REVIEW® of Ophthalmology

September 2015

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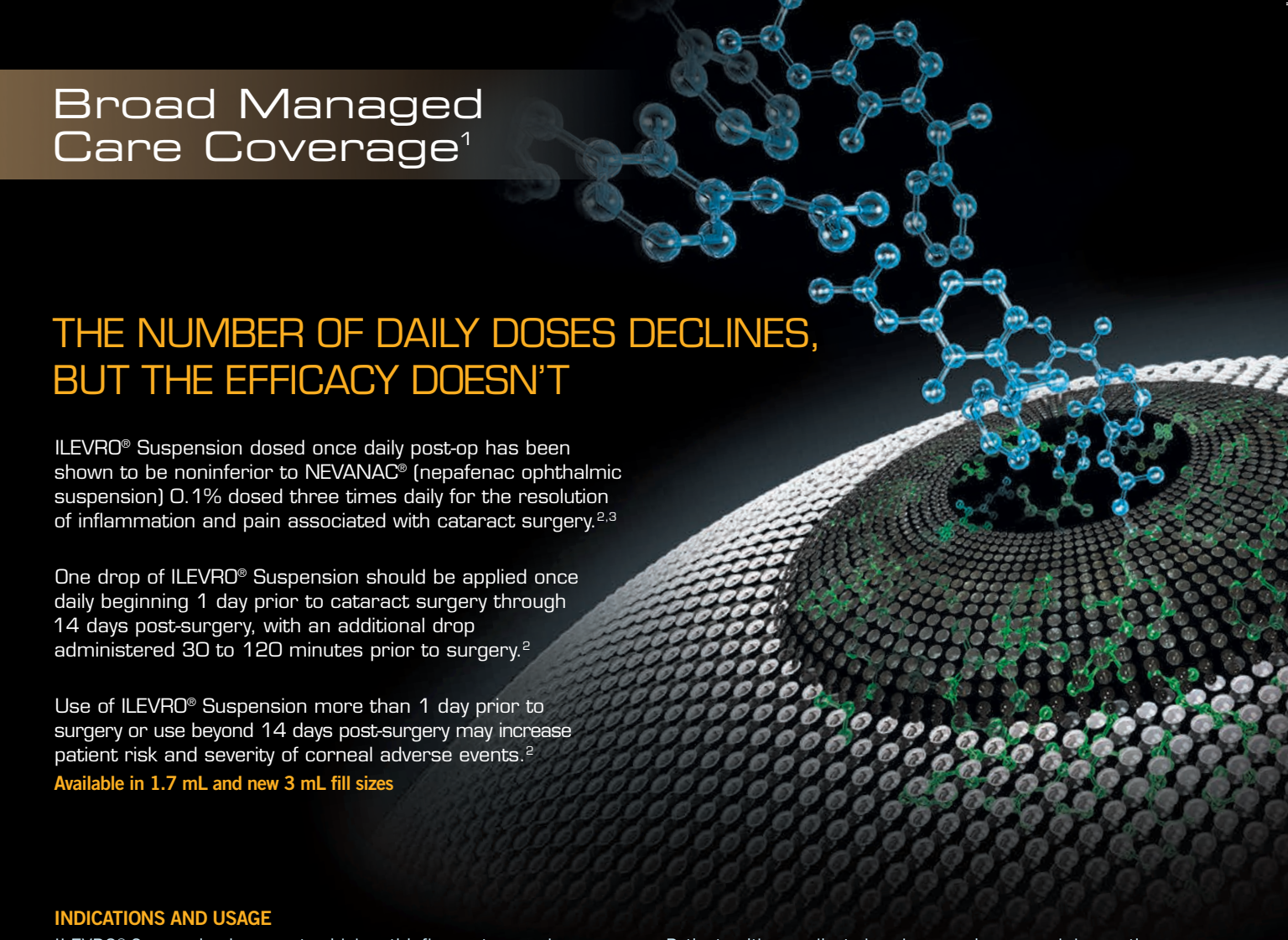
Broad Managed Care Coverage[1]



THE NUMBER OF DAILY DOSES DECLINES, BUT THE EFFICACY DOESN'T

ILEVRO® Suspension dosed once daily post-op has been shown to be noninferior to NEVANAC® (nepafenac ophthalmic suspension) 0.1% dosed three times daily for the resolution of inflammation and pain associated with cataract surgery.[2,3]

One drop of ILEVRO® Suspension should be applied once daily beginning 1 day prior to cataract surgery through 14 days post-surgery, with an additional drop administered 30 to 120 minutes prior to surgery.[2]

Use of ILEVRO® Suspension more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.[2]

Available in 1.7 mL and new 3 mL fill sizes

INDICATIONS AND USAGE

ILEVRO® Suspension is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

IMPORTANT SAFETY INFORMATION

Contraindications

ILEVRO® Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

Warnings and Precautions

- Increased Bleeding Time – With some nonsteroidal anti-inflammatory drugs including ILEVRO® Suspension there exists the potential for increased bleeding time. Ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphema) in conjunction with ocular surgery.
- Delayed Healing – Topical nonsteroidal anti-inflammatory drugs (NSAIDs) including ILEVRO® Suspension may slow or delay healing. Concomitant use of topical NSAIDs and topical steroids may increase the potential for healing problems.
- Corneal Effects – Use of topical NSAIDs may result in keratitis. In some patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use.

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

  Use more than 1 day prior to surgery or use beyond 14 days post-surgery may increase patient risk and severity of corneal adverse events.
- Contact Lens Wear – ILEVRO® Suspension should not be administered while using contact lenses.

Adverse Reactions

The most frequently reported ocular adverse reactions following cataract surgery occurring in approximately 5 to 10% of patients were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation.

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

References: 1. Formulary data provided by Pinsonault Associates, LLC, PathfinderRx, June 2014. **2.** ILEVRO® Suspension prescribing information. **3.** NEVANAC® Suspension prescribing information.

For more resources for eye care professionals, visit MYALCON.COM/ILEVRO

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
ILEVRO® Suspension is indicated for the treatment of pain and inflammation associated with cataract surgery.

DOSAGE AND ADMINISTRATION
Recommended Dosing
One drop of ILEVRO® Suspension should be applied to the affected eye one-time-daily beginning 1 day prior to cataract surgery, continued on the day of surgery and through the first 2 weeks of the postoperative period. An additional drop should be administered 30 to 120 minutes prior to surgery.

Use with Other Topical Ophthalmic Medications
ILEVRO® Suspension may be administered in conjunction with other topical ophthalmic medications such as beta-blockers, carbonic anhydrase inhibitors, alpha-agonists, cycloplegics, and mydriatics. If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

CONTRAINDICATIONS
ILEVRO® Suspension is contraindicated in patients with previously demonstrated hypersensitivity to any of the ingredients in the formula or to other NSAIDs.

WARNINGS AND PRECAUTIONS
Increased Bleeding Time
With some nonsteroidal anti-inflammatory drugs including ILEVRO® Suspension, there exists the potential for increased bleeding time due to interference with thrombocyte aggregation. There have been reports that ocularly applied nonsteroidal anti-inflammatory drugs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with ocular surgery. It is recommended that ILEVRO® Suspension be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.

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

Corneal Effects
Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. These events may be sight threatening. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs including ILEVRO® Suspension and should be closely monitored for corneal health. Postmarketing experience with topical NSAIDs suggests that patients with complicated ocular surgeries, corneal denervation, corneal epithelial defects, diabetes mellitus, ocular surface diseases (e.g., dry eye syndrome), rheumatoid arthritis, or repeat ocular surgeries within a short period of time may be at increased risk for corneal adverse events which may become sight threatening. Topical NSAIDs should be used with caution in these patients.

Postmarketing experience with topical NSAIDs also suggests that use more than 1 day prior to surgery or use beyond 14 days post surgery may increase patient risk and severity of corneal adverse events.

Contact Lens Wear
ILEVRO® Suspension should not be administered while using contact lenses.

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

Ocular Adverse Reactions
The most frequently reported ocular adverse reactions following cataract surgery were capsular opacity, decreased visual acuity, foreign body sensation, increased intraocular pressure, and sticky sensation. These events occurred in approximately 5 to 10% of patients.

Other ocular adverse reactions occurring at an incidence of approximately 1 to 5% included conjunctival edema, corneal edema, dry eye, lid margin crusting, ocular discomfort, ocular hyperemia, ocular pain, ocular pruritus, photophobia, tearing and vitreous detachment.

Some of these events may be the consequence of the cataract surgical procedure.

Non-Ocular Adverse Reactions
Non-ocular adverse reactions reported at an incidence of 1 to 4% included headache, hypertension, nausea/vomiting, and sinusitis.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects.
Pregnancy Category C: Reproduction studies performed with nepafenac in rabbits and rats at oral doses up to 10 mg/kg/day have revealed no evidence of teratogenicity due to nepafenac, despite the induction of maternal toxicity. At this dose, the animal plasma exposure to nepafenac and amfenac was approximately 70 and 630 times human plasma exposure at the recommended human topical ophthalmic dose for rats and 20 and 180 times human plasma exposure for rabbits, respectively. In rats, maternally toxic doses ≥10 mg/kg were associated with dystocia, increased postimplantation loss, reduced fetal weights and growth, and reduced fetal survival.

Nepafenac has been shown to cross the placental barrier in rats. There are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, ILEVRO® Suspension should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Non-teratogenic Effects.
Because of the known effects of prostaglandin biosynthesis inhibiting drugs on the fetal cardiovascular system (closure of the ductus arteriosus), the use of ILEVRO® Suspension during late pregnancy should be avoided.

Nursing Mothers
ILEVRO® Suspension is excreted in the milk of lactating rats. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when ILEVRO® Suspension is administered to a nursing woman.

Pediatric Use
The safety and effectiveness of ILEVRO® Suspension in pediatric patients below the age of 10 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Nepafenac has not been evaluated in long-term carcinogenicity studies. Increased chromosomal aberrations were observed in Chinese hamster ovary cells exposed *in vitro* to nepafenac suspension. Nepafenac was not mutagenic in the Ames assay or in the mouse lymphoma forward mutation assay. Oral doses up to 5,000 mg/kg did not result in an increase in the formation of micronucleated polychromatic erythrocytes *in vivo* in the mouse micronucleus assay in the bone marrow of mice. Nepafenac did not impair fertility when administered orally to male and female rats at 3 mg/kg.

PATIENT COUNSELING INFORMATION
Slow or Delayed Healing
Patients should be informed of the possibility that slow or delayed healing may occur while using nonsteroidal anti-inflammatory drugs (NSAIDs).

Avoiding Contamination of the Product
Patients should be instructed to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to 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.

Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

Contact Lens Wear
ILEVRO® Suspension should not be administered while wearing contact lenses.

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

Concomitant Topical Ocular Therapy
If more than one topical ophthalmic medication is being used, the medicines must be administered at least 5 minutes apart.

Shake Well Before Use
Patients should be instructed to shake well before each use. U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767.

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REVIEW NEWS
Volume XXII • No. 9 • September 2015

Data Shows Avastin No Greater Infection Risk Than Lucentis

Eye injections of the drug Avastin (bevacizumab) bring no greater risk of endophthalmitis than injections with the much more expensive drug Lucentis (ranibizumab) made by the same company, according to new research from the Perelman School of Medicine at the University of Pennsylvania. The findings were published in *JAMA Ophthalmology*.

The study, based on insurance claims data from across the United States, was conducted in response to reports of Avastin-related endophthalmitis, which led the Food and Drug Administration recently to propose significant restrictions on use of the drug for eye conditions.

"Our analysis of a national dataset shows that the risk for endophthalmitis is no higher with Avastin and hints that there may actually be a lower endophthalmitis risk compared to Lucentis, so the proposed FDA restrictions for Avastin might have the unintended consequence of increasing the infection risk for patients," said senior author Brian L. VanderBeek, MD, MPH, an assistant professor of ophthalmology at Penn.

Dr. VanderBeek and his colleagues' findings come after years of tension between eye doctors and Avastin's maker Genentech over the drug's ophthalmic use.

Avastin is an injectable solution of monoclonal antibodies targeted at the blood vessel growth factor VEGF. It was the first drug designed to inhibit angiogenesis, and was approved by the FDA in 2004 for treating colorectal cancers—which typically boost angiogenesis to keep themselves well supplied with oxygen and nutrients.

Common age- and diabetes-related retinal diseases, such as wet macular degeneration, also result in part from VEGF-driven processes, so ophthalmologists soon began to use Avastin off-label to treat these conditions. Avastin as distributed for cancer treatment is frequently repackaged by compounding pharmacies into smaller doses suitable for use in the eyes, which drives the cost of the medication down to about $50 per eye injection.

Genentech has also developed a similar eye-specific angiogenesis-inhibiting, anti-VEGF monoclonal antibody, Lucentis. It was FDA-approved in 2006 and costs as much as $2,000 per dose, even though it is closely related to the Avastin antibody and multiple clinical trials have found that the two drugs have virtually the same efficacy.

To promote the use of the more expensive Lucentis, Genentech announced in 2007 that it would block Avastin's ophthalmic use by prohibiting its sale to compounding pharmacies, but the company backed away from this plan after strong protests from eye doctors.

Then in 2012, a few reports in the media noted endophthalmitis outbreaks following repackaged Avastin injections. The endophthalmitis outbreaks were limited to specific compounding pharmacies. Amid a general concern over potential substandard practices at compounding pharmacies nationally, the FDA announced in February of this year that it planned to restrict the ophthalmic use of Avastin to the five-day period following the repackaging of the drug by a compound pharmacy.

"This would effectively prevent most ophthalmic use of Avastin," Dr. VanderBeek said. "Compounding pharmacies require 14 days after repackaging just for sterility testing, and without this critical step, ophthalmologists will lack confidence in the safety

AstraZeneca Cancer Drug Fails Uveal Melanoma Phase III Trial

AstraZeneca's cancer treatment selumetinib failed to significantly prolong survival in a study on melanoma that has spread to the eye, a late-stage setback for a drug once considered a bright spot in the company's oncology pipeline.

In a 152-patient Phase III trial, a combination of selumetinib and the common chemotherapy dacarbazine failed to improve progression-free survival compared with the old drug alone, the company said. Uveal melanoma affects about 2,000 Americans each year.

Selumetinib's failure comes on the heels of some promising mid-stage data in which the treatment more than doubled progression-free survival in uveal melanoma patients, jumping from seven weeks in the chemotherapy arm of the study to 15.9 weeks in the drug arm. Those results, presented at 2013's American Society of Clinical Oncology meeting, raised hopes that AstraZeneca was on track to win the first-ever approval for uveal melanoma, which has no effective therapies.

The drug continues to be studied for lung and thyroid cancer, and neurofibromatosis.

of the repackaged Avastin and unlikely to use it."

To get a better picture of Avastin's true endophthalmitis risk, Dr. VanderBeek and his colleagues looked at the medical claims database for a large American insurance company, covering the years 2005 through 2012. The data they reviewed contained no information identifying patients.

Analyzing the 296,565 injections of Avastin and 87,245 injections of Lucentis that met their inclusion criteria, the Penn researchers found 49 and 22 cases, respectively, of endophthalmitis. Thus the rate of the complication in this dataset was very low, 0.017 percent for Avastin, and still low but slightly higher, 0.025 percent, for Lucentis.

The 35-percent lower rate of endophthalmitis seen in Avastin wasn't statistically significant, but the authors say the data at least suggest strongly that on a nationwide basis, Avastin repackaged by compounding pharmacies doesn't involve greater endophthalmitis risk than Lucentis packaged by its manufacturer.

The American Academy of Ophthalmology has been lobbying against the proposed new FDA regulations. "The findings from our study support their stance," Dr. VanderBeek said. Co-authors of the study were Sarah G. Bonaffini and Liyuan Ma, both of Penn Medicine at the time of the research.

New Clues to AMD Vision Loss

Scientists have identified a pathway that leads to the formation of atypical blood vessels that can cause blindness in people with age-related macular degeneration.

The research, at Washington University School of Medicine in St. Louis, sheds light on one of the leading causes of blindness in industrialized countries and offers potential targets for treating the disease.

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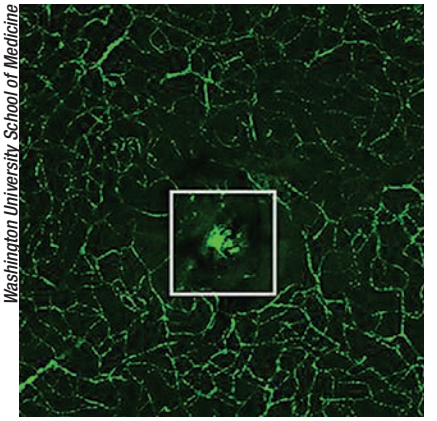


Washington University School of Medicine

In this image of the retina, normal blood vessels (green) surround a clump of new, abnormal vessels that has formed beneath the center of the retina. Scientists at Washington University School of Medicine have identified a molecular pathway that leads to the formation of such blood vessels.

The study was published online Aug. 11 in the journal *Nature Communications*.

"Our research increases our understanding of how specific immune cells can contribute to vision loss in macular degeneration, and it also may help us identify treatments by giving us a molecular pathway to target," said principal investigator and retina specialist Rajendra S. Apte, MD, PhD. "When we inhibit this pathway, we can alter the immune cells and interfere with abnormal blood vessel growth in mice. Doing so might open therapeutic avenues to halt vision loss or even restore sight in people who have macular degeneration, the leading cause of blindness in people over 50."

Dr. Apte, the Paul Cibis distinguished professor of ophthalmology and visual sciences at the School of Medicine, has spent years studying the immune system in the eye to distinguish changes related to aging from those related to disease. In earlier work, he found that a cell-signaling molecule called interleukin-10 plays a role in the formation of blood vessels involved in the wet form of macular degeneration.

Before vision loss occurs, IL10 levels increase in the eye, as do the number of specific immune cells, M2 macrophages. These macrophages are known to contribute to the development of damaging blood vessel growth beneath the retina.

