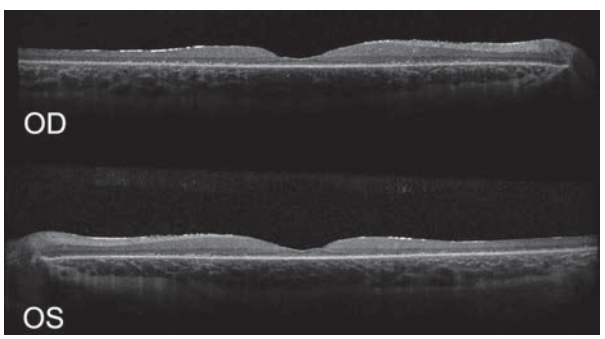

Figure 4. Spectral-domain OCT of the right and left eyes at follow-up visit show resolution of cystoid macular changes, with persistence of retinal thinning and abnormal foveal contour.

Discussion

The neuronal ceroid lipofuscinoses are a group of inherited progressive neurodegenerative disorders, characterized by abnormal accumulation of ceroid and lipofuscin in neurons and other cell types. Otto Christian Stengel first described neuronal ceroid lipofuscinosis in the medical literature as a juvenile-onset disorder with blindness and progressive dementia.[1] A similar clinical entity was later described by Frederick Batten in 1903, and Walter Spielmeyer and Oskar Vogt in 1905.[2-4]

Prior to the discovery of causative genes associated with the disorder, the neuronal ceroid lipofuscinoses were classified based on age at onset (infantile, late infantile, juvenile and adult). More recently, their classification has been based on the mutated genes.[5] The genetic basis for the classic juvenile-onset form is due to mutation in the CLN3 gene, located on chromosome 16.[6] The gene codes for a lysosomal transmembrane protein of unknown function. In 81 to 85 percent of CLN3 disease, patients are homozygous for the 1.02kb deletion seen in our patient.[6,7] Point mutations and insertions have also been found to be causative.[7]

JNCL has an estimated incidence of one in 25,000 births.[8] The incidence is higher in northern European populations.[8] The average age of onset is 4 to 7 years old. CLN3 disease is characterized by rapid visual decline secondary to retinal degeneration associated with progressive cognitive decline, seizures,

motor dysfunction and, ultimately, death.[9]

Patients with CLN3 have intracellular deposition of lipopigment, resulting in loss of cells in the RPE, photoreceptor, outer nuclear and outer plexiform layers. Previous electron microscopy studies have shown that ocular damage starts with the photoreceptors and outer retina.[10] Degeneration tends to progress from the macula to the periphery.[10] On clinical examination, there are variable fundus findings associated with degeneration of the retina and optic nerve. Macular abnormalities include loss of foveal reflex, "bull's-eye" maculopathy and macular orange pigment deposition.[11,12] Mid-peripheral retinal pigmentary changes range from "bone spicule" pigmentary clumping to mild focal deposits.[13] Secondary optic nerve atrophy and vascular attenuation are also common findings.[13] A recent study found that patients diagnosed with JNCL may have macular striations.[13] These striations may represent pathological degeneration or secondary inflammatory process within the internal limiting membrane and nerve fiber layer,[13] and can be seen in many juvenile retinal dystrophies.

The initial diagnosis may be challenging due to non-specific retinal findings. Patients may be misdiagnosed as having Stargardt's disease, retinitis pigmentosa or rod-cone dystrophy.[11,12] Perhaps the most important clues to the diagnosis are rapid visual deterioration in a child accompanied by neurologic signs. Of note, the retinal dystrophy may be present before the onset of neurologic decline. In patients suspected of having a neuronal lipofuscinosis, genetic testing can be performed. Testing the five common mutations in CLN1, CLN2 and CLN3 may identify more than 70 percent of pediatric cases.[14]

There is currently no cure for the neuronal lipofuscinosis, although multiple treatments are being investigated.[15,16] Previous studies have found autoantibodies present in cln3 -/- mice, suggesting an autoimmune component to the pathogenesis of the disease.[17] There is a Phase II clinical trial under way evaluating the efficacy of mycophenolate mofetil in decreasing circulating autoantibodies. At the present time, management is mainly centered on potential enrollment in clinical trials as well as support and counseling for the patient and family.

JNCL is an autosomal recessive neurodegenerative disease presenting in childhood, characterized by relatively rapid vision loss and neurologic decline. The disease should be considered in any child less than 10 years old presenting with relatively rapid vision loss and signs of a retinal dystrophy. REVIEW

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(continued from page 35)

The next thing I expect the field to deliver is proof of efficacy, in Phase II or III studies that are well-designed, that will convince everyone that there is merit to this kind of approach.

"If you think about it, in medicine we've had success with solid organ transplantation and bone marrow transplants for a long time," he continues. "Today we can do partial face and hand transplants. So far, we haven't been able to do that with the eye, brain or spinal cord. But with neural stem cells, we have the ability to go down that path. We know that the concept of transplantation works; it's just a question of how we can dial it in for the retina and the eye."

Dr. Temple says she's been thinking a lot about the state of stem cell research in general because she'll become president of the International Society for Stem Cell Research starting in June of this year. "There's a lot of exciting research taking place," she notes. "Understanding the process of human development and the production of retina, brain and other tissues is really important. Stem cells are giving us the opportunity to learn things that have been out of our reach until now. In the past we've been able to study the development of tissues in rats and mice, but we now know that more than 60 percent of gene expression in mice is different from humans. That means we need to have human RPE cells in the dish so that we can truly understand human-related mechanisms.

"Creating disease-in-a-dish models is burgeoning right now," she continues. "For example, microcephaly has been in the news a lot because of the Zika virus, but it can occur through a number of different genetic perturbations. Now researchers are using little 3-D organites created in a dish from stem cells to study processes like microcephaly formation. Also, there's

a big push to screen small molecules to see if they can revert disease phenotypes and prevent the development of disease. I predict that's going to become an even bigger focus of research as we get better disease models and streamline the process of integrating these methods with high-throughput screening."

Dr. Temple notes that transplantation-based treatments are still the focus of a significant amount of stem cell research. "We've seen success with limbal cell transplants for many years now," she points out. "There are many groups around the world working on RPE transplantations for macular degeneration, in Israel and Japan and the U.K. and here in the United States. If we can get this type of procedure working and approved, it will provide a revolutionary new treatment for macular degeneration. Meanwhile, the disease-in-a-dish model may allow us to create therapies for earlier-stage disease that won't require a cell transplant and immunosuppression. We'll be able to just use small molecules and prevent the RPE from degenerating."

Other areas of stem cell research not directly involving the eye will also likely have a positive impact on ocular diseases. "Researchers at a company called ViaCyte who are working to manage diabetes have developed a device that incorporates pancreatic islet cells—the ones that normally make insulin—generated from pluripotent stem cells," says Dr. Temple. "In this device the cells are shielded from the immune system, but they'll be able to respond to the levels of glucose in the bloodstream and produce insulin accordingly. It's going to be much more responsive than the typical insulin injection regimen. This could go a long way toward helping people who might otherwise suffer from diabetic retinopathy, and the device is already in clinical trials."

Dr. Temple says she hopes that within five years her team's transplant procedure will be in clinical trials, and their methods for activating the RPE stem cells that already exist inside the eye will be moving toward a clinical trial as well. "It's a very exciting time to be part of this field," she says. "I can see a future in which regenerative medicine is one of the services doctors offer their patients, and I can see doctors specializing in this type of stem-cell-based therapy. In the meantime, I think what stem cells can tell us about human cells and health and disease is enormously promising." REVIEW

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