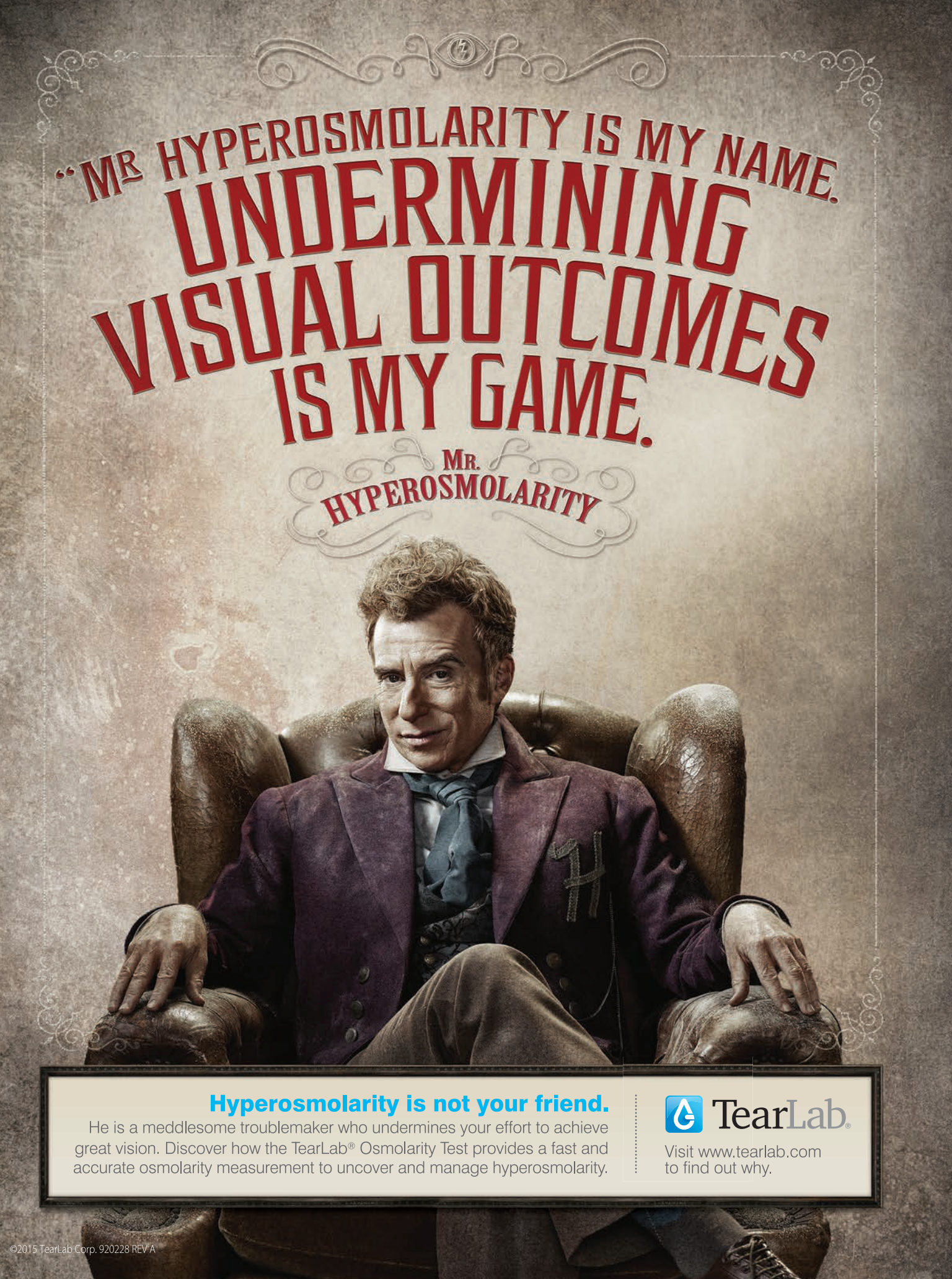
Until now, though, how IL10 actually contributed to the proliferation of macrophages and damaging blood vessels wasn't well understood. So Dr. Apte and his colleagues engineered mice in which various cell-signaling pathways were disabled. Those experiments led them to discover that a specific signaling pathway involving a protein called STAT3 was activating and altering immune cells in the eye, and those cells then spurred the formation of harmful blood vessels.

Further, they examined eye tissue from patients treated in the 1980s and 1990s, when surgery to remove abnormal blood vessels from underneath the retina was routinely performed on patients with the wet form of macular degeneration. There, too, the same STAT3 protein that was abundant and active in M2 macrophages in mice also was found in high levels in the human tissue.

The findings suggest that the causes of damaging blood vessel growth in people are the same as what the researchers had observed in mouse models, Dr. Apte said. In both mice and in patients, abnormal blood vessel growth was linked to macrophages with high levels of the active form of STAT3.

That a cause of significant vision loss appears to be the same in mice and people is good news, Dr. Apte said, because some compounds can disrupt the actions of STAT3 in mice and keep the pathway from spurring blood vessel growth. Those same compounds may alter the course of macular degeneration in people with the condition.

"Now that we have a better idea of how these macrophages are activated at the molecular level, we may be able to use those drugs to halt or reverse the disease process," Dr. Apte said. REVIEW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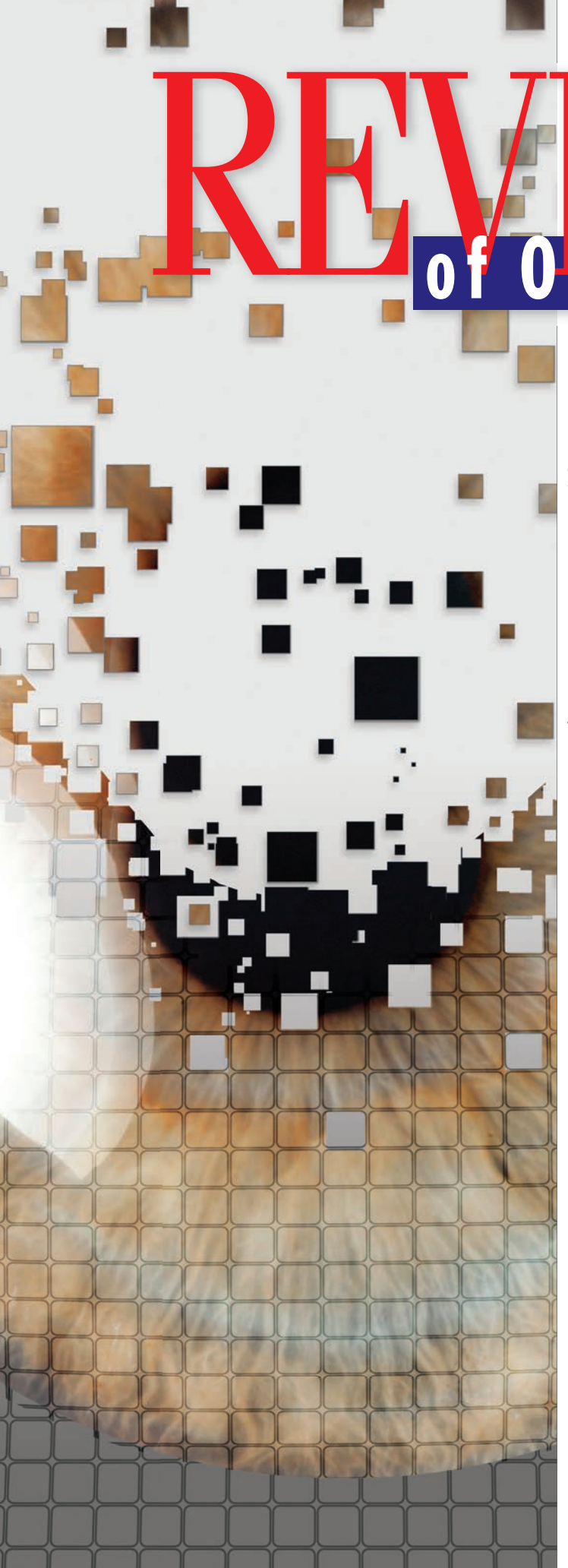

REVIEW® of Ophthalmology

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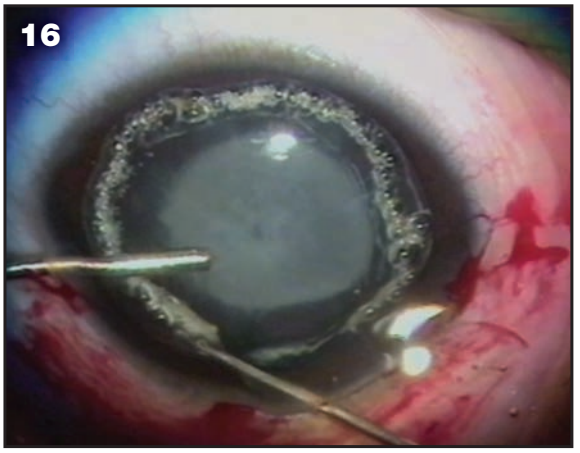
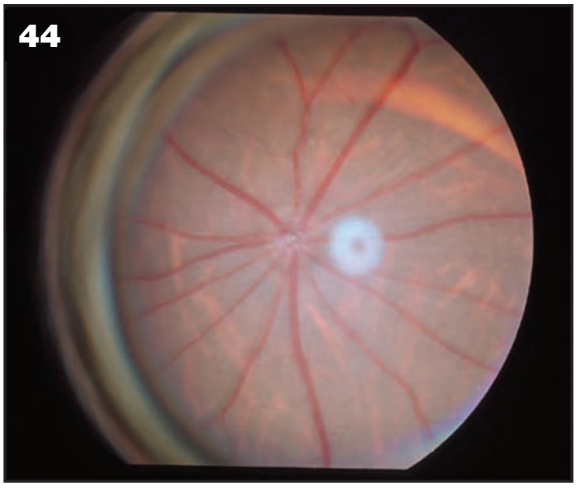
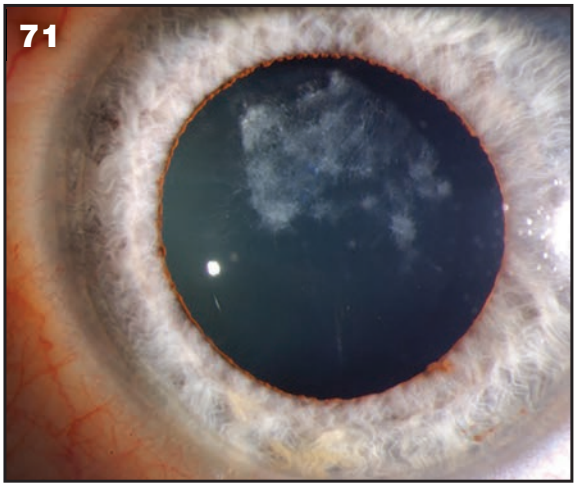
Cover Focus

Departments







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BACITRACIN OPHTHALMIC OINTMENT USP

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

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

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

Important Safety Information

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

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

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

www.perrigobacitracin.com

Please see adjacent page for full prescribing information.

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

Perrigo® Specialty Pharmaceuticals

Bacitracin Ophthalmic Ointment USP

STERILE **Rx Only**

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

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

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

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

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

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

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

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

HOW SUPPLIED:

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

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

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Plasma Technology in Ophthalmology

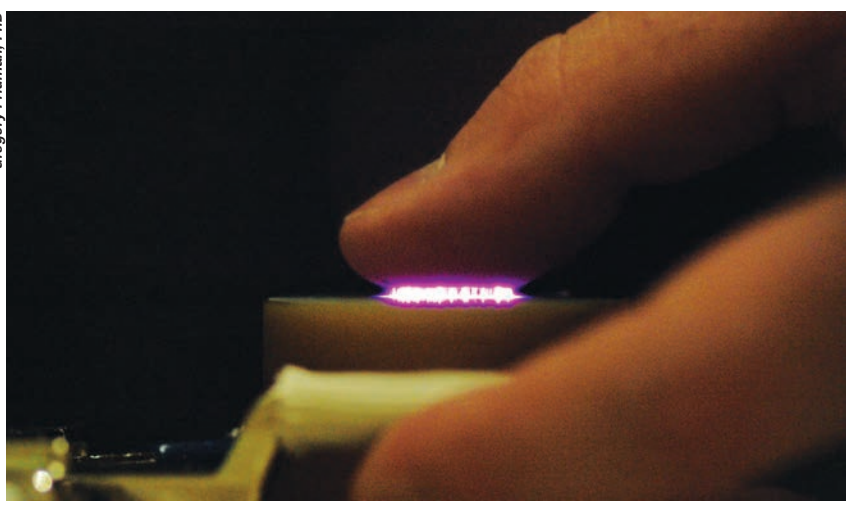
lonized gases are showing promise in medicine as a means of sterilizing tissue, incising tissue and potentially killling tumors.

Christopher Kent, Senior Editor

As medicine advances, it sometimes moves incrementally; other times it makes a leap forward, thanks to new technologies and ideas. The unique characteristics of plasma (considered the fourth state of matter—after solid, liquid and gas) have helped to open up new frontiers in many areas of modern living. Recently those unique characteristics have been leading to the development of new ophthalmic tools.

Plasma is a term used to describe certain types of ionized gases. It comes in many different forms, some of which make modern technologies like cellular telephones and plasma televisions possible. It can be generated in ways that produce heat (e.g., the YAG laser, welding arcs, lightning in a thunderstorm or the sun) and in ways that do not (e.g., plasma television, fluorescent bulbs and the aurora borealis). Medical devices may be designed to produce either thermal or non-thermal plasma, depending on the purpose of the device. When plasma comes into contact with tissue, depending on the nature of the plasma being generated, it can act as a blade, disintegrating tissue in its path; it can kill bacteria without causing structural tissue damage; or it can trigger apoptosis in cancer cells without harming healthy cells.

Here, three individuals working with these types of plasma applications discuss their work.



Gregory Fridman, PhD

The ionized gases known as plasma can be extremely hot or room temperature, and can be used in numerous ways, including triggering apoptosis in cancer cells, sterilizing living tissue without structural damage and as a means of resistance-free incising of tissue.

Attacking Tumors

Michael Keidar, professor of mechanical and aerospace engineering at the School of Engineering and Applied Science, professor of neurological surgery at the School of Medicine and Health Sciences, and director of the GW Institute for Nanotechnology at The George Washington University, has done extensive work over the past several years in the area of using plasma to cause selective destruction of cancer tumors. "I got interested in the biomedical application of plasma about seven years ago," he explains.

An NSAID formulated to penetrate target ocular tissues

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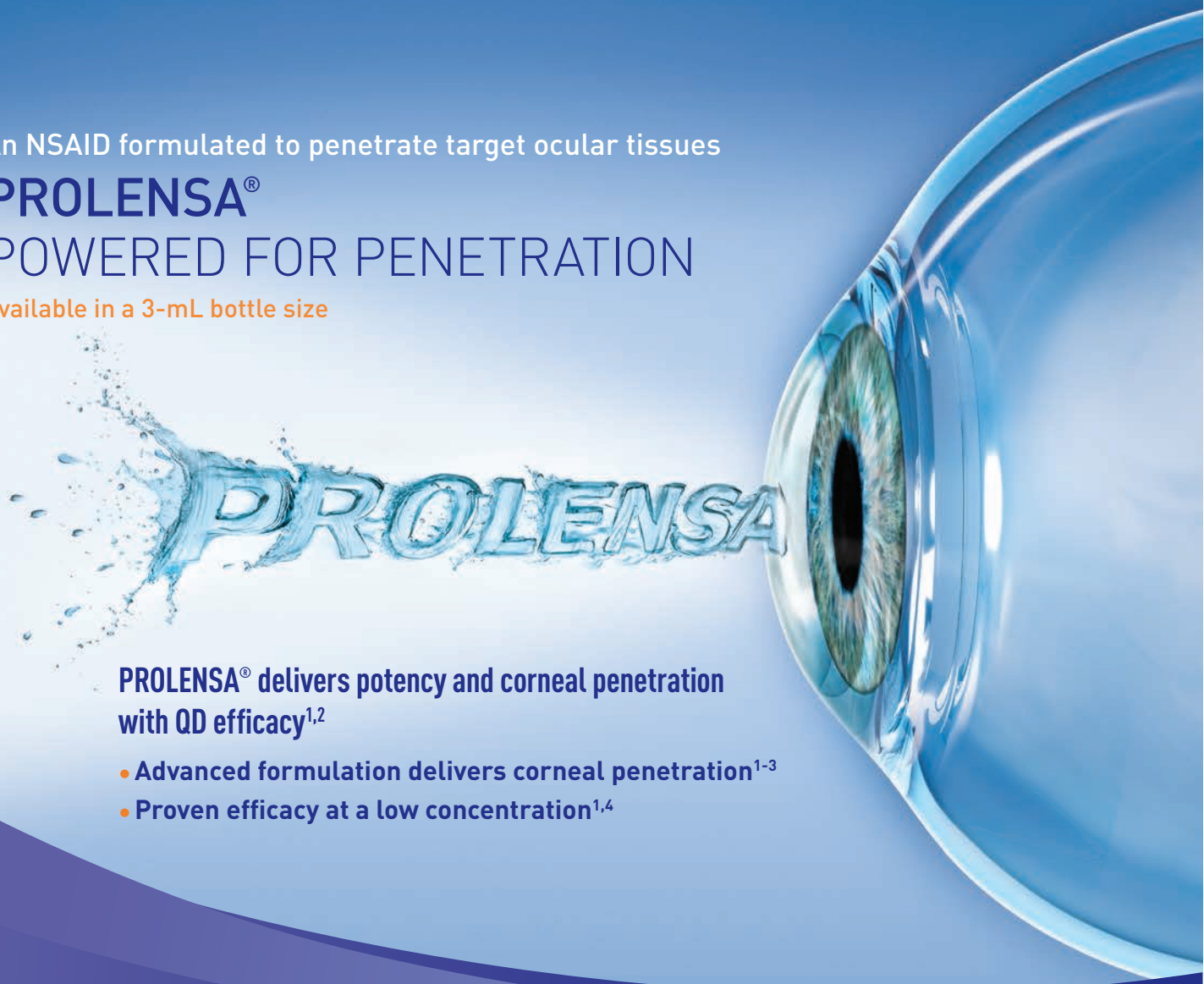

PROLENSA® delivers potency and corneal penetration with QD efficacy[1,2]

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

INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION ABOUT PROLENSA®

Warnings and Precautions

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

Adverse Reactions

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

Please see brief summary of Prescribing Information on adjacent page.

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

BAUSCH + LOMB

PROLENSA®
(bromfenac ophthalmic solution) 0.07%

BAUSCH + LOMB

PROLENSA® (bromfenac ophthalmic solution) 0.07%

Brief Summary

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

Use with Other Topical Ophthalmic Medications

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

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

Slow or Delayed Healing

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

Potential for Cross-Sensitivity

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

Increased Bleeding Time

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

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

Keratitis and Corneal Reactions

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

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

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

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

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

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

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

Sterility of Dropper Tip

Advise patients to replace bottle cap after using and to not touch dropper tip to any surface, as this may contaminate the contents.

Advise patients that a single bottle of PROLENSA® ophthalmic solution, be used to treat only one eye.

Concomitant Use of Contact Lenses

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

Concomitant Topical Ocular Therapy

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

Rx Only

Manufactured by: Bausch & Lomb Incorporated, Tampa, FL 33637
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9317600
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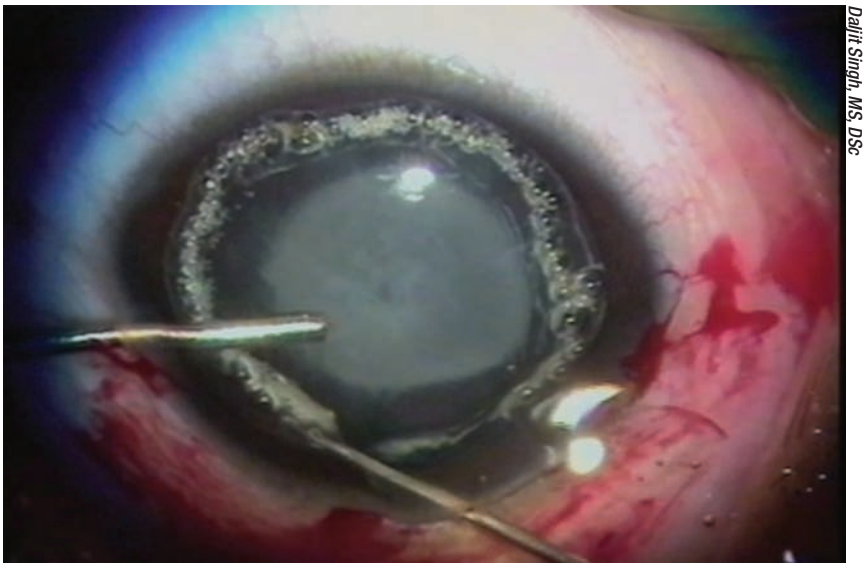
"Plasma is an ionized gas that is typically generated in high-temperature laboratory conditions. Recent progress in atmospheric plasmas, however, has led to the creation of cold atmospheric plasmas, or CAP, with ions at close to room temperature. Today, 20 years of intense research effort applying CAP to bioengineering has led to the foundation of a new field: plasma medicine. And the most recent research area in the field of plasma medicine is the application of CAP to cancer therapy."

Recent studies have shown that CAP has the ability to induce cell death via apoptosis and cell cycle arrest, both *in vitro* and *in vivo*. While malignant tumors can become resistant to chemotherapy, they appear to have a specific vulnerability to treatments involving the production of reactive oxygen and nitrogen species. *In vivo*, CAP has been shown to inhibit tumor growth, decrease proliferation, reduce tumor size and induce apoptosis. Furthermore, it's been shown to affect at least 20 different varieties of cancer (including breast, colon, lung, bladder, ovarian, skin, pancreatic and prostate).[1-14]

Perhaps most important, unlike conventional cancer therapies, CAP seems to selectively kill cancer cells. "Based on many results to date, CAP could potentially be used to treat retinoblastoma," he notes. "Plasma can be applied directly to a tumor with a penetration of about 5 mm, and no thermal damage is associated with its use."

Professor Keidar says they're still working on understanding the mechanism by which plasma affects cancer cells. "CAP produces various chemically reactive species such as reactive oxygen and nitrogen species, as well as generating an electric field and UV radiation," he explains. "We know that these reactive species have biological effects on prokaryotic and eukaryotic cells and can trigger signaling pathways in cells. It's also been shown that CAP leads to modification of cell migration, and that can help to mitigate scar formation." He adds that because plasma is a "cocktail" of various species that can be relatively easily controlled, it can be used in other applications as well, including treating HIV and in the field of dermatology.



Daljit Singh, MS, DSc

A capsulotomy being done in a pediatric case using the Fugo plasma blade, which cuts without resistance. The chamber is kept deep by injecting viscoelastic from the side port. The incision is seen as a line of cavitation bubbles.

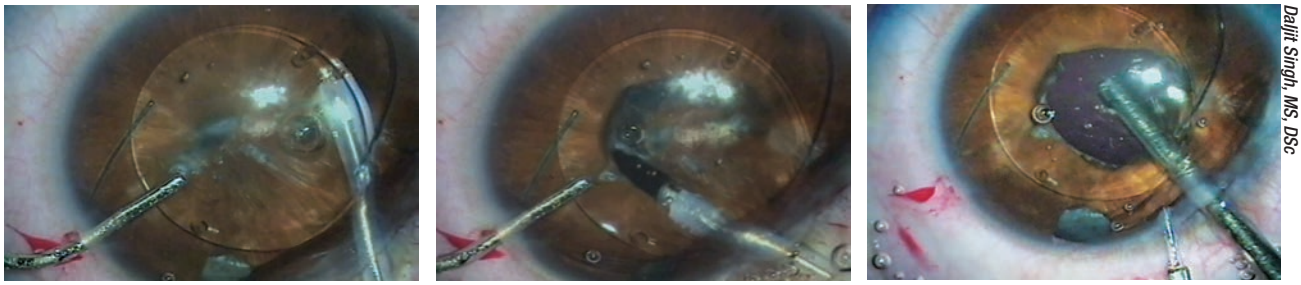
Professor Keidar says that handheld CAP tools are already available, and his group is developing new ones. However, he believes the ones they're developing are several years away from being clinically available.

Cutting Without Resistance

Although some uses for plasma technology are still in the investigative stages, at least one plasma tool has been available for several years: the Fugo blade, a handheld surgical instrument invented by Richard Fugo, MD, PhD, (Norristown, Pa.) that allows sharp, resistance-free cutting. The blade works by generating a cloud of plasma particles around a tiny filament at the end of a handpiece; the plasma dissolves the molecular bonds of any material it comes into contact with. As a result, the blade creates an incision sharper than an incision made with a diamond blade, and it can cut through thick, tough tissue easily. It also causes almost no bleeding if small vessels and capillaries are cut. Because of these characteristics, surgeons can perform operations that would be nearly impossible with a standard blade, causing little, if any, trauma to the eye.

Daljit Singh, MS, DSc, is the founder of the Daljit Singh Eye Hospital in Amritsar, India, and coauthor of the book *Ocular Applications of the Fugo Blade*. Dr. Singh (who has no financial interest in the Fugo blade) has used it for more than 15 years, pioneering numerous procedures that take advantage of the unique abilities of the instrument, including anterior capsulotomy, transciliary filtration and peripheral iridotomy (all approved by the U.S. Food and Drug Administration).

"The Fugo blade brings laser-like plasma to the fingertips of the surgeon," explains Dr. Singh. "The plasma is created by focused electromagnetic waves generated by four rechargeable batteries; when in use,



Daljit Singh, MS, DSc

A pupilloplasty performed using the Fugo plasma blade. Left: The pupil has been closed by scar formation; the plasma blade is moved into position. Center: The pupiloplasty is half completed. Right: The debris has been removed by a vitrector.

the plasma is visible as a throbbing yellow glow of light. When an activated tip touches tissue, the energy is transferred via the process of resonance. The tissue molecules become unstable and shatter, thus creating an incision path without burning or charring, and histology has confirmed the absence of collateral thermal damage. In fact, the Fugo blade incision is actually an ablation. The plasma also ablates any blood vessels in the incision path, resulting in a bloodless cut."

Dr. Singh says the plasma blade is especially useful for creating an anterior capsulotomy. "It's the best tool for creating a capsulotomy that I've found," he says. "It successfully tackles any kind of capsule, at any age. Whether the capsule is normal, thick and scarred, or of unequal thickness, it cuts easily and the cut never runs out to the periphery. It's quite different from older approaches because the surgeon perceives no tactile sensation; the cutting is resistance-free."

Dr. Singh uses the blade for many other types of ocular surgery as well, and finds it especially suited to pupilloplasty and membranectomy. "The fact that it creates tracks in a bloodless manner and without collateral thermal damage has allowed me to develop procedures like transciliary filtration—into the posterior chamber—and microtrack filtration—into the anterior chamber," he notes. "These are the least-traumatic filtration procedures I've ever used, and they were not possible without this device. It also makes it easy to manage previous filtration surgery that has failed, as well as Tenon cysts. In cases of congenital trichiasis it only takes seconds to permanently destroy whole rows of cilia roots. In cases of meibomian gland dysfunction, all the gland openings and ducts can be efficiently cleared in little time."

Dr. Singh says he has also used the plasma blade to develop strabismus surgery techniques, for both weakening and strengthening, that maintain the insertion line by preserving the muscle strips at the margins. "This prevents the surgery from causing any misalignment," he explains. "These strabismus techniques are bloodless and only take a short time to perform, and the postoperative course is inflammation-free, thanks to the peculiar cutting properties of the plasma blade. I've also been able to develop unique fornix and orbital approaches to levator and Müller muscle plication, for all grades of ptosis. I do this through three vertical fornix incisions made with the plasma blade. And because it ablates tissue, it takes only seconds to do punctoplasty or to clear blocked canaliculi." Dr. Singh says that during the past 10 years, the retina surgeon at his eye hospital has successfully operated on three cases of Sturge-Weber syndrome caused by vascular tumors on the retina, using the Fugo blade. "All of these cases were refused by the best retina centers in India," he notes.

"This is an very versatile surgical tool," he concludes. "I believe many more eye surgeons around the world will eventually be using it."

Plasma Disinfection

Another medical use for plasma is the sterilization of tissue, which can be done without causing structural damage using the right parameters. One surgeon working on making this a practical reality is David S. C. Pao, MD, who practices in Levittown, Pa. Early in his career, Dr. Pao invented and patented numerous ophthalmic instruments, including one of the first irrigation/aspiration machines for use in extracapsular cataract surgery; one of the first electroretinography instruments, designed to record the electrical signals generated by the retina and transmitted to the occipital cortex, which is still in use worldwide; and one of the first instruments used for coaxial bipolar cautery. One of the instruments he's currently developing will use plasma to sterilize tissue, with the goal of helping to reduce the incidence of endophthalmitis.

"This instrument will produce a non-thermal plasma between the probe and the tissue being treated, a space of 3 mm or less," he explains. "It will ionize gases that are present in the air, primarily oxygen, nitrogen and hydrogen. The effect this has on the tissue will depend on the parameters used, which published reports show can range from antibacterial effects to enhancing tissue healing, as well

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Gregory Fridman, PhD

Non-thermal plasma is used to sterilize a pig's cornea *in vivo*.

as the destruction of melanoma cells through apoptosis. As a tool for sterilization, this could be used on cataract corneal wounds, retinal surgery scleral wounds or intravitreal conjunctival-scleral injection sites."

Dr. Pao became interested in the potential for sterilizing tissue using non-thermal plasma after meeting professor Gregory Fridman at the A.J. Drexel Plasma Institute in Philadelphia. Professor Fridman was conducting plasma experiments with *Staphylococcus aureus* contamination of the spinal cord of New Zealand white rabbits. Wanting to see whether this could be applied to the eye, Dr. Pao began inoculating the rabbits' corneas with the bacteria and then treating it using a prototype plasma device. This early work showed that simple treatment resulted in a two-log reduction in *S. aureus* from an initial concentration of ~106 CFU/mL.

Dr. Pao notes that antibiotics are commonly used following the 2 to 3 million cataract surgeries performed each year. "Using a plasma probe like this for a few seconds could provide as much protection as an antibiotic," he says. "It could also be used following intravitreal injections, where the risk of infection is still real. If an instrument like this can minimize the need for antibiotics, the cost savings and reduced risk of developing bacterial resistance would be significant."

Dr. Pao notes that there are many potential uses for a non-thermal plasma probe like this, beyond ocular surgery. "A device like this could be used to reduce contamination during medical procedures in rural areas where there are few medical resources," he points out. "It could be used in combat zones to clean wounds. It could be used to sanitize hands in hospitals without risking creating bacterial resistance. Think of having a machine on the wall that you place your hands inside; it lights up for three seconds and sterilizes your hands. A device using this technology could decontaminate the walls, floors and ceilings of operating rooms as well as patient rooms in hospitals. Certainly it could be used to sterilize surgical equipment. It's possible that it might even work on biological entities such as prions that are resistant to heat sterilization, although that remains to be proven."

Because excess treatment can cause structural damage to the tissue, Dr. Pao is currently working with live rabbit and porcine eyes at the Drexel School of Medicine Animal Lab, studying the impact of different voltages, pulse durations and energy frequencies, to refine the ideal parameters for causing sterilization without tissue damage. (He credits Kristina Pao, MD, Justine Han, BS, and Ralph Eagle, MD, with major contributions to this work.) He's also working toward making the device available to the medical community. "Right now, we're meeting with a company that's interested in commercializing this," he says. "The final commercial unit should be similar to many of the devices we already use in cataract surgery; the prototype's design is similar to the Alcon crescent blade. Hopefully this will become available within the next year or two." REVIEW

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Cross-linking: Finding The Right Parameters

Christopher Kent, Senior Editor

Strengthening the cornea has a host of potential uses—but the ideal parameters are still being worked out.

The process of cross-linking the corneal stroma to strengthen it, using riboflavin and UVA light, continues to be the focus of researchers' attention in laboratories around the world. It's clear that the process is beneficial in numerous situations, most notably in preventing or minimizing the progression of keratoconus. But because the procedure has only been around for a few years and is not approved for clinical use by the U.S. Food and Drug Administration, some basic issues about the most effective ways to do the procedure remain unanswered.

Here, several surgeons with experience using the procedure discuss what they've learned about cross-linking with the epithelium on (rather than off); which parameters of light, riboflavin and timing work the best; and how these answers are modified when cross-linking is used in different ways.

Epi-on vs. Epi-off

In order for stromal cross-linking to take place, riboflavin must make it past the epithelium and permeate the corneal stroma. Because the corneal epithelium is an effective barrier to most formulations of riboflavin, the original protocol for cross-linking, now known as the Dresden protocol, required removing the epithelium before applying the riboflavin solution to the cornea. While this protocol is undeniably effective, from the outset researchers hoped to find a way to make the procedure work without having to remove the epithelium.

A. John Kanellopoulos, MD, clinical professor of ophthalmology at NYU Medical School and medical director of the Laservision.gr Institute in Athens, Greece, notes that the desire to make epi-on cross-linking work is understandable. "If collagen cross-linking were to become a purely epithelium-on procedure, the morbidity, the patient's everyday activity disturbance and possibly a large number of potential complications that relate to healing and infection could be minimized," he says. "In the early 2000s I saw a few of the initial epi-on treatment attempts in the United States in an investigative protocol. Four out of the five ectasia patients I saw continued to progress. In fact, *in vitro* work in the laboratory showed that using the classic Dresden protocol with the epithelium on resulted in almost no riboflavin penetrating the epithelium and little cross-linking taking place in the stroma.

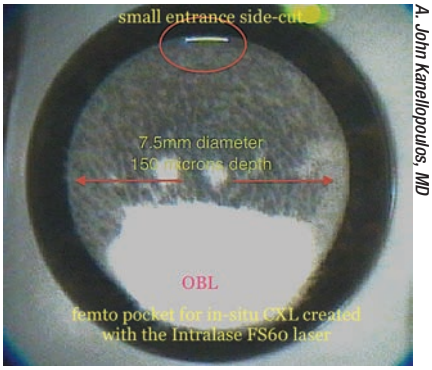
"However, a lot of things have changed since then," he continues. "Multiple techniques have been de-

This article has no commercial sponsorship.

veloped that help to get the riboflavin molecules past the epithelium, such as iontophoresis, adding special 'epi-abrasive' ingredients to the riboflavin solution, using higher concentrations of riboflavin, and also a technique that we introduced: creating a femtosecond laser pocket in the cornea and placing the riboflavin inside it, thus bypassing the issue of riboflavin penetrating through the intact epithelium. Some of the data regarding these variations, although anecdotal, appears promising. If we can facilitate riboflavin penetrance into the cornea, I think epi-on will be a valid technique."

Dr. Kanellopoulos points out that leaving the epithelium on not only makes it difficult to get the riboflavin into the stroma but also can minimize passage of the UV light into the stroma. "If you place the riboflavin solution on the cornea with the epithelium intact, the epithelium becomes soaked with riboflavin molecules," he explains. "Then, during the exposure to UV light, the epithelium acts as an umbrella, absorbing a lot of the light. Depending on which study you look at, 20 to 80 percent of the UV light intended to reach the corneal stroma may be blocked. Clearly, this will reduce the amount of cross-linking achieved. Also, based on what I've seen clinically and the laboratory work we've done *ex vivo*, I'm convinced that effective epi-on cross-linking will require increasing the amount of energy we deliver."

Despite these caveats, Dr. Kanellopoulos says some of his group's work with using cross-linking to cause a refractive change has supported the potential efficacy of epi-on approaches. "In a study we conducted of the refractive effect of customized, very high-fluence cross-linking, the epi-on cases did have a quite impressive refractive effect," he says. *(See example, p. 26.)* "This demonstrates that epi-on cross-linking can be effective in certain areas of the cornea, although it



A. John Kanellopoulos, MD

One way to get the riboflavin into the stroma without having to remove the epithelium is to create a pocket into which the riboflavin can be inserted, using a femtosecond laser. Above: One of the early attempts to create such a pocket, using the FS60 Intralase laser.

appears to be about half or one-third of the amount achieved using epi-off."

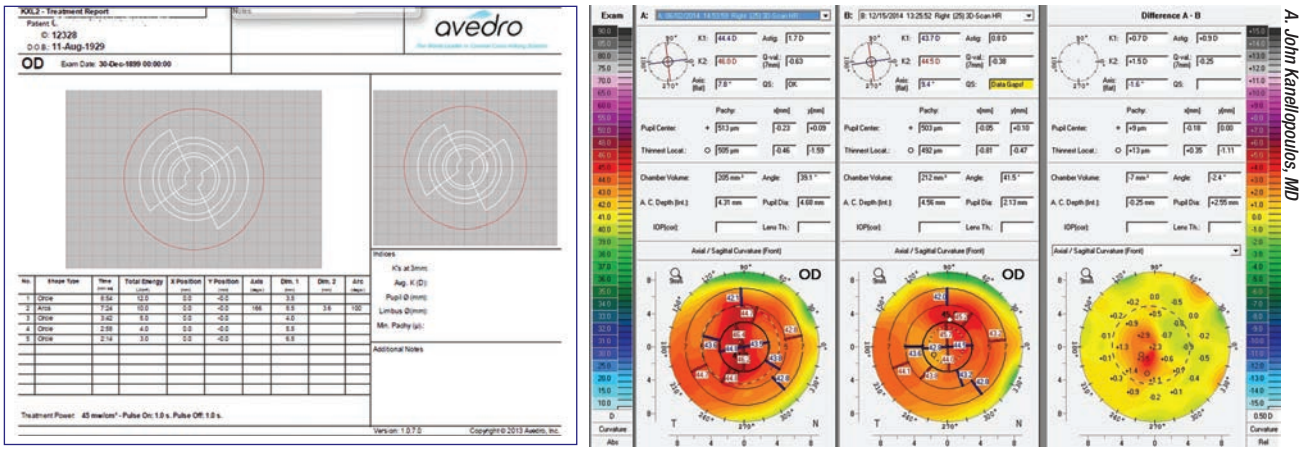
Of course, in some cases an epi-off procedure may be a good thing; there can be advantages to removing the epithelium besides giving the riboflavin easier access. Like many surgeons who perform cross-linking, Arturo S. Chayet, MD, who practices at the CODET Vision Institute in Tijuana, Mexico, still does epi-off exclusively. "The potential advantages of epi-on are obvious, but we still use the Dresden protocol," he says. "One reason for this is that most of our patients receiving cross-linking have a moderate to high spherical equivalent and amount of cylinder, so we're removing the epithelium using phototherapeutic keratectomy. This has an effect similar to topography-guided ablation; the epithelium breaks first in the area of the steeper cornea where the cone is. We're getting really good refractive results just by doing this, followed by the cross-linking. So at this point, even if I had the opportunity to do epi-on, I would continue to do epi-off because of the refractive issues."

Dr. Chayet says he may also do a little PRK if the patient has a lot of refractive error. "I'll start with PTK and then do a little PRK," he says. "Typically I'll do 70 µm of PTK, which includes about 40 µm of epithelium. So on average there's a 30-µm stromal ablation at the keratoconus site on the cornea." He adds that cross-linking by itself causes a certain amount of refractive change. "Cross-linking actually flattens the cornea by about 2 D," he says. "Using the Dresden protocol we're getting between 1.5 and 2 D of corneal flattening. It's part of how cross-linking works."

Putting It in the Pocket

One approach that allows riboflavin to get into the stroma without having to breach the epithelium is the creation of a corneal pocket using a femtosecond laser. Dr. Kanellopoulos describes the method his group has developed. "In our original study we created a femtosecond laser pocket and placed riboflavin 0.1% in the pocket, avoiding any contamination of the riboflavin solution with the surface of the cornea," he says. *(See picture, above.)* "Then we performed high-fluence, high-energy cross-linking using 10 mW/cm^2 exposure for about 10 minutes. The cross-linking this produced was very similar to that achieved with the Dresden protocol, although the corneal strength measurement methods we used to gauge the results were a bit different.

"We've studied this technique more elaborately *ex vivo* in the past few years, comparing the use of a femtosecond laser pocket, and/or a LASIK flap," he continues. "In one set of eyes we placed the riboflavin in the corneal pocket. We performed mock LASIK in the LASIK eyes, placed riboflavin in the stromal bed and replaced the flap. Then we exposed both sets of corneas to very high-fluence and high-energy UV light. To determine how much cross-linking took place, we analyzed the corneas biomechanically by two-



An example of using cross-linking to effect refractive change. The treatment pattern (left) shows the areas of different energy delivered in order to achieve a significant refractive change, correcting -2, -1 @ 170 to +0.25. The pre-, post- and comparison Pentacam readings show the effective correction with six-months of follow-up. (This procedure was done epi-on, using a popular riboflavin formula.)

dimensional stretching and by resistance to enzymatic digestion. In the pocket eyes we found almost a 100-percent increase in the biomechanical rigidity of the cornea. So *ex vivo* we showed that we can double the strength of the cornea if we place riboflavin in the cornea and have the UV light go through the intact epithelium and reach that riboflavin midway in the cornea.

"As you might expect, the corneal strength was not as great in the mock-LASIK eyes, because we were only cross-linking the part of the cornea left after making the flap," he notes. "When we create a pocket, the rest of the cornea is intact and it retains its biomechanical stability. In the LASIK corneas, we were trying to minimize the flaps' exposure to the riboflavin, and we succeeded; postop, control and cross-linking flaps had equal biomechanical strength. That means that after the LASIK procedure we were testing the biomechanical rigidity of just the residual cornea—perhaps a 320-µm cornea instead of a 550-µm cornea. And of course the strongest tissue in the cornea is in the anterior cornea, which becomes part of the flap."

Dr. Kanellopoulos notes several advantages to the pocket technique. "This is a surgical procedure, of course, but horizontal incisions in the cornea do not affect biomechanics," he says. "It's the vertical incisions made in LASIK flaps that cause more than 95 percent of the biomechanical changes in the cornea after LASIK. When creating a pocket, the only biomechanically active part of the pocket would be the little incision that gives you access to the pocket; the rest of the pocket has no effect on the biomechanical strength of the cornea. There's also minimal danger of cutting corneal nerves. The nerve plexus is in the anterior 100 µm of the cornea, while the pocket is between 150 and 200 µm in depth, so you're way under the superficial cornea nerve plexus. Of course, it's possible that the cross-linking procedure itself may affect the nerves, but that's entirely theoretical at this point."

Cristhian Sancho, MD, who works at the Laser Center Visión 20/20 in Pichancha, Ecuador, and is an ophthalmology consultant at Fundacion Vista Para Todos, has been using cross-linking since 2008. "At this point in time we've tried most of the cross-linking machines," he says. "We've tried treatments ranging from 3 to 45 mW and from 3 to 15 J. We've done monocular and binocular treatments and tried both epi-off and epi-on. In terms of epi-on, we've tried different riboflavin formulations without much success, so I recommend using epi-on only in very mild cases."

Dr. Sancho says he has also tried the technique of using a femtosecond laser to create a pocket for the riboflavin solution. "The advantage is the recovery time," he notes. "The downside is the cost."

Independent Research

The problems with epi-on cross-linking center around the difficulty of getting riboflavin through the intact corneal epithelium. However, different formulations have different levels of success because of their chemical structure, and it appears that a consortium of American doctors interested in studying cross-linking, known as CXL-USA, may have discovered a formulation that penetrates the epithelium quite rapidly.

"CXL-USA is an IRB-approved group of physicians conducting multiple studies, working on innovating and optimizing the science and practice of corneal strengthening," explains Roy S. Rubinfeld, MD, MS, in private practice in Rockville, Md., and Fairfax, Va., a clinical associate professor at Georgetown University Medical Center in Washington,

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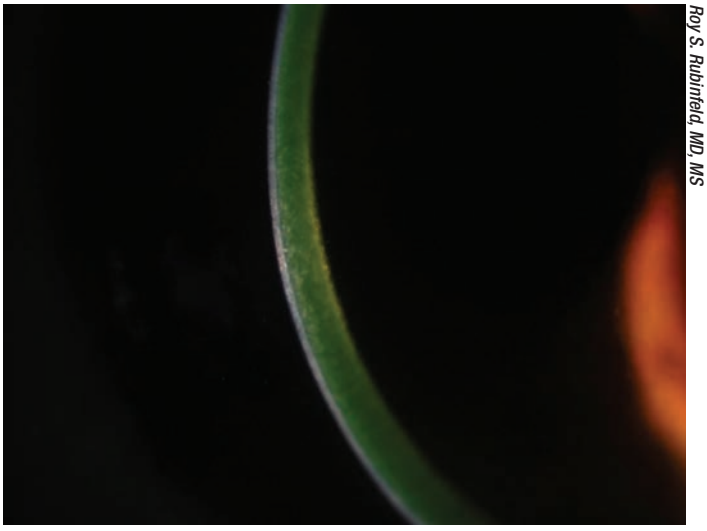
D.C., and a member of the consortium. "CXL-USA has been up and running and treating patients actively since 2009. We've done our best to make cross-linking available in our clinical trials, and we continue to innovate and publish, spreading information and sharing our experiences. We're focused on the science part of this, not the commercial side."

Dr. Rubinfeld says it's been very helpful to do this research without commercial involvement. "In a commercial trial, whatever protocol you go in with is what you have to continue to do for the next few years," he says. "Once you set up an FDA trial, for example, you have to stay with the chosen technique, metrics and timing. In general, no matter what you learn during the years of conducting the trial, you can't use any of that knowledge to innovate and improve. You have to follow the pre-established protocol.

"In our world, because we write our protocols with some flexibility in them and the ability to incorporate innovation, we haven't had that limitation," he says. "When we've figured out that something works better, we've switched to it. For example, we tried many riboflavin formulations that took one to three hours to load into the stroma through intact epithelium. We just kept modifying them and the delivery techniques until we found ways to consistently, reliably and homogenously load through intact corneal epithelium in 20 minutes or less, and then we switched to that protocol. We've been able to be much more innovative and agile than commercial trials can be."



Roy S. Rubinfeld, MD, MS

A new proprietary riboflavin formula created by CXL-USA successfully penetrates the epithelium quickly without soaking it. Above: The new formulation used on the eye of a 20-year-old patient with keratoconus. After 15 minutes of epithelium-on soaking, this slit lamp photo shows a well-loaded stroma (green) and a clear epithelium (white). (Photo used with permission of *EyeWorld*.)

Perfecting Epi-on

Dr. Rubinfeld notes that finding a formulation of riboflavin that could readily penetrate intact epithelium has been a central focus of the CXL-USA group. "If you can do cross-linking without scraping off the epithelium, anybody would prefer that," notes Dr. Rubinfeld. "Even people who have strongly defended the epi-off approach are now saying, 'If you can get the riboflavin in, and the UVA light gets in and the oxygen is present in the corneal stroma, you're going to get good cross-linking.' And everyone agrees that it would be great if patients didn't have to undergo four to seven days of discomfort and the risk of infection, haze, scarring and perforation—all of which have been reported with epi-off. Epi-on is an inherently noninvasive treatment, and everybody wants epi-on to work.

"At CXL-USA we have developed a proprietary, patent-pending riboflavin formula that's specifically formulated for rapid, consistent, homogeneous riboflavin stromal loading with the epithelium intact," he explains. "We've tried and observed many other formulations in our many studies, including two commercial formulations available in Europe that are specifically designed for transepithelial cross-linking. However, we were disappointed with the results they produced. Using our new formulation, our investigators across the United States have been able to load both eyes in 20 minutes or less. We also have a proprietary, patent-pending loading delivery system that does not involve iontophoresis. Based on our formulation and protocol, we're consistently able to load the stroma quickly and easily and get very effective cross-linking. *(See example, above.)* Of course I'm biased, but if I were having cross-linking, this would be my preferred approach. In fact, William Trattler, MD, one of our key investigators, did treat his 12-year-old daughter with our epi-on technology. It not only stopped her disease progression but improved her acuity as well."

Dr. Rubinfeld says the surgeons in CXL-USA started with epithelium-off treatments at the outset. "Like everyone else, we simply didn't believe that epi-on could work," he notes. "With those early formulations, it took two to three hours or more to get adequate stromal loading through the epithelium in the first set of corneas we treated. It was not a pleasure for the patients or the staff. Over time we've adjusted key characteristics of the formulation until we developed the current version. It makes the loading process work consistently, smoothly and easily. Patients really appreciate a short procedure—lying there for

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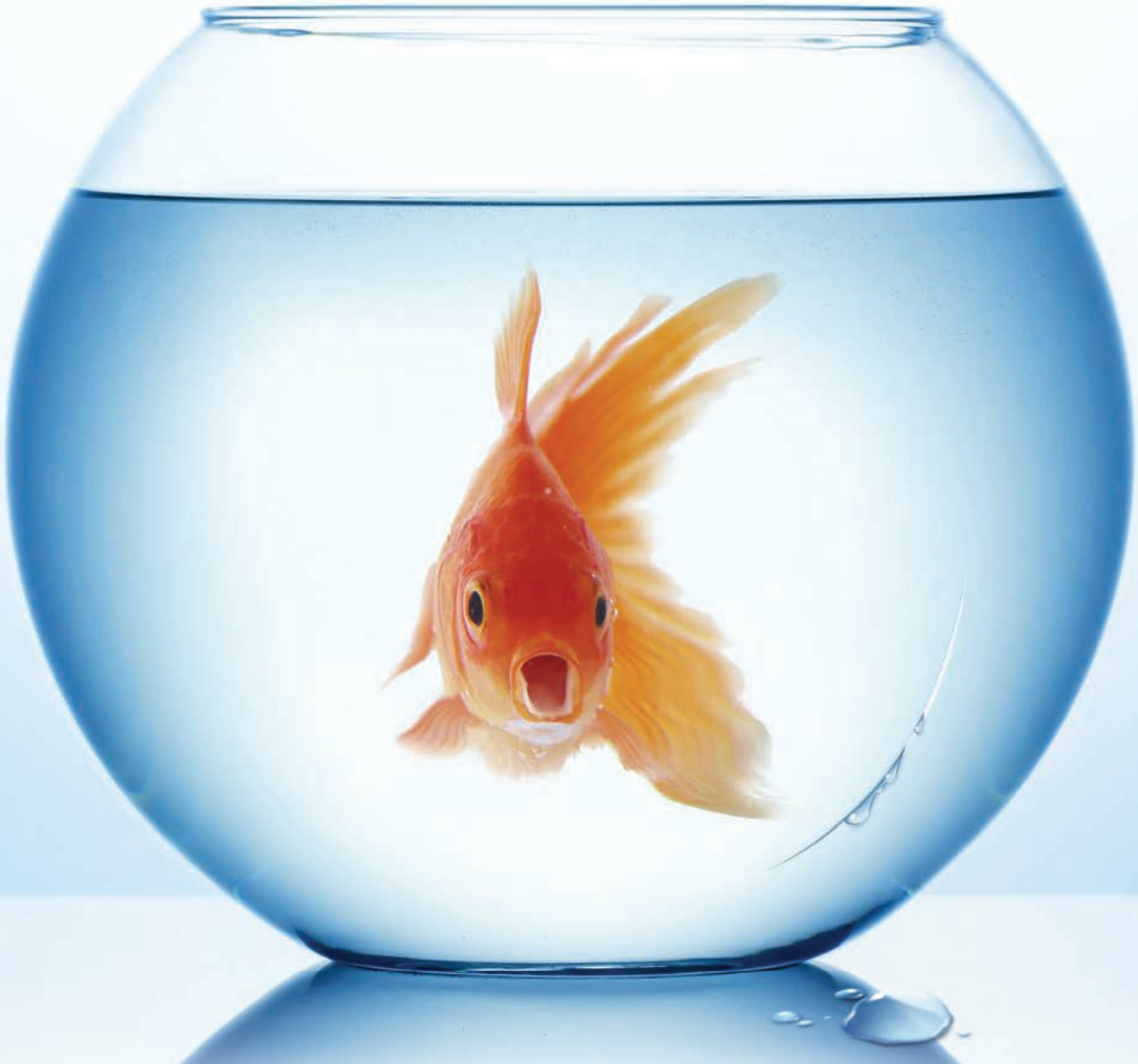

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20 minutes listening to music, as opposed to an hour or more. The next day, they're back to their normal activities because we haven't removed their epithelium. They're seeing well. Usually they drive to the office for their one-day-postoperative visit."

Dr. Rubinfeld notes that all of the cross-linking approaches are possible in part because of specific characteristics associated with riboflavin. "One of the good clinical aspects of riboflavin is that it's easy to see," he says. "It's a bright yellow-green color that's readily visible. So, after loading, anyone can take a slit lamp and see where the riboflavin is, how much is there and whether or not it's evenly and adequately distributed. Then when you apply UV light, it fluoresces. It's essentially its own marker. If it didn't have that vivid color, we'd have to have some sort of advanced technology to measure where it is.

"The other nice thing is that once you get the riboflavin through the epithelium, it diffuses nicely through the stroma," he adds. "The epithelium has a lot of lipids and other barriers to penetration of water-soluble solutions on the surface, whereas the stroma is mostly water and is completely water-soluble. Riboflavin is also incredibly water-soluble, so it diffuses easily throughout the stroma. That's one reason other innovations like femto pockets or channels or partial-scraping procedures work. They just need to get the riboflavin through the intact epithelium; then it spreads throughout the stroma. Of course, with our riboflavin formulation, laser pockets and channels are not necessary. Those approaches were developed because other riboflavin formulations are unable to penetrate the epithelium well."

Dr. Rubinfeld agrees that riboflavin in the epithelium can theoretically block some of the UV light from reaching the stroma. "Not only will that block some UVA light, it will also consume some of the oxygen needed in the stroma for cross-linking to occur," he says. "We don't want that. But in our proprietary technique the epithelium is crystal clear after loading, indicating that the riboflavin isn't getting trapped there. At the same time, the stroma is well-loaded with green in a homogeneous concentration. So our protocol avoids this problem."

Fine-tuning Parameters

One of the big questions still being resolved is what combination of fluence and timing is most effective in any given version of cross-linking. In theory, increasing the amount of light being used should decrease the time required to complete the cross-linking.

"This is another point that has not been studied thoroughly," says Dr. Kanellopoulos. "I know that Avedro has conducted a multicenter study in the United States addressing this question by comparing the effect of several different fluences, and I understand that the preliminary data in-

Combining Cross-linking and Conductive Keratoplasty

One of the applications for cross-linking currently being investigated is using it to stabilize the refractive changes produced by conductive keratoplasty. In CK, the surgeon uses a probe inserted into the cornea to a depth of about 500 µm to increase the temperature in a circumferential series of eight or more spots placed 6, 7 or 8 mm from the corneal center. The heat causes controlled shrinkage of the tissue, resulting in a tightening effect on the mid-peripheral cornea, increasing refractive power. CK has been used to treat astigmatism, decentered ablations, keratoconus and trauma, as well as to produce a moderate refractive correction. In general, the procedure has not been widely adopted due to the tendency for the changes to regress over time. Researchers realized, however, that cross-linking might minimize or eliminate that drawback.

"Over time, we found it frustrating for patients (and surgeons) to do a cross-linking procedure which stopped vision loss but did not do much to improve the patient's poor vision," says Roy S. Rubinfeld, MD, MS, a clinical associate professor at Georgetown University Medical Center in Washington, D.C., and a member of CXL-USA. "Over the past several years, to improve vision in these patients we've been doing a lot of conductive keratoplasty to regularize the corneal shape, followed by cross-linking, both to lock in the beneficial effects of the CK and to stabilize the cornea. We call this 'CK-plus' or refractive CXL. CK is a noninvasive, very well-tested and safe procedure that's been around for a long time, but one of its limitations has always been the tendency for the improved visual results to regress. When we combine it with cross-linking, the corneal changes seem to stick. We have one- and two-year data now that demonstrates substantial, statistically significant clinical improvement in both uncorrected and best-corrected vision. *(See chart, p. 32.)* It's been really fulfilling for both patients and surgeons."

Dr. Rubinfeld says it took investigators some time to figure out the sequence in which the procedures should be done. "The literature shows that when you do CK at the same time as cross-linking, the results are probably going to regress," he notes. "But our colleague Arthur Cummings, MD, in Dublin found that leaving an interval between the CK and cross-linking helped to prevent the effect from regressing. So, we wait a day after the CK procedure before doing the cross-linking, and that seems to make all the difference. We don't have final data yet, but the people who had the procedures a day apart have had notably better long-term data that those who were done on the same day."

Dr. Rubinfeld adds that they perform the CK with real-time monitoring. "I'm able to watch the intraoperative keratometry when I do the CK," he explains. "If I find I'm ending up with an oval-shaped or pear-shaped ring on the cornea because of astigmatism, I can make it round with an extra spot or two. I sometimes take a Pentacam before the procedure and again after a few spots and then decide if it's enough. It's a great technique, because we can see what we're doing while we're doing it."

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dicate pretty similar results. However, we'd like to see this studied by an independent body or in a multicenter trial, because Avedro has a vested interest in higher-fluence cross-linking being better. I believe their instrument is still the only device that can generate more than 30 mW/cm² of fluence.

"We use a big spectrum of fluences and energy levels in our practice," he continues. "They've changed significantly over the years. Cross-linking is 50 percent of our practice, and the standard keratoconus patient—usually a young male—accounts for about 80 percent of the cross-linking we perform. In the great majority we perform the Athens protocol, which has now been established as a valid treatment, although many centers use slight variations of it under a different name such as the Dubai protocol, the Montreal protocol or the Dublin protocol. The Athens protocol combines a very frugal topography-guided excimer normalization of the cornea with high-fluence cross-linking. Using that protocol we've tried higher and lower fluences over the years; for the past three years we've used 6 mW/cm² for 15 minutes. This delivers 5.5 J of total energy, which is double the fluence but the same total energy delivered as the classic Dresden protocol. Doing this cuts the treatment time in half, from 30 minutes to 15 minutes. That has been our standard for the past eight years, and we've reported extensively on the refractive effects and stability of this protocol."

Dr. Kanellopoulos adds that when performing epi-on cases he may use energies up to 20 J. "This is four times the Dresden protocol," he notes. "But as I said before, one has to take into account that a lot of this energy may get lost on its way to meeting the riboflavin in the cornea."

In terms of finding the right protocol for a basic epi-off procedure, Dr. Kanellopoulos notes that you have to balance the advantages and disadvantages of changing the parameters. "We started using double the classic Dresden protocol energy levels as far back as 2006," he says. "We found that doubling the levels minimized most of the corneal dehydration problems and corneal thinning, while shortening the procedure from 30 minutes to 15. When higher-fluence devices became available, we tried using even more fluence for less time, but we found that we achieved a more superficial cross-linking effect. That is not ideal, because in keratoconic eyes we want to cross-link as deeply as possible to ensure long-term stability. So we went from 6 mW/cm² to 10, to 15, to 30. Finally we went back to 6 mW/cm², because we found by studying these corneas with OCT that we had the deepest and widest distribution of cross-linking effect in the corneas at this fluence. These parameters gave us the greatest efficacy, while minimizing dehydration problems and potential epithelial toxicity.

"I'm aware that some surgeons are currently using higher fluence," he adds. "I applaud them for collecting data and showing its effect. But I think for the patient, going from 15 minutes to 10 or 8 minutes doesn't make that much difference. On the other hand, I think going from 30 minutes to 15 is a huge difference."

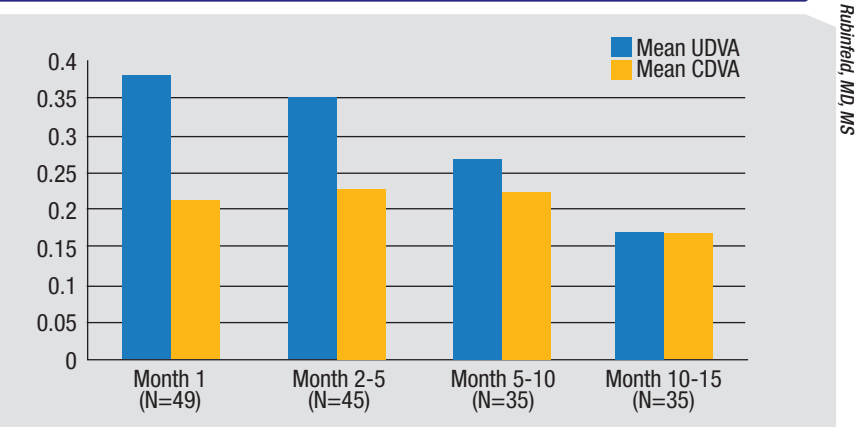
Dr. Rubinfeld says he is not an advocate of high fluence. "More is not always better," he notes. "The rate-limiting factor in the cross-linking reaction is oxygen, and the more UV you use, the more you deplete that rate-limiting agent. I think of it as being like a recipe. If the recipe says to bake a pan of brownies for 30 minutes at 300 degrees, trying to bake it for three minutes at 3,000 degrees probably won't produce the result you're hoping for. You might be able to improve upon the original formula, but there are bound to be limits. We [at CXL-USA] have aimed to create a highly effective corneal strengthening procedure that's the least inflammatory and most respectful of the health of the corneal cells and the patient's comfort."

Adjusting by Procedure

As surgeons around the world try cross-linking for purposes beyond controlling keratoconus and ectasia,

Postop Distance VA (logMAR) Following CK with CXL

Roy S. Rubinfeld, MD, MS



Results of combining cross-linking with conductive keratoplasty in eyes with keratoconus or corneal ectasia, with preop corrected distance visual acuity of 20/40 or worse. More recent follow-up data suggests that the benefits seen at months 10 to 15 have been maintained. Similar tests conducted without cross-linking have regressed more quickly and produced significantly worse long-term results.

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they're finding that different parameters make sense in different situations. "Today we're using cross-linking technology not only for keratoconus but for refractive corrections and treating bacterial keratitis and corneal ulcers," says Dr. Sancho. "When treating bacterial keratitis, I've found that a long exposure time is better, since we're using the UV light to eradicate the bacteria. We also combine refractive surgery with cross-linking. We don't need too much exposure time to get a reproducible result in refractive cases."

"Our second most popular cross-linking technique is combining cross-linking with LASIK," says Dr. Kanellopoulos. "We consider this a necessity in hyperopic LASIK; in fact, we haven't performed any hyperopic LASIK without cross-linking for the past four years. The reason is that a study we conducted in-house proved, at least in our eyes, that hyperopic LASIK produced far better long-term results when cross-linking was performed. We compared fellow eyes that underwent hyperopic LASIK done by the same surgeon, using the same device and parameters. One eye received cross-linking, using 30 mW/cm^2, which is very high fluence, for 60 seconds; the other received no cross-linking. The contralateral control eyes had significant regression over the next two years; the cross-linked eyes did not. We also use cross-linking for stability and to prevent ectasia when performing LASIK on patients who are under 30 years of age who have more than 6 D of myopia. In these cases we use the same fluence, but for 80 seconds."

"The protocols we use are always changing depending on the case to be treated," notes Dr. Sancho. "The fluence we use depends on the instrument being used and the riboflavin vehicle; there are different indications depending on the manufacturer. Using the wrong fluence or riboflavin can produce severe endothelial damage. At the same time, using less than sufficient energy produces less effect and not much change in keratometry. Generally, we've gotten better results with more fluence. That's especially true with our new custom system with eye tracking that makes it possible to apply different fluences in different areas. To treat keratoconus I currently use 7.2 J at 30 mW with 10 minutes of induction time. That has resulted in reproducible results for the past two years.

"There are still many pieces missing from the scaffold [of knowledge] we're building. We need to be cross-referencing our work. What is the actual effect of each different technique?
—J. Kanellopoulos, MD

"Using more fluence we're able to get refractive changes," he adds, "but it's important to choose the case. In the future I believe we will be able to do effective refractive correction by reshaping the cornea with cross-linking. I'm working on that today, with very promising early results. So far I've only done 120 cases, with various results, but I believe that's the future."

What We've Learned

As individuals and groups continue to research cross-linking, several things are becoming clear.

• ***It's reasonable to expect some individual variation in outcomes.*** Dr. Kanellopoulos notes that when performing refractive cross-linking with an epi-on protocol, some patients showed less of an effect than others. "We've had good results in most patients, but there have been a few outliers who showed little or no effect from the procedure," he says. "We have no explanation for that. We don't know if it's because of a glitch in the epithelium, a problem with our technique or an intrinsic behavior of the cornea. Maybe not every cornea reacts the same to the cross-linking effect.

"It's worth noting that we see far less variability in the effect in different corneas when performing epi-off procedures," he adds. "The standard deviation is smaller by a factor of four when you're studying epi-off."

• ***More riboflavin is not necessarily better.*** Dr. Rubinfeld says that many surgeons believe that using more riboflavin is better because it will result in more cross-linking. "That's not correct," he says. "Riboflavin acts much like a catalyst. Chemists used to talk about 'adding a pinch of catalyst.' The reality is, you need a certain amount of riboflavin to trigger the cross-linking reaction, but adding more doesn't make the reaction go faster or produce better results. In fact, if you get too much riboflavin in the path of the UV light, you'll just attenuate or block the light available for the reaction."

• ***Previous cross-linking doesn't seem to reduce the effect.*** "We've been surprised to discover that we are able to get a significant refractive cross-linking effect in corneas that were previously cross-linked," says Dr. Kanellopoulos. "If I had to guess, I would have thought that in corneas that had been cross-linked before you'd see less of a cross-linking effect. But we found that even patients who had the Athens protocol six years ago showed a very compelling refractive effect when treated with refractive

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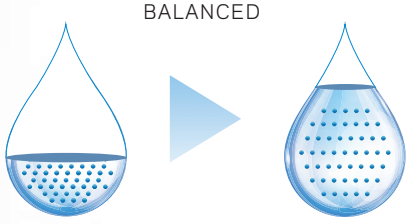

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Reference: 1. Research in dry eye report of the Research Subcommittee of the International Dry Eye WorkShop (2007). *Ocul Surf.* Apr 2007; 5(2): 179-193.

cross-linking this year."

• ***The presence of oxygen may be crucial.*** "The chemistry involved in the cross-linking process isn't complicated," says Dr. Rubinfeld. "You need an adequate amount of riboflavin; you need UV light; and you need oxygen. We used to think that oxygen didn't play a very important role, but it turns out that it does—in fact, it's the rate-limiting factor. The problem is, when the light is on, you're depleting molecular oxygen in the cornea, and oxygen can't diffuse back into the cornea to replenish the supply with the UVA light on. Essentially, you're making the cornea hypoxic. That's why oxygen is the rate-limiting factor in the cross-linking reaction.

"To manage that problem, we've been using the light in a discontinuous way," he says. "Since 2010 we've been applying the light for a brief period of time, which induces cross-linking and consumes oxygen, and then turning the light off for a period of time. When the light is off, oxygen can then diffuse back into the cornea to replenish that reactant and allow the cross-linking to continue without building up toxic products like peroxide, which kills keratocytes. Surgeons often look for demarcation lines as a sign that cross-linking has occurred; we believe those lines mark where you've killed corneal cells. Essentially, you want to do a procedure that maximizes the cross-linking while minimizing the production of toxic by-products. Cycling the light on and off is one way to accomplish that."

What's Next?

With so many different ways of using cross-linking, and so many ideas about the optimum parameters, the field of cross-linking is currently awash with uncorrelated observations and data sets. "I think the global ophthalmic community has matured to the point that we need to correlate the work we've done so far before we make another leap forward," says Dr. Kanellopoulos. "We're growing exponentially in completely different directions without finding the correlations between the different pathways we're taking.

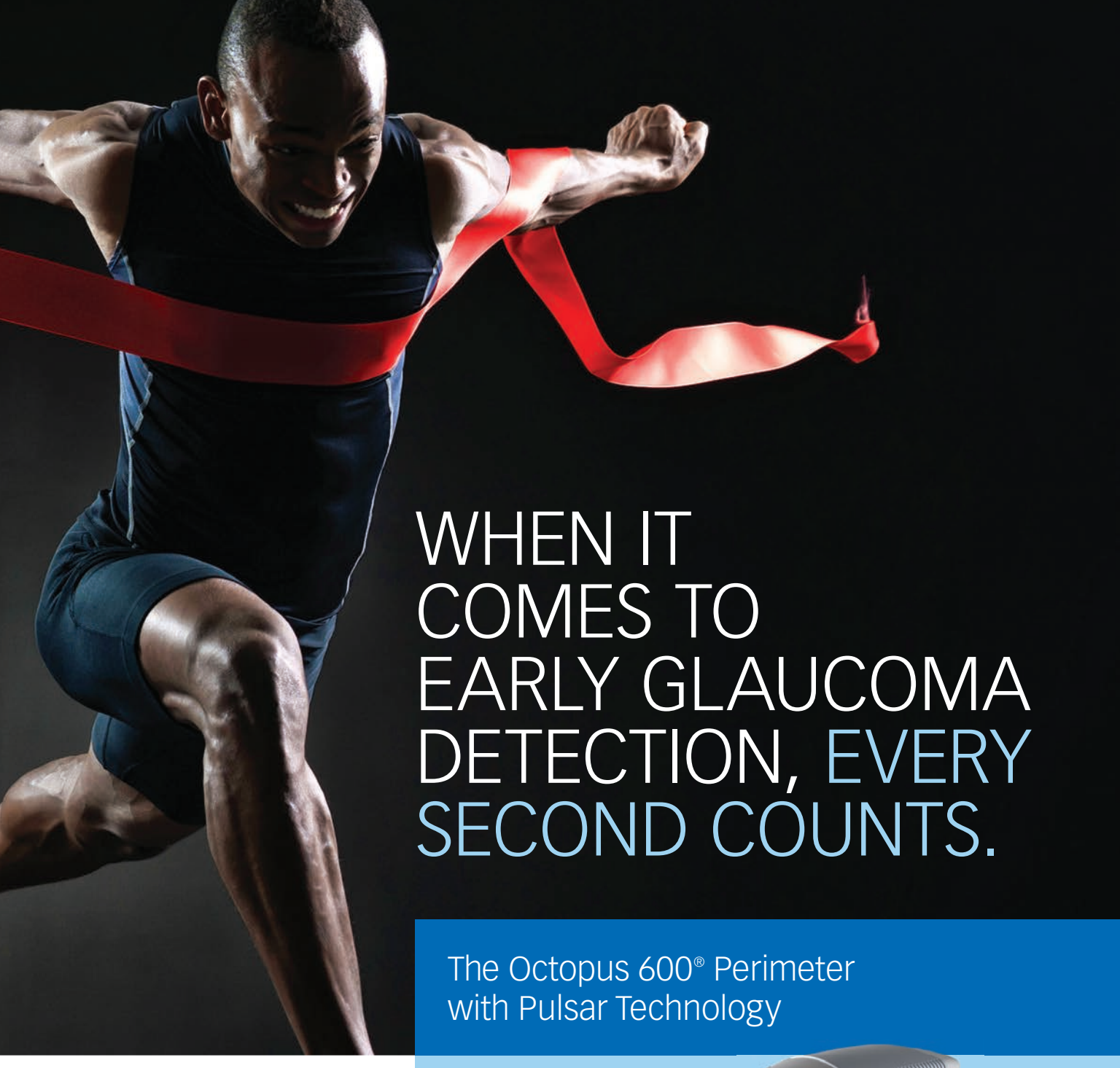
"At the European Society of Cataract and Refractive Surgery meeting last year our team submitted a protocol for studying different collagen cross-linking epi-on and epi-off techniques *ex vivo*, to try to establish some order of relative efficacy between the different techniques," he continues. "We need a large study comparing difference fluences, techniques and riboflavin solutions. We don't know how much we're achieving with each one of these techniques. We've yet to define the actual spectrum of cross-linking's use, titrate its effect and above all establish its safety.

"The ophthalmic community has to push the industry to conduct these studies," he continues. "Our center is just a small, clinical investigative center, and we have no financial interest in any of the studies we've conducted. We conducted them purely because we saw the void and pieces of the puzzle missing from the literature. In the meantime, there are still many pieces missing from the scaffold we're building. We need to be cross-referencing our work. What is the actual effect of each different technique?

"Once those questions have been answered, there are other horizons for cross-linking," he notes. "Cross-linking may be a valuable adjunct or even primary treatment for infection. In the developing world, this treatment only costs a few cents, and it could save hundreds of thousands of people from blindness. In the meantime, once the United States' clinical body of work becomes a part of cross-linking technique and technology development, I believe cross-linking will become the mainstay of ectasia stabilization, as well as a tool for biomechanically modulating corneas."

And what about the ongoing debate regarding epi-on vs. epi-off treatment? Asked whether he thinks epi-on will eventually replace epi-off as the cross-linking procedure of choice, Dr. Rubinfeld gives a qualified yes. "If the patient just needs cross-linking to stabilize the cornea, then I think epi-on will become the standard over time," he says. "Cross-linking is great at stopping the progression of vision loss. So, if someone comes into the office and has early keratoconus and hasn't yet lost vision, cross-linking is the procedure for that person. In that situation, if epi-on works fine, why wouldn't you use it? But if a patient is only correctable to 20/80 because of advanced keratoconus and irregular astigmatism, then you'll want to try and find a way to not just stop the progression but also make the patient see better. Cross-linking alone is not very good at that, for most patients. That's where you want to combine cross-linking with something else, such as Intacs, topography-guided ablation or standard PRK. If you're going to do PRK, you're going to have to remove the epithelium anyway, so in some situations, epi-off will continue to make sense."

"The reality is, regardless of how much finesse we think we have incorporated into cross-linking, it's currently a very gross procedure," concludes Dr. Kanellopoulos. "We're throwing flour and water into a pot and hoping to get the same result at the end of the day. The cornea is a living, dynamic structure; we don't even know if the riboflavin bioavailability in the cornea is the same from patient to patient. Corneal curvature, corneal density and even keratocyte population may play a role in the efficacy of the procedure. There are so many variables in corneas from patient to patient that even though we've worked with cross-linking for 15 years, I personally think we've only scratched the surface." REVIEW



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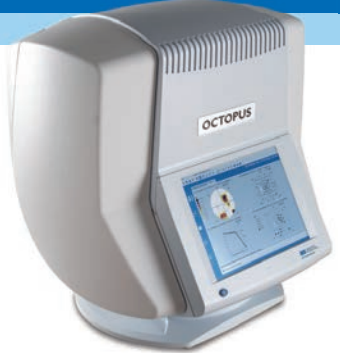

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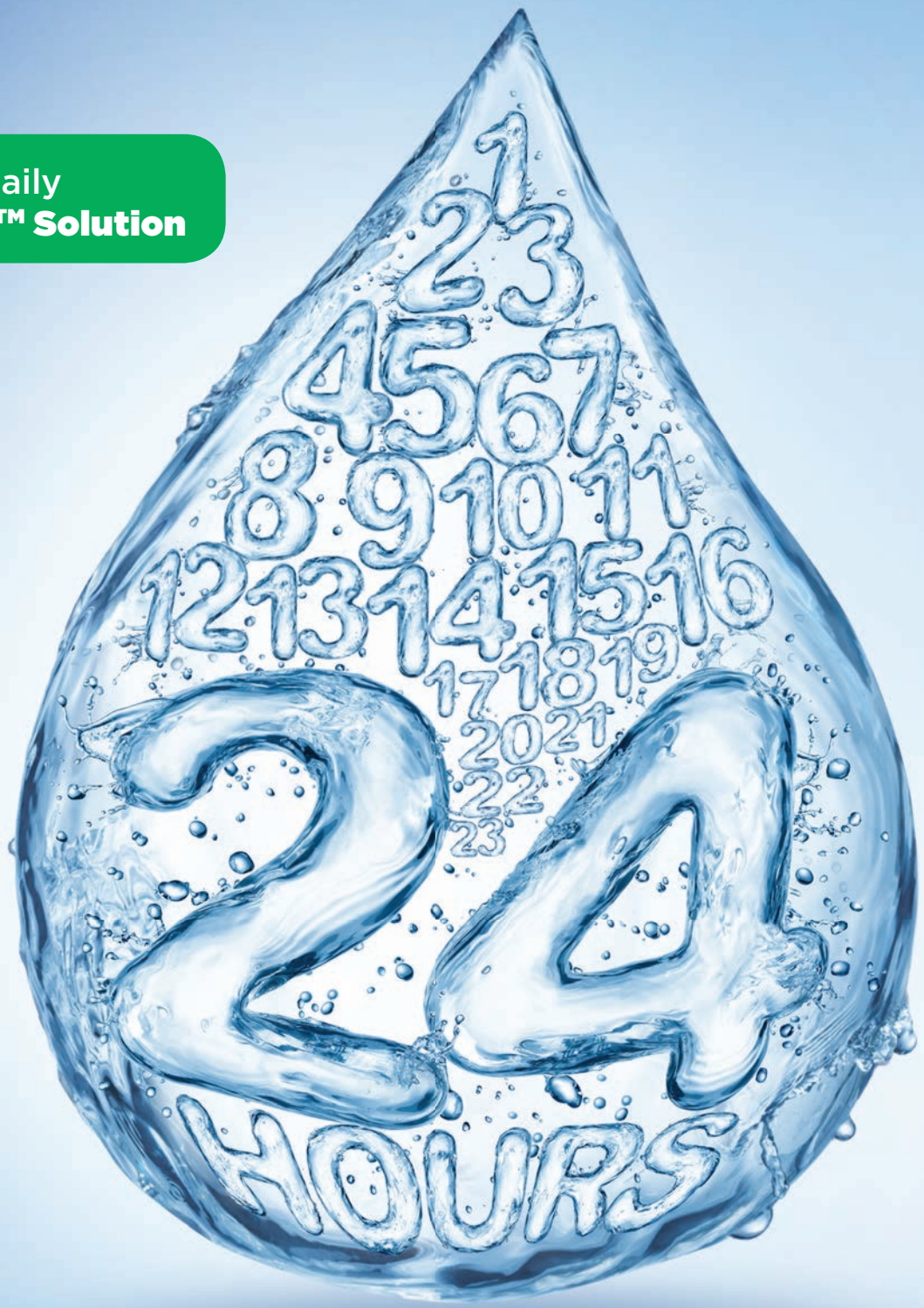

INDICATION AND DOSING

PAZEO™ Solution is indicated for the treatment of ocular itching associated with allergic conjunctivitis. The recommended dosage is to instill one drop in each affected eye once a day.

IMPORTANT SAFETY INFORMATION

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

Patients should not wear a contact lens if their eye is red. PAZEO™ Solution should not be used to treat contact lens-related irritation. The preservative in PAZEO™ Solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red should be instructed to wait at least five minutes after instilling PAZEO™ Solution before they insert their contact lenses.

24 HOURS OF OCULAR ALLERGY ITCH RELIEF IN ONE DROP

Once-Daily **PAZEO™ Solution** for relief of ocular allergy itch:

- The first and only FDA-approved **once-daily** drop with demonstrated 24-hour ocular allergy itch relief[1]
- Statistically significantly improved relief of ocular itching compared to **PATADAY® (olopatadine hydrochloride ophthalmic solution) 0.2%** at 24 hours post dose (not statistically significantly different at 30-34 minutes)[1]
- Statistically significantly improved relief of ocular itching compared to vehicle through 24 hours post dose[1]

Study design: Two multicenter, randomized, double-masked, parallel-group, vehicle- and active-controlled studies in patients at least 18 years of age with allergic conjunctivitis using the conjunctival allergen challenge (CAC) model (N=547). Patients were randomized to receive study drug or vehicle, 1 drop per eye on each of 2-3 assessment days. On separate days, antigen challenge was performed at 27 (±1) minutes post dose to assess onset of action, at 16 hours post dose (Study 1 only), and at 24 hours post dose. Itching scores were evaluated using a half-unit scale from 0=none to 4=incapacitating itch, with data collected 3, 5, and 7 minutes after antigen instillation. The primary objectives were to demonstrate the superiority of **PAZEO™ Solution** for the treatment of ocular allergy itch. Study 1: **PAZEO™ Solution** vs vehicle at onset of action and 16 hours. Study 2: **PAZEO™ Solution** vs vehicle at onset of action; **PAZEO™ Solution** vs **PATADAY® Solution**, PATANOL® (olopatadine hydrochloride ophthalmic solution) 0.1%, and vehicle at 24 hours.[1-3]

PAZEO™ Solution: Safety Profile

- Well tolerated[1]
- The safety and effectiveness of **PAZEO™ Solution** have been established in patients two years of age and older[1]
- The most commonly reported adverse reactions, occurring in 2% to 5% of patients, were blurred vision, dry eye, superficial punctate keratitis, dysgeusia, and abnormal sensation in eye[1]

Once-daily dosing[1]

Give your patients 24 HOURS OF OCULAR ALLERGY ITCH RELIEF with once-daily PAZEO™ Solution[1]

IMPORTANT SAFETY INFORMATION (cont'd)

The most commonly reported adverse reactions in a clinical study occurred in 2%-5% of patients treated with either PAZEO™ Solution or vehicle. These events were blurred vision, dry eye, superficial punctate keratitis, dysgeusia, and abnormal sensation in eye.

For additional information on PAZEO™ Solution, please refer to the brief summary of the full Prescribing Information on the following page.

References: 1. PAZEO™ Solution Package Insert. **2.** Data on file, 2011. **3.** Data on file, 2013.

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BRIEF SUMMARY

PAZEO (olopatadine hydrochloride ophthalmic solution) 0.7%. For topical ophthalmic administration.

The following is a brief summary only; see full prescribing information for complete product information.

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

Contamination of Tip and Solution

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

Contact Lens Use

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

The preservative in PAZEO solution, benzalkonium chloride, may be absorbed by soft contact lenses. Patients who wear soft contact lenses and whose eyes are not red, should be instructed to wait at least five minutes after instilling PAZEO before they insert their contact lenses.

ADVERSE REACTIONS

Clinical Trials Experience

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

In a randomized, double-masked, vehicle-controlled trial, patients at risk for developing allergic conjunctivitis received one drop of either PAZEO (N=330) or vehicle (N=169) in both eyes for 6 weeks. The mean age of the population was 32 years (range 2 to 74 years). Thirty-five percent were male. Fifty-three percent had brown iris color and 23% had blue iris color. The most commonly reported adverse reactions occurred in 2-5% of patients treated with either PAZEO or vehicle. These events were blurred vision, dry eye, superficial punctate keratitis, dysgeusia and abnormal sensation in eye.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate or well-controlled studies with PAZEO in pregnant women. Olopatadine caused maternal toxicity and embryofetal toxicity in rats at levels 1,080 to 14,400 times the maximum recommended human ophthalmic dose (MRHOD). There was no toxicity in rat offspring at exposures estimated to be 45 to 150 times that at MRHOD. Olopatadine should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Animal Data

In a rabbit embryofetal study, rabbits treated orally at 400 mg/kg/day during organogenesis showed a decrease in live fetuses. This dose is 14,400 times the MRHOD, on a mg/m^2 basis.

An oral dose of 600 mg/kg/day olopatadine (10,800 times the MRHOD) was shown to be maternally toxic in rats, producing death and reduced maternal body weight gain. When administered to rats throughout organogenesis, olopatadine produced cleft palate at 60 mg/kg/day (1080 times the MRHOD) and decreased embryofetal viability and reduced fetal weight in rats at 600 mg/kg/day. When administered to rats during late gestation and throughout the lactation period, olopatadine produced decreased neonatal survival at 60 mg/kg/day and reduced body weight gain in offspring at 4 mg/kg/day. A dose of 2 mg/kg/day olopatadine produced no toxicity in rat offspring. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were 45 to 150 times higher than the observed human exposure [9.7 ng·hr/mL] following administration of the recommended human ophthalmic dose.

Nursing Mothers

Olopatadine has been identified in the milk of nursing rats following oral administration. Oral administration of olopatadine doses at or above 4 mg/kg/day throughout the lactation period produced decreased body weight gain in rat offspring; a dose of 2 mg/kg/day olopatadine produced no toxicity. An oral dose of 1 mg/kg olopatadine in rats resulted in a range of systemic plasma area under the curve (AUC) levels that were 45 to 150 times higher than the observed human exposure [9.7 ng·hr/mL] following administration of the recommended human ophthalmic dose. It is not known whether topical ocular administration could result in sufficient systemic absorption to produce detectable quantities in the human breast milk. Nevertheless, caution should be exercised when PAZEO is administered to a nursing mother.

Pediatric Use

The safety and effectiveness of PAZEO have been established in pediatric patients two years of age and older. Use of PAZEO in these pediatric patients is supported by evidence from adequate and well-controlled studies of PAZEO in adults and an adequate and well controlled study evaluating the safety of PAZEO in pediatric and adult patients.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity

Olopatadine administered orally was not carcinogenic in mice and rats in doses up to 500 mg/kg/day and 200 mg/kg/day, respectively. Based on a 35 µL drop size and a 60 kg person, these doses are approximately 4,500 and 3,600 times the MRHOD, on a mg/m^2 basis.

Mutagenesis

No mutagenic potential was observed when olopatadine was tested in an *in vitro* bacterial reverse mutation (Ames) test, an *in vitro* mammalian chromosome aberration assay or an *in vivo* mouse micronucleus test.

Impairment of fertility

Olopatadine administered at an oral dose of 400 mg/kg/day (approximately 7,200 times the MRHOD) produced toxicity in male and female rats, and resulted in a decrease in the fertility index and reduced implantation rate. No effects on reproductive function were observed at 50 mg/kg/day (approximately 900 times the MRHOD).

PATIENT COUNSELING INFORMATION

• Risk of Contamination: Advise patients to not touch dropper tip to eyelids or surrounding areas, as this may contaminate the dropper tip and ophthalmic solution.

• Concomitant Use of Contact Lenses: Advise patients not to wear contact lenses if their eyes are red. Advise patients that PAZEO should not be used to treat contact lens-related irritation. Advise patients to remove contact lenses prior to instillation of PAZEO. The preservative in PAZEO solution, benzalkonium chloride, may be absorbed by soft contact lenses. Lenses may be reinserted 5 minutes following administration of PAZEO.

Patents: 8,791,154

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When Corneal Cross-Linking Goes Bad

Walter Bethke, Managing Editor

Making sure the epithelium heals quickly can avoid many problems, surgeons say.

By all accounts, corneal cross-linking is generally a safe procedure that's saved many patients from having to undergo corneal transplants as a result of their keratoconus or corneal ectasia. Like any surgical intervention, however, it's not without risks, so it pays to know what can go wrong so you can avoid problems and prepare for those infrequent occasions when complications occur. In this article, cross-linking experts share their tips for sidestepping and managing problems.

Delayed Re-epithelialization

In cases of epithelium-off cross-linking, which many surgeons currently use due to its effectiveness, one of the chief complications to be wary of is a delay in re-epithelialization, since this leaves the cornea open to other problems.

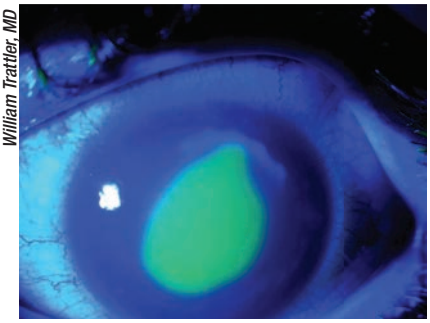
"The most common complication I've had is delayed re-epithelialization, occurring in 2 to 5 percent of cases," says Singapore surgeon Jerry Tan. "The delay can go as long as two weeks. To avoid it, you have to get the epithelium to heal quickly. For this I use autologous serum and a bandage contact lens. I also keep the eye as moist as possible postop, which means lots of artificial tears."

Miami surgeon William Trattler says he's noticed risk factors for delayed healing. "They include very steep corneas, as well as patients with steep corneas in whom you place a bandage contact lens," he says. "What can occur is the bandage lens can rub the apex of the cornea and prevent the epithelium from healing. In such cases, remove the contact lens and consider using a ProKera [corneal bandage device]."

When he performs an epi-off cross-linking procedure, Jodi Luchs, MD, co-director of refractive surgery for the North Shore/Long Island Jewish Health System, says he follows the patient very closely. "I like to see the patient every day or every other day," he says. "And, if I find that the epithelium isn't healing, I'm aggressive with the use of punctal plugs and preservative-free lubricants. I also use the minimum amount of medications that might retard re-epithelialization, such as steroids. I may also cut back on or eliminate the NSAID. You can include ointments along with a preservative-free lubrication, such as bacitracin antibiotic or various other over-the-counter lubricating ointments." Surgeons also say changing the brand of bandage lens can help in some cases.

Close follow-up can also allow the surgeon to remedy the situation, based on what he sees in the exam. "In rare

cases, epithelial cells will be heaped up at the edge of the epithelial defect and won't migrate over," says Toronto surgeon Raymond Stein, who was the first surgeon to perform corneal cross-linking in Canada eight years ago. "If we see that appearance, especially at seven days postop—where most cases would have healed in four or five days—we'll often scrape the edge of the heaped-up epithelium to induce healing."



William Trattler, MD

Haze and a corneal infiltrate appeared two days postop in this cross-linking patient.

Corneal Haze

Surgeons say any time you debride the epithelium, introduce a chemical into the cornea and then bombard it with UV light, haze is a possibility, though they acknowledge that it's less likely in epi-on procedures.

"Haze is very transient," says Dr. Tan. "It starts at about three weeks after surgery, then increases a little for one to two months, and then by six months is almost completely gone. Also, it's not more than 1+ haze, and is so mild many patients often don't realize they have it."

As in many postop situations, complications can be interrelated, and this appears to be the case with corneal haze and re-epithelialization. "Haze is also related to a delay in epithelial recovery," says Jorge Alio, MD, of Alicante, Spain. "Most of the cases I've seen with this complication are patients in whom the epithelium takes time to recover. This extra time increases the wound healing and this wound healing results in a haze that can take many months to resolve." Dr. Alio says that an over-response to cross-linking can also result in haze. "Over-responders are rare, and occur at a rate of maybe one in 200 cases," Dr. Alio says. "These patients wind up with an extremely flat cornea with a reduction of the myopia to minimal levels postop, and even occasionally the development of hyperopia. In addition to the problem of developing a refractive error that the patient never had before, over-responders can develop corneal haze that can affect the cornea for a long time or can even be permanent. This is rare, but it can happen."

Surgeons say managing corneal haze after cross-linking is similar to dealing with post-PRK haze. "Treat it with a topical steroid such as FML or loteprednol, one drop four or six times per day until the recovery is evident," says Dr. Alio. "Then, decrease the dose with time. The patient should also wear sunglasses whenever he's outside, especially if he lives in a sunny region, because haze increases with sun exposure."

Corneal scarring, which occurred in 2.8 percent of epi-off cross-linking patients in one prospective study, can be a result of dense haze.[1] "If a scar is more peripheral, the patient can still have good vision," says Dr. Luchs. "If the scar is causing some irregular astigmatism, which keratoconus patients have already, the patient may see well as long as the opacity isn't in the center of vision. He can often get good vision with the use of a rigid contact lens or a scleral lens. However, if a scar is dense and large enough, and interferes with the line of sight, the surgeon's only recourse may be a corneal transplant."

Inflammation

Surgeons say opening up the epithelium also leaves the eye vulnerable to sterile inflammatory infiltrates as well as the rare case of infection.

If a patient develops sterile infiltrates, a complication that occurred in 7.6 percent of eyes in one study,[1] surgeons say they'll increase the steroid dosage. If an entity is infectious, however, it naturally poses a greater diagnostic and management challenge. "Number one: Culture it," says Dr. Luchs. "Often, most physicians will be able to tell the difference between an infection and a sterile infiltrate. But when in doubt, treat it as infectious. This involves increasing the antibiotics to every hour or every two hours depending on the clinical appearance and the cultures, and then proceed accordingly. Also, reduce your steroids."

To help decrease the infection risk, Dr. Tan pretreats the eye for two days preop with antibiotics. "I use a combination of tobramycin and levofloxacin," he explains. "I like to include tobramycin because it's inexpensive and sometimes you'll have a patient with a gram negative bacterial infection, which is susceptible to tobramycin. I believe infections with cross-linking develop after the operation. Usually, it's because the patient hasn't been following the postop regimen: He hasn't been instilling the eye drops or his contact lens has become contaminated. Handling the contact lens and placing it in the eye postop must be done under sterile conditions."

Corneal cross-linking can trigger a reactivation of herpes simplex virus, and some surgeons consider a history of HSV a contraindication to cross-linking.[2] If you are going to proceed with cross-linking in a patient with a history of herpes, surgeons recommend antiviral prophylaxis preop and continuing into the postop period. If someone develops herpes simplex keratitis postop, treat it aggressively. "If you see herpes," recommends Dr. Trattler, "the patient needs topical ganciclovir, Zirgan and/or oral Valtrex. My regimen for any herpes keratitis is Zirgan five times a day for a week to 10

days, and Valtrex 500 mg t.i.d."

If you think you're dealing with a case of herpes keratitis, stop and really scrutinize the eye, because it could be a notorious masquerader, the pseudodendrite. "A pseudodendrite is caused by an atypical healing response in which the epithelium from one side of the cornea meets the epithelium from the other side and creates the appearance of a herpes dendrite in the area where they meet," says Dr. Stein.

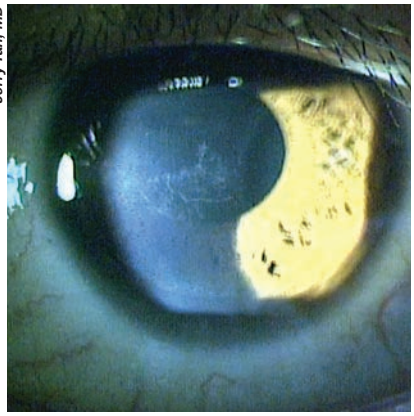
Endothelial Issues

To prevent the treatment from damaging the endothelium, surgeons say adherence to the cross-linking protocol is crucial, especially with regard to corneal thickness.

Dr. Stein says a patient with a thin cornea is a concern. "We know we need a cornea around 400-µm thick to be safe with corneal collagen cross-linking, since this prevents the UV light from damaging the corneal endothelium," he says. "We've found that there are a variety of riboflavin drops that can induce swelling in the cornea. For patients with a clear cornea, even if their corneal thickness is as low as 320 µm, we can induce enough swelling with these drops to get their cornea above 400 µm to allow us to perform cross-linking safely. The drop is a hypotonic solution of riboflavin, and we have ours made up by a specialty pharmacy in Toronto. There are other drops that are available in Europe, and quite a few compounding pharmacies can make them."

Dr. Stein says he's seen patients have a stromal reaction postop that includes some edema, but hasn't had any permanent corneal edema after cross-linking. "This would be a serious issue and, if it happened, you'd be concerned about damage to endothelial cells," he avers. "But as long as we've been respecting the 400-µm minimum thickness, we haven't seen it."

In the rare instance that there does



Jerry Tan, MD

Surgeons say that most cases of corneal haze after cross-linking are transient.

appear to be some endothelial damage, Dr. Luchs says all may not be lost. "Were it to happen, the first thing you want to do is simply wait," he says. "The endothelium can recover after undamaged endothelium slides in and takes over the function in the area where the damaged endothelium had been present. You can often see some visual recovery over time after this happens; the endothelium could be damaged but not dead, and there could be potential for recovery. In general, you want to wait at least three months after the onset of the problem for endothelial recovery. If recovery doesn't occur, then you have to consider some sort of transplantation procedure, whether it be DSAEK or, more likely since these corneas are usually already misshapen, a full-thickness transplant."

Treatment Failure

Though it's not a complication per se, an undesirable outcome of cross-linking would be for the patient's corneal disease to continue to progress.

Dr. Stein says that, in his experience, most cases will remain stable. "In general, if the patient's corneal steepness is 58 D or less, there's a 98- to 99-percent chance that the cornea will be stable after cross-linking and won't need an additional treatment," he says. "We'll wait six to 12 months before observing that, because it's hard to tell if the cornea's stabilizing on topography maps before six months. However, if we see progressive steepening after six months we'd become concerned and offer a second treatment." Retreatments are performed exactly like the primary treatment, surgeons say.

Dr. Trattler says that a cornea in which keratoconus progresses after cross-linking isn't exactly a failure, it just had a severe case of the disease. "When you do a cross-linking treatment, you make the cornea stronger," he says. "So, if a cornea is exceptionally weak, and you then strengthen it by a certain amount, it still might not be strengthened enough to keep it from progressing. It's kind of like a barrier in the road that may slow a car but not stop it. In that case, you might need two barriers. In cross-linking, a second treatment strengthens the cornea further. Hopefully, with a second treatment you get a stiff enough cornea that it doesn't progress anymore. One key that we've learned is, if you want to reduce the chance of failure in a cross-linking patient, stress to him to not rub his eyes. Rubbing contributes to progression."

Dr. Luchs says that, when the proper protocols are followed, corneal cross-linking is, on balance, a safe and effective procedure. "We have something on the order of 16 years of data demonstrating the efficacy of this procedure for keratoconus," he says. "The upside of this procedure is high: Patients can lock down their disease in an early state before it progresses and prevent the need for a corneal transplant in their lifetime. And the downside risk is very small because of the low risk of complications, especially with epithelium-on but even with epi-off procedures. Patients have very little to lose, and everything to gain." REVIEW

1. Koller T, Mrochen M, Seiler T. Complication and failure rates after corneal crosslinking. J Cataract Refract Surg 2009;35:8:1358-62.
2. Kymionis GD, Portaliou DM, Bouzoukis DI, et al. Herpetic keratitis with iritis after corneal crosslinking with riboflavin and ultraviolet A for keratoconus. J Cataract Refract Surg 2007;33:1982.


Targeting Fas in Retinal Disease

Novel research is exploring protecting photoreceptors and the retinal pigment epithlium in multiple models of retinal disease.

David M. Kleinman, MD, MBA, Rocherster, N.Y., and David N. Zacks, MD, PhD, Ann Arbor, Mich.

There is a significant unmet need for next-generation retinal therapeutics capable of improving visual outcomes in age-related macular degeneration, retinal detachment and other diseases in which damage to photoreceptors and the underlying retinal pigment epithelium limits long-term visual function. Recent work on photoreceptor survival and death in animal models of retinal detachment and AMD, along with clinicopathologic correlations, have led to a better understanding of the role of apoptosis and the Fas pathway in human retinal disease. As the common final pathway of RPE and photoreceptor cell death, Fas-mediated apoptosis represents an excellent clinical target. Inhibitors of the Fas pathway amenable to local delivery have been identified and evaluated in animal models of retinal detachment and AMD, where they show promising early signs of efficacy.

Background

The last decade has witnessed tremendous improvements in the medical and surgical management of retinal diseases, including the introduction of anti-vascular endothelial growth factor therapy, long-acting corticosteroid implants and small-gauge vitrectomy. These technologies have benefited patients tremendously, leading to a marked reduction in vision loss resulting from a broad spectrum of retinal diseases. However, despite these advances, significant vision loss still occurs, both in the acute disease setting and over time in chronic diseases such as AMD.

For example, although 95 percent of AMD patients with a new choroidal neovascular membrane maintain vision for the first two years following the initiation of anti-VEGF therapy, stability is traditionally defined as less than 15 letters lost. As such, a significant percentage of patients with wet AMD lose some vision despite the early initiation of therapy, successful resolution of macular fluid and prevention of major complications, such as submacular hemorrhage or disciform scarring. This vision loss can occur within weeks or months and is likely due to molecular pathways triggered within the retina. Similarly, patients undergoing chronic treatment for wet AMD show significant amounts of progressive vision loss despite the initial stabilization afforded by anti-VEGF therapy. The SEVEN-UP study documented a mean loss of 8.6 ETDRS letters in study subjects over an average of 7.3 years, and 34

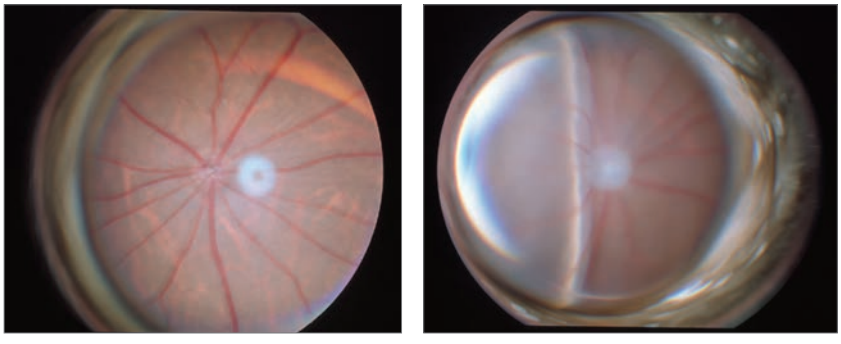


Figure 1. Example of experimentally induced retinal detachment in rat model.[4]

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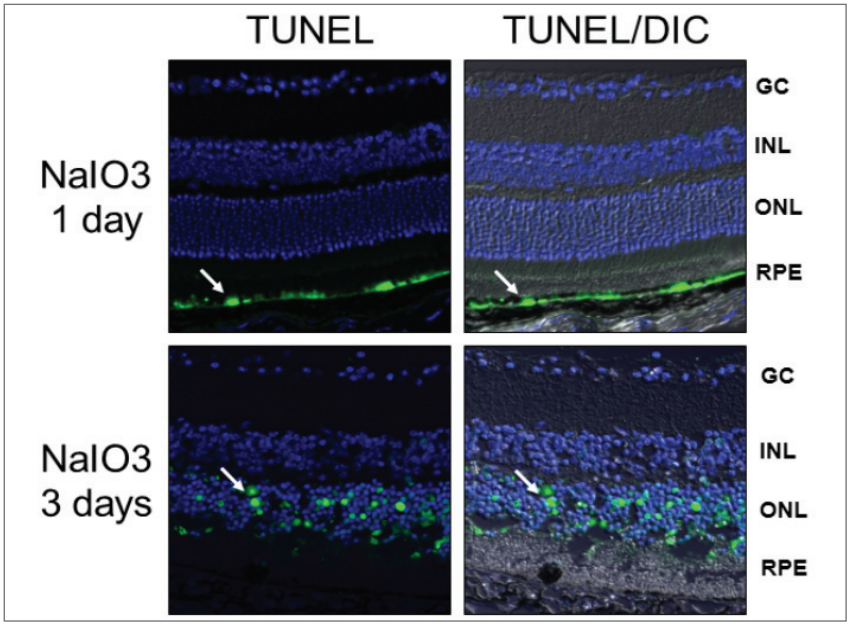

Figure 2. Retinal pigment epithelium apoptosis precedes photoreceptor apoptosis after NaIO3 treatment. TUNEL staining is apparent in RPE layer at day one, followed by increased TUNEL in photoreceptors at day three. *(Besirli CG, et al. IOVS 2011;52:ARVO E-Abstract 4458.)*

percent showed visual acuity decreases by 15 letters or more. Macular atrophy was detected in 98 percent of study eyes.[1] These findings are clinically relevant and concerning, as otherwise functional individuals develop visual disability that leads to suffering and loss of independence.

There are equally important visual impairment concerns related to dry AMD, which is present in all wet AMD patients. Here, though, the critical pathological processes do not necessarily involve VEGF upregulation. While anti-VEGF therapy may be able to effectively limit a rapid worsening of central visual function due to wet AMD in a vast majority of treated individuals, it has little effect on the progression of retinal atrophy due to the underlying dry component. This issue is critical as dry AMD accounted for approximately 55 percent of patients with AMD in 2000, and its impact on the AMD patient landscape is growing. With dry AMD projected to affect nearly 3 million Americans by 2020, it is readily apparent that an alternative therapeutic approach is needed to address vision loss in these patients.[2]

Even though AMD often dominates the retinal disease discussion, there are also less prevalent conditions leading to significant vision loss for which retina specialists are seeking better therapies. An example is macula-off retinal detachment, which affects about 25,000 people in the United States each year. Surgical therapy for retinal detachment is highly effective at re-attaching the retina but it is unable to consistently prevent vision loss caused by the condition. A recent prospective trial in macula-off retinal detachment showed that the average postoperative visual acuity at one year was 0.57 logMAR or approximately 20/70.[3] Clearly, a pharmacologic approach that could be combined with surgical care to improve visual outcomes in macula-off retinal detachment would provide great value to both patients and physicians. Interestingly, it may be through investigating non-neovascular retinal disease such as retinal detachment that new targets for enabling the preservation of vision, generally, are better understood.

It is widely known that photoreceptor cell death is the ultimate cause of permanent vision loss across a wide spectrum of retinal diseases. A series of studies evaluating photoreceptors in animal models of retinal detachment and cadaver eyes has enhanced our understanding of retinal and RPE cell survival and death. Specifically, it is now understood that Fas-mediated programmed cell death, including apoptosis, plays a critical role in photoreceptor loss in many retinal diseases. Disruption of photoreceptor-RPE homeostasis leads to upregulation of the Fas receptor and Fas ligand and the initiation of programmed cell death. Retinal detachment is the obvious leading example of this disruption, since the photoreceptors are physically separated from the RPE by subretinal fluid as is seen in a neurosensory detachment. Evidence is mounting that other disease processes also trigger these same cellular events seen in retinal detachment. It is worthwhile to take a closer look at the evidence pointing to the role of Fas in photoreceptor and RPE cell death in several key retinal diseases, and at potential therapeutic agents.

Apoptosis & the Role of Fas in RD

Researchers have studied the mechanism of photoreceptor cell death in retinal detachment in a rat model of the condition. Photoreceptors were found to show well-known characteristics of apoptosis such as pyknotic nuclei, TUNEL positive staining and caspase activation.[4] Additional work with this model demonstrated a time-dependent formation of the FAS-receptor/FAS-ligand complex following experimental detachment, as well as upregulation of the Fas receptor and Fas ligand.[5] Confirming the role of the Fas pathway in photoreceptor cell

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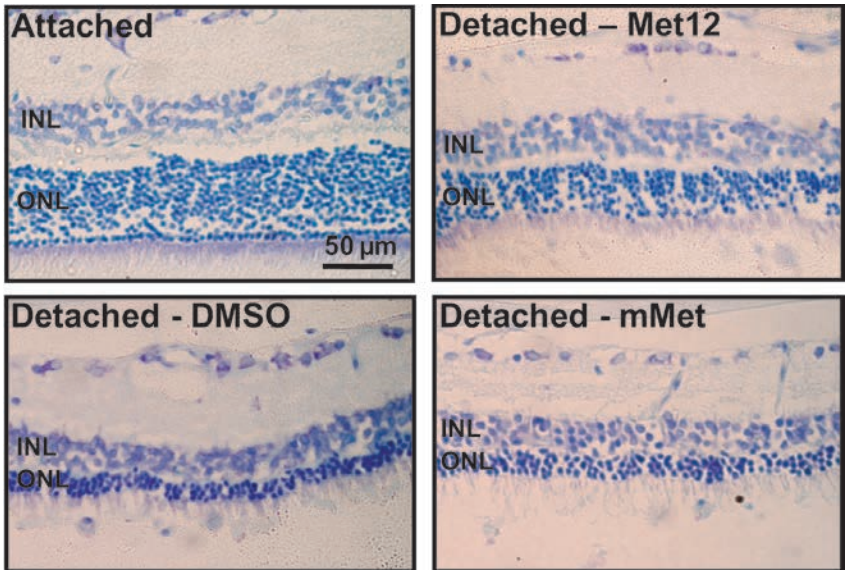

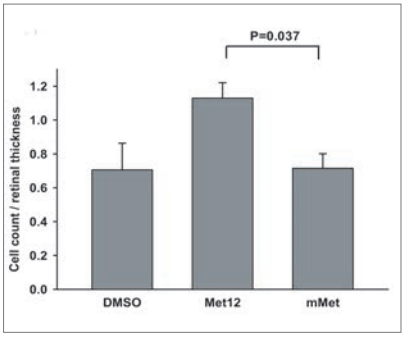

Figure 3B. Outer nuclear layer cell counts normalized to retinal thickness.[25]

Figure 3A. Representative photomicrographs show decreases in caspase activation and number of TUNEL-positive cells corresponding to increased long-term survival of photoreceptors. Retinas were detached in the presence of Met12 (50 ug), scrambled peptide mMet (50 ug) or vehicle (dimethylsulfoxide), injected into the subretinal space at the time of detachment. Eyes were enucleated after two months of detachment, and paraffin sections were stained with 0.5% toluidine blue. INL: inner nuclear layer; ONL: outer nuclear layer.[25]

death, researchers have showed that inhibition of the Fas receptor in this model leads to photoreceptor survival in treated vs. control eyes.[6-8]

An important correlation to human disease was provided by a separate clinicopathologic case series in which retinal tissue fragments were excised during retinal detachment surgery and subsequently analyzed microscopically. The outer nuclear layer (location of the cell bodies of the photoreceptors) showed TUNEL positivity, leading to the conclusion that human photoreceptor cells follow a similar pattern of apoptosis to that seen in animal models.[8] Taken together, this research suggests that it is likely that photoreceptor cell death due to apoptosis (and to a lesser degree, necroptosis*) is a major cause of reduced vision in macula-off retinal detachment. Inhibiting Fas-receptor activation should lead to improved photoreceptor cell survival in the clinic.

*(*Necroptosis is a more organized form of necrosis in which cellular components are released into the extracellular space rather than packaged into apoptotic bodies for degradation, which occurs in apoptosis. Retinal detachment also leads to necroptosis of the photoreceptor. Activation of necroptosis, however, is downstream of the Fas-receptor. Blocking Fas-receptor activation prevents both photoreceptor apoptosis and necroptosis.[26] Thus, apoptosis and necroptosis are triggered by the upstream activation of the Fas receptor by Fas ligand.)*

Fas Activation in Wet AMD

The hallmark of wet AMD is the development of a choroidal neovascular membrane. CNV, in turn, leads to leakage of plasma into the subretinal space, as well as intraretinal edema. Alterations in the relationship between the photoreceptor layer and the RPE thus occur at a very physical level. Clearly, although the extent of fluid collecting under the neurosensory retina may be much greater in a bullous macula-off retinal detachment, the fundamental process is similar—a separation between the RPE and photoreceptors. And, not surprisingly, photoreceptor apoptosis has been demonstrated in a mouse model of laser-induced CNV. Further research with cadaver eyes provides clinical support for photoreceptor death by apoptosis through the demonstration of TUNEL-positive staining and Fas receptor upregulation in the macular region of human eyes with wet AMD.[11] Additionally, work on both surgically excised CNV in AMD and on relevant animal models has described apoptosis in RPE cells.[12,13]

This information is important for several reasons. First, it confirms activation of the Fas pathway in wet AMD in humans. Second, it shows that the RPE as well as photoreceptors undergo Fas-induced apoptosis in human retinal disease. Third, the death of the RPE will inevitably lead to a separation between RPE and photoreceptors in wet AMD. Thus, a mechanism for both RPE and photoreceptor apoptotic cell death in wet AMD has been identified.

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection is contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous floaters, intraocular pressure increased, and vitreous detachment.

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

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For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

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

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Manufactured by:
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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

Fas Activation in Dry AMD

The role of Fas-mediated photoreceptor apoptosis also extends to the area of dry AMD, as supported by data from both animal and human studies. In animal models of retinal degeneration, including light-induced damage in rats and in mice strains with genetic mutations, the death of photoreceptors via apoptosis has been clearly demonstrated. It has been proposed that despite different species, genotypes and phenotypes, photoreceptor apoptosis is the final common pathway in these pathological processes.[14-18] Additionally, more than a decade of clinical research into the underlying mechanisms of exudative AMD has delivered findings that support the likelihood that dry AMD leads to photoreceptor cell death via Fas-induced apoptosis.[11,19]

But what of the RPE? Even if in dry AMD photoreceptors die from a pathway amenable to intervention such as targeting the Fas receptor, is it realistic to think that vision in patients could be preserved over significant periods of time when the RPE—which provides critical metabolic support to the photoreceptor—is also dying? The answer is likely that for long-term retinal stability both functional RPE and photoreceptors are needed. If, however, RPE cells were dying in dry AMD from the same pathway as the photoreceptor, then it is possible that a therapeutic agent targeting that pathway could be beneficial to both cell types.

To this end, evidence is mounting that the RPE does die through Fas-induced apoptosis:

- Human RPE cells normally express low levels of the Fas receptor; oxidative stress regulates the expression of Fas-receptors in the RPE; and stressed human RPE shows increased Fas receptor expression.[20,21]
- Dry AMD, Fas and changes to the blood retinal barrier are implicated in a positive feedback loop leading to RPE apoptosis.[22]
- Aging in animal models is associated with increased blood concentration of soluble Fas ligand, a finding that also correlates with a risk factor for dry AMD—age.[23]
- In a sodium-iodate RPE toxicity model, RPE cells die by apoptosis before photoreceptors secondarily die by apoptosis. *(Besirli CG, et al. IOVS 2011;52:ARVO E-Abstract 4458.)*

Based on this broad collection of research, it is highly likely that vision loss in dry AMD is a Fas-dependent apoptotic process and the Fas pathway leads to cell death in both photoreceptors and RPE cells. Accordingly, the opportunity to simultaneously target RPE and photoreceptor survival via a single inhibitor of Fas-receptor activation is feasible.

Inhibitors of Fas Activation

Fortunately, therapeutic agents capable of inhibiting Fas activation exist. Furthermore, these agents are amenable to ocular delivery. Approaches include a Fas-receptor-neutralizing antibody, small inhibitory RNA against the Fas receptor and a small peptide inhibitor of the receptor. Each approach has demonstrated decreased rates of apoptosis of photoreceptors following experimental retinal detachment.[24,25] In particular, a small peptide inhibitor called Met12, which originated from knowledge of the met oncoprotein, has shown significant promise in this setting.

Today, as outgrowths of experimental work on Fas and apoptosis in retinal detachment, novel research is being conducted on protecting photoreceptors and the RPE in multiple models of retinal disease. Molecules identified in the laboratory may promise patients better visual outcomes in the face of retinal detachment, AMD and other retinal conditions. A clear link between Fas pathway activation and a number of blinding human retinal diseases has been successfully demonstrated, leading to the belief that Fas inhibition represents a potential breakthrough approach aimed at preserving vision in at-risk patients. ONL Therapeutics Inc., a biopharmaceutical company developing novel therapies for preserving sight in a range of retinal diseases, has recently identified a more potent analog of Met12, and is planning to initiate clinical studies in 2016. REVIEW

Dr. Kleinman is a part-time associate professor of ophthalmology at the Flaum Eye Institute at the University of Rochester where he specializes in the medical and surgical care of patients with retinal disease. He has spent more than 10 years working in retinal pharmaceutical development and currently serves as the chief medical officer at ONL Therapeutics Inc.

Dr. Zacks is a professor of ophthalmology and a clinician-scientist at the University of Michigan, Kellogg Eye Center. Over the past 15 years his research has focused on the molecular regulatory mechanisms controlling photoreceptor death or survival in retinal disease. He is a co-founder of ONL Therapeutics and serves as its chief science officer.

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Keys to Success as a **Corneal Surgeon**

A host of suggestions from **the professional to the personal** on achieving long-lasting satisfaction.

By Edward Holland, MD

Early in my ophthalmic career I decided that I wanted to become a corneal surgeon. I can still remember the photo of the perfectly centered, clear penetrating keratoplasty with the perfectly symmetric running suture in place. I knew immediately that I wanted to perform that surgery.

Corneal disease can result in profound visual loss, and corneal transplantation can provide near normal vision to many patients. Corneal surgery now more than ever encompasses a variety of diverse surgical procedures that go far beyond penetrating keratoplasty and frequently result in outstanding visual outcomes. For many decades, penetrating keratoplasty was the predominant procedure performed for many corneal disorders. Over the last decade, new techniques of lamellar surgery allow for replacing only the layers of the corneal that are abnormal and leaving the normal layers: endothelial keratoplasty (DSEK and DMEK) for endothelial disease; DALK for stromal disease; and ocular surface transplantation for epithelial disease. In addition keratoprosthetic devices, laser vision correction, collagen cross-linking, intrastromal implants are additional procedures that have greatly expanded the scope of practice of corneal surgeons.

I have been fortunate enough to have a career as a corneal surgeon and strongly recommend this field to any resident looking to subspecialize. The following concepts are what I feel have been important keys that I feel have helped me in my career as a corneal surgeon:

• ***Find a mentor.*** Most residents have the opportunity to work with several corneal surgeons during their residency. Identify the corneal surgeon who you believe has the willingness and wisdom to guide you during your residency and assist you in selecting the most appropriate fellowship for you. I was fortunate to have access to one of the most talented and skilled corneal surgeons and teachers in the United States during my residency. Dick Lindstrom was the director of the cornea service at the University of Minnesota. As a first year resident I sought out Dick's guidance. He is a superb surgeon, great clinician and talented researcher. Dick was a tremendous mentor to me during my residency. He was always willing to take time to talk and give great counsel to me. Dick continues to be a trusted friend and advisor to this day.

Your fellowship is one of the most important years of your life. Seek the program and the fellowship director who is the best fit for your goals both as a fellow and a practicing corneal specialist. I have been fortunate to help train 45 corneal fellows during my career. I am a colleague, collaborator and friend to many of my former

fellows, and I feel I learn as much from them as they learn from me after they finish and establish successful corneal practices.

• ***Practice your surgical techniques.*** The cornea, more than any structure of the eye, allows for the practice of surgical techniques. Eye banks are very willing to provide eyes for training. Take advantage of this opportunity. Beginning corneal surgeons often have trouble with efficiently tying sutures. As residents no longer perform a significant number of extracapsular cataract surgeries, they do not get the opportunity to master suturing. Hours of practice will make suturing second nature. This practice method can be utilized throughout a corneal surgeon's career. As new techniques are developed, such as in the case DSEK and DMEK, eye bank eyes can be taken to the operating room and corneal surgeons can practice these procedures until they're comfortable and ready to perform these surgeries on patients.

• ***Collaborate with colleagues both within and outside your practice***. It is valuable to discuss surgical techniques and case management with other clinicians throughout your career. Having an ongoing interaction with other corneal surgeons whom you trust is an important asset. This collaboration has kept me current and continues to make me a better clinician and surgeon. Never be unwilling to learn, and always keep an open mind to new ideas and surgical techniques.

I have been fortunate to work with some very talented corneal surgeons who have guided and challenged me throughout my career. At the Cincinnati Eye Institute, we have many skilled cornea and cataract surgeons. My anterior segment partners such as Michael Nordlund, Robert Osher, Michael Snyder and Michael Hater continue to teach me surgical innovations.

It is more of a challenge but in many ways more important to seek colleagues outside of your practice as trusted advisors. Steve Lane, Eric Donnenfeld, Mark Mannis and Roger Steinert are a few of the many individuals that have taught, motivated and inspired me. I have found my continued interaction with these talented individuals invaluable to my career. I have also sought to reach out to the next generation of corneal surgeons to keep me current and on the cutting edge. Terry Kim and Barry Lee among others are the next wave of leaders, and I have enjoyed working with and learning from them.

• ***Join and participate in ophthalmic organizations***. By being active in the various ophthalmic societies you can keep your education current and allow you to help shape your field. The American Academy of Ophthalmology is vital to all ophthalmologists and should be supported. With regard to corneal surgery itself, the American Society of Cataract and Refractive Surgery (ASCRS) and its Corneal Clinical Committee, the Cornea Society and the Eye Bank Association of America (EBAA) are the most important organizations to the field of corneal surgery. Be active in these organizations and seek leadership positions. Corneal surgeons' involvement is desperately needed and vital to the assurance that the eye banking system in the United States continues to be successful at providing an adequate amount and a high quality of corneal tissue for our patients. The EBAA needs physician leadership for the development of medical standards, for the accreditation of Eye Banks and for interaction with the Food and Drug Administration, to name a few of the important physician activities. The Cornea Society is an essential organization for education and policy making for the specialty of cornea. Numerous committee positions are available for physician involvement. ASCRS is the educational and political voice for all anterior segment surgeons and its Corneal Clinical Committee is yet another opportunity to participate in corneal education and policy making. It is important to attend major meetings to continue progressing your education. It is also very rewarding to work in these organizations' committees and lead the educational efforts to shape the future of corneal surgery. Engagement in the activities in these societies will not only make you a better corneal surgeon but will make you a more well-rounded person, particularly in the areas of business, politics and process.

• ***Stay current with new techniques.*** It is easy to get complacent and not adopt new surgical techniques especially later in one's career. For most of my career, penetrating keratoplasty made up the vast majority of the corneal surgery that I performed. As stated above, the last decade has seen new, innovative surgical procedures. It wasn't easy to learn all these new techniques. Change can be difficult. If surgeons don't continue to stay current, like learning the latest endothelial keratoplasty techniques or the DALK procedure, their patients won't receive the best surgical options and eventually the field will pass the surgeon by. Surgeons should challenge themselves to be on the cutting edge and perform the most innovative surgeries like they did just after their

fellowship and also seek modifications or improved instrumentation to make the procedures safer, easier and better. A surgeon should continue to evaluate where he is in comparison to the rest of his colleagues throughout his career.

• ***Diversify your practice.*** In order to avoid the potential monotony of what you do, it is worthwhile and stimulating to develop a variety other aspects to your activities in addition to patient care.

1. Be active in clinical research and teach at major meetings. Every busy clinician has potential data that can be evaluated and reported. The involvement in clinical research keeps you current and involved. The concept of being "academic" has certainly changed over the years. One does not have to have an appointment at a university to be "academic." I know clinicians who practice at universities who do not publish papers, contribute to textbooks or present at meetings. Their entire effort is the delivery of patient care. On the other hand, I know clinicians in private practice who conduct clinical research, publish papers and book chapters and present at meetings and are involved in the major ophthalmic organizations. Which is the more "academic" clinician? We all have something to contribute.

2. Work with industry as a consultant or become involved in clinical trials. Lately some individuals in government and the press portray interaction with industry as a negative activity. On the contrary, I have found collaboration with industry to be valuable for me and a benefit to my patients. It is an opportunity to help develop new products, and physician involvement is critical for this development. Working with industry also allows my patients access to the latest technology or medications. I have found that the majority of patients are interested in clinical research and are supportive of my involvement.

• ***Find balance in your life.*** One of the most difficult challenges we all have is finding the right balance between work, family, friends and personal interests. Maintaining surgical skills and devoting your life to patient care takes significant time out of your life. We should all remember to allot and protect time for family and for ourselves. This proper balance keeps you grounded. Life outside your practice should be as fulfilling as your work life. Family and close friends help stabilize your life and keep things in the right perspective. It is easy to get too caught up in career and forget those who have stood beside you. Make time for them while you can and don't put it off until later, as later may never come.

Being a corneal surgeon is an enormously fulfilling career and one that allows a surgeon to make a tremendous impact on the quality of life of patients. The above keys have helped to make my career interesting, rewarding and given me the ability to provide what I hope has been the highest of quality of care for my patients. REVIEW

Dr. Holland is the director of cornea services at Cincinnati Eye Institute and a professor of ophthalmology at the University of Cincinnati. He served as the president of the American Society of Cataract and Refractive Surgery from 2011 to 2012, and was a member of the Executive Committee and now serves as the program chair. He was a member of the Board of Trustees for the American Academy of Ophthalmology. He has been the Secretariat of the AAO's Annual Meeting. He was awarded the AAO's Life Achievement Honor Award in 2012. Contact Dr. Holland at eholland@holprovision.com.

(continued from page 51)

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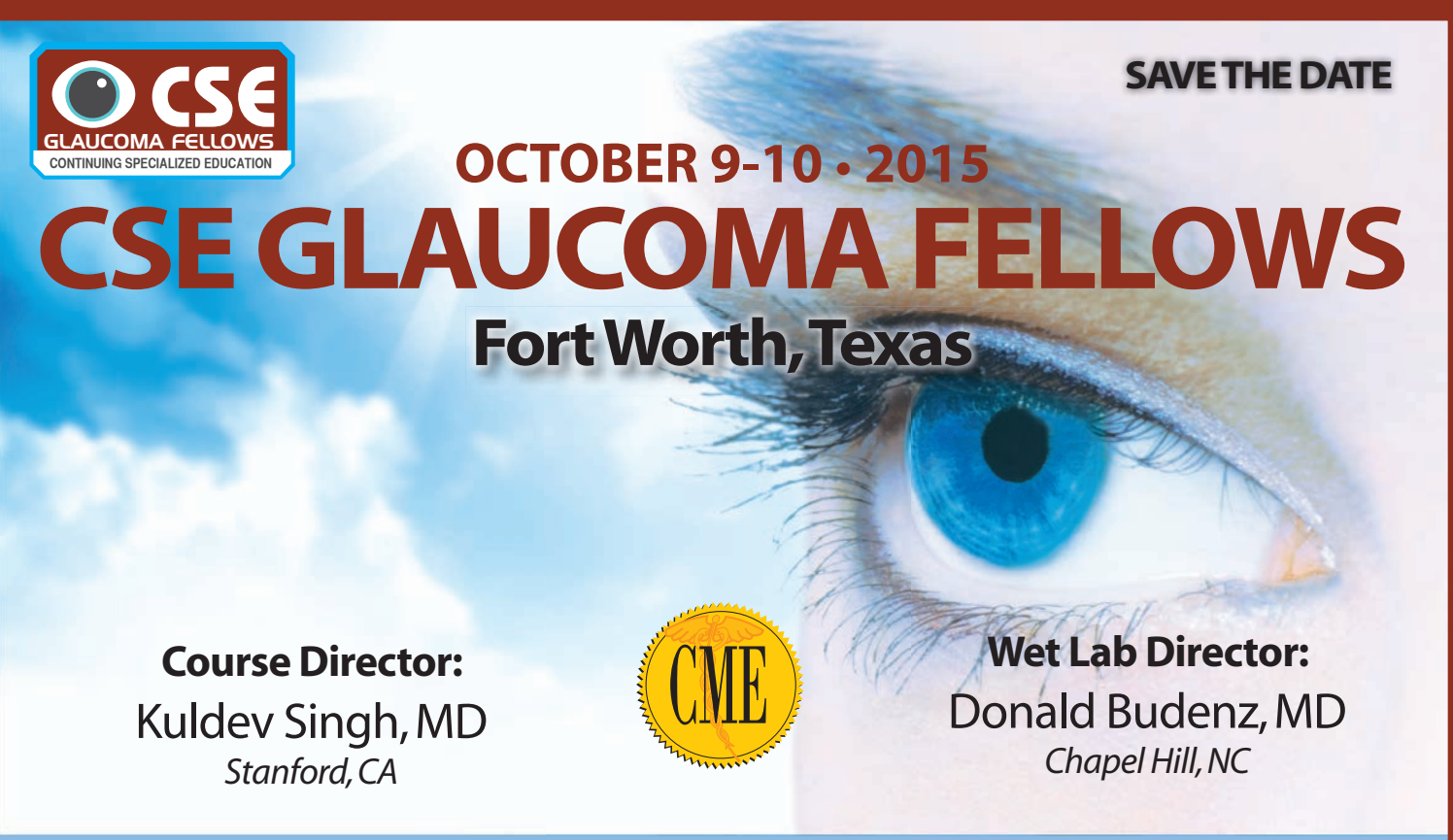

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Breaking Down the Enigma of Dry Eye

A look at the science behind the development of lifitegrast, and where it fits into the therapeutic puzzle.

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

It's not a stretch to equate the science and art of medical diagnosis with wartime code-breaking, the likes of which is portrayed in books and films such as *The Imitation Game*. Each patient is a transmission to be decoded, interpreted and added to the sum of data that allows us to translate the disease signs and symptoms into a tractable etiology to which we can then direct a strategic response. Dry eye represents a disease with an exceedingly complex encryption: Signs and symptoms of the disease appear to rise and fall independently and are subject to variation according to time of day, season, weather and a handful of other factors. Deciphering the dry-eye disease code is complex, and we have yet to translate that code into a diagnostic rubric that can point the way to a broadly applicable therapeutic.

The current treatment paradigms include tear substitutes, punctal plugs, autologous serum drops, topical steroids or calcineurin inhibitors.[1] Despite some refinements in recent years, these therapeutic options provide limited relief for most dry-eye patients. At the same time, methods of clinical assessment have been slow to evolve with our understanding of dry eye as a disease of multiple etiologies and a long, diverse natural history. Further complications arise from complexities that can cloud efficacy measures, including large and variable placebo effects and compensatory mechanisms such as altered blink behavior.[2]

Efforts to surmount these two issues appear to have hit pay dirt with the recent clinical development of the integrin antagonist lifitegrast (Shire). Knowledge of immune-cell interactions led to the identification of a new drug target, while progress in clinical research helped to define patient populations in ways that allow for apples-to-apples clinical assessment and an optimal chance for a therapeutic breakthrough. This month, we will look at lifitegrast and examine its unique mechanism of action and the path that led to recent clinical success and an upcoming review by the Food and Drug Administration.[3]

Inflammation Is Key

In the search for therapeutic options it's thought that one of the keys to a successful dry-eye treatment is to address the fundamental importance of inflammation in the disease,[4,5] even though to date most anti-inflammatories have been found lacking in some way. Our best anti-inflammatory treatments, corticosteroids, act by diminishing expression of the cytokines and other signaling molecules, and thus dampening the entire response machinery. While they do provide relief for some patients, overall the response is mixed, and prolonged ocular steroid therapy is problematic.[6] We are left to seek other targets in the inflammatory cascade for potential therapeutic intervention.

An inflammatory response can be initiated by any number of events, including trauma and bacterial or viral infiltration. *(See the May 2014 Therapeutic Topics for an in-depth review of ocular inflammation.)* The initial response awakens an intercellular protein complex called an inflammasome that converts preformed interleukin precursors, especially IL-1β and IL-6, to their active forms.[7,8] These are released into circulation where they act as attractants for leukocytes, granulo-

This article has no commercial sponsorship.

cytes and macrophages that congregate at the sites of insult. Immune cell recruits propagate and amplify the initial response with the release of additional cytokines, and also respond to chemo-attractants to move to the site of inflammation and initiate vasodilation and extravasation of immune cells out of circulation and into the inflamed tissues. This cycle is normally self-limiting, but in some conditions an inappropriate, chronic inflammatory state develops.

On the horizon, there are new therapies that target steps in this inflammation pathway, and one of the most promising of these is lifitegrast, a topically active compound that is specifically designed to disrupt the cell-to-cell interactions following the initial inflammatory trigger. The target for lifitegrast is Lymphocyte Function Antigen-1, first identified as a membrane protein required for cytotoxic T cell activity.[9] The literature surrounding LFA-1's importance is somewhat confusing because it was independently identified as LFA-1, as a dimeric surface marker of lymphocyte cell differentiation (CD11/CD18), and as the integrin dimer $\alpha_L\beta_2$.[10,11] In understanding how lifitegrast can elicit an anti-inflammatory response, it's most useful to consider the drug target as a member of the integrin family, a class of proteins that mediate cell-to-cell contact and communication.[12,13]

There are several protein families that have been implicated in the cell-to-cell communication that's key to immune-cell recruitment: cell-adhesion molecules; selectins; and integrins.[11-13] Through a combination of interactions between proteins on the immune cell surface and their surroundings, cells are mobilized to sites of inflammation response. This recruitment involves several specific, pairwise interactions between the cells and their surrounding endothelium. Movement of leukocytes and other cells through small arterioles and capillaries occurs by a rolling mechanism in which selectins bind and unbind with opposing glycoproteins at relatively low affinity; some integrins may also participate in this process. Key to this phase of the recruitment process is the low affinity that allows the cells to move over the endothelial surface.

When the rolling cell arrives at or near the site of trauma, local cytokine release has already been at work, increasing expression of endothelial cell adhesion molecules like ICAM-1 and V-CAM. These are the receptors for leukocyte integrins $\alpha_L\beta_2$ and $\alpha_4\beta_1$. Surface expression of both ICAM-1 and V-CAM is upregulated by IL-1β and by interferon-γ,[14,15] and the binding of ICAM-1 to $\alpha_L\beta_2$ is a high-affinity interaction that blocks the leukocyte rolling and triggers cytoskeletal rearrangements within the endothelial cell, leading to increases in permeability, breakdown of extracellular matrices and an increase in the access of leukocytes to interstitial space.[16]

The regulated expression of ICAM-1 is a key event in the inflammatory process and in the pathological subversion of that process that occurs in dry eye. Several studies have demonstrated an increase in ICAM-1 expression in both humans and dogs diagnosed with keratoconjunctivitis sicca.[17,18] Perhaps more important were studies demonstrating that antibodies directed against ICAM-1 or LFA-1 could decrease inflammatory infiltration in a mouse model of ocular inflammation.[17] These studies validated the LFA-1/ICAM interaction as an appropriate therapeutic target.

Early work targeting this interaction focused on specific regions of each molecule involved in the binding interaction.[19] Using these binding domains as a template, Thomas Gadek, PhD, currently CEO of Rogne Bioscience, and his colleagues tested a series of isoquinolones for their ability to interfere with LFA-1 binding to ICAM-1. One of these, designated SAR 1118, bound to LFA-1 and blocked subsequent interaction with

Integrins as Drug Targets

DRUG	TARGET INTEGRIN	INDICATION	STATUS	COMMENTS
Abciximab (Reopro; Janssen Biologics), **Eptifibatide** (Integrilin; Merck),	α2b	Thrombosis	FDA-approved	thrombocytopenia limits use
Cilengitide (Merck) **Intetumumab** (Janssen Biologics)	α5	Glioblastoma, other metastatic cancers	Phase II/III	variable effects on survival; may be used in combination therapies
Natalizumab (Tysabri; Biogen)	α4	Relapsing MS	FDA-approved	rare, fatal adverse effect: progressive multifocal leukoencephalopathy
Vedolizumab (Entyvio; Takeda)	α4	Crohn's, ulcerative colitis	FDA-approved	risk of progressive multifocal leukoencephalopathy
Lifitegrast (Shire)	αL	Dry eye	Phase III	under review at FDA

ICAM-1 with IC50 concentrations in the 1 to 10 nM range.[20] This action blocked infiltration of leukocytes, and attenuated release of inflammatory cytokines *in vitro*, including several that are elevated in dry eye in human tears: INF-γ; IL-1β; IL-6 and IL-10.[21] SAR-1118 (now lifitegrast) is an excellent example of rational drug design: a compound whose structure was refined to optimize antagonist activity, and at the same time pharmacokinetic properties were tailored to best suit a topical medication. This yielded a drug with good ocular absorbance and rapid systemic elimination.[20]

From Lab to Clinic

Preclinical studies confirmed that lifitegrast was an effective anti-inflammatory, and specifically showed significant improvements in dogs diagnosed with KCS.[18] Schirmer's scores increased from a mean value (n=12) of 3.4 mm to 5.8 mm following 12 weeks of treatment. In Phase I studies, the safety of the drug was established, and in particular there was little systemic effect of the drug on lymphocyte markers or other measures of normal immune function.[22] The only limitation to this study was that patients were primarily young (all were under 50, and 75 percent were under 40) and all were male. While this does not represent the typical dry-eye patient, results did confirm that the drug is safe up to doses of 5%.

Like all clinical studies of dry-eye treatments, Phase II and Phase III trials of lifitegrast faced the difficulty of a diverse pool of potential study patients and the high variability seen in both signs and symptoms of the disease. To address this, a Phase II dose-ranging study used ORA's controlled adverse environment model.[23] A total of 228 subjects participated in this prospective, multicenter, randomized, placebo-controlled, double-masked study, with patient inclusion enrichment based upon CAE responses. As part of the inclusion criteria, subjects for the study had to show a consistent exacerbation in both signs and symptoms of dry eye when exposed to the ocular stress of the CAE. The CAE consists of a specialized room (either a permanent site or a mobile unit) where humidity, temperature and air-flow are regulated. In this setting, potential subjects are exposed to environmental conditions associated with dry eye. Those who showed no evidence of worsening of signs and/or symptoms following exposure to the CAE were not eligible for enrollment in the study. Use of the CAE allows for a focus on those patients with the most reproducible disease. These patients represent an optimized study population that provides the best response window in which to assess treatment efficacy.

The primary endpoint was improvement in inferior corneal staining versus placebo at 12 weeks, and although the study did not meet this criterion for any of the three treatment groups, there was strong evidence of dose-dependent improvements in staining, and a consistent improvement in all groups compared with placebo. Inferior staining for both 1% and 5% lifitegrast was significantly improved when compared to baseline measures, and dose-dependent improvements in other secondary signs, such as Schirmer's tests, were also significant.

Another promising result from the Phase II study was that symptomatic improvements in dry eye were also seen.[22] Compared to baseline measures, dose-dependent improvements in ocular surface disease visual function scores were statistically significant ($p<0.05$) with both 1% and 5% lifitegrast.

In addition, the Ora ocular discomfort score also showed dose-dependent improvements and was significantly improved ($p=0.044$) for the group receiving the 5% dose.

With these encouraging results, the follow-up Phase III (OPUS-1) study looked at signs (inferior corneal staining) and symptoms (visual function component of OSDI) in a population of 588 dry-eye subjects.[23] This trial used the same protocol used for the Phase II study, including CAE-based inclusion criteria and the Ora Calibra staining scales, a refined system of assessment optimized for measures of staining due to dry eye. Use of this grading scale involved training the investigators in the use of a metric distinct from traditional Oxford or National Eye Institute scales; in this way efficacy measures benefit from greater uniformity of assessment. The staining scores reflected this: mean change from baseline staining for 5% lifitegrast was highly significant at $p=0.0208$ (Phase II), and $p=0.0007$ (Phase III). While OSDI visual function improvements did not reach statistical significance, symptomatic improvements, including eye dryness ($p=0.029$) and Ora ODS ($p=0.0273$) were both significantly improved.

Collectively, the Phase II study and the OPUS-1 trial demonstrated a remarkable degree of reproducibility, a key goal for any drug development program and a particularly encouraging one for an indication such as dry eye, which is known for its variable nature. A second Phase III study with a larger patient population (n=720; NCT01743729) confirmed the ability of lifitegrast to provide clinically meaningful symptomatic relief for dry eye sufferers.

In recent years, a number of new therapies for dry eye have faced clinical hurdles because of the disconnect between signs and symptoms of the disease. This is what we've referred to as the enigma of dry eye. The development program exemplified by lifitegrast gives us hope that we may have cracked the code. Clearly, a better understanding of the underlying

pathophysiology and a rational approach to development of new chemical entities can be critical elements to solving this puzzle. Equally important is a rigorous approach to clinical design, including CAE-based inclusion criteria and optimized clinical scales. These improvements should provide the therapeutic bandwidth necessary to decipher the challenge that is dry eye. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School, and emeritus surgeon at the Massachusetts Eye and Ear Infirmary. Mr. Ousler is vice president of dry eye at Ora Inc. Dr. McLaughlin is a medical writer at Ora Inc.

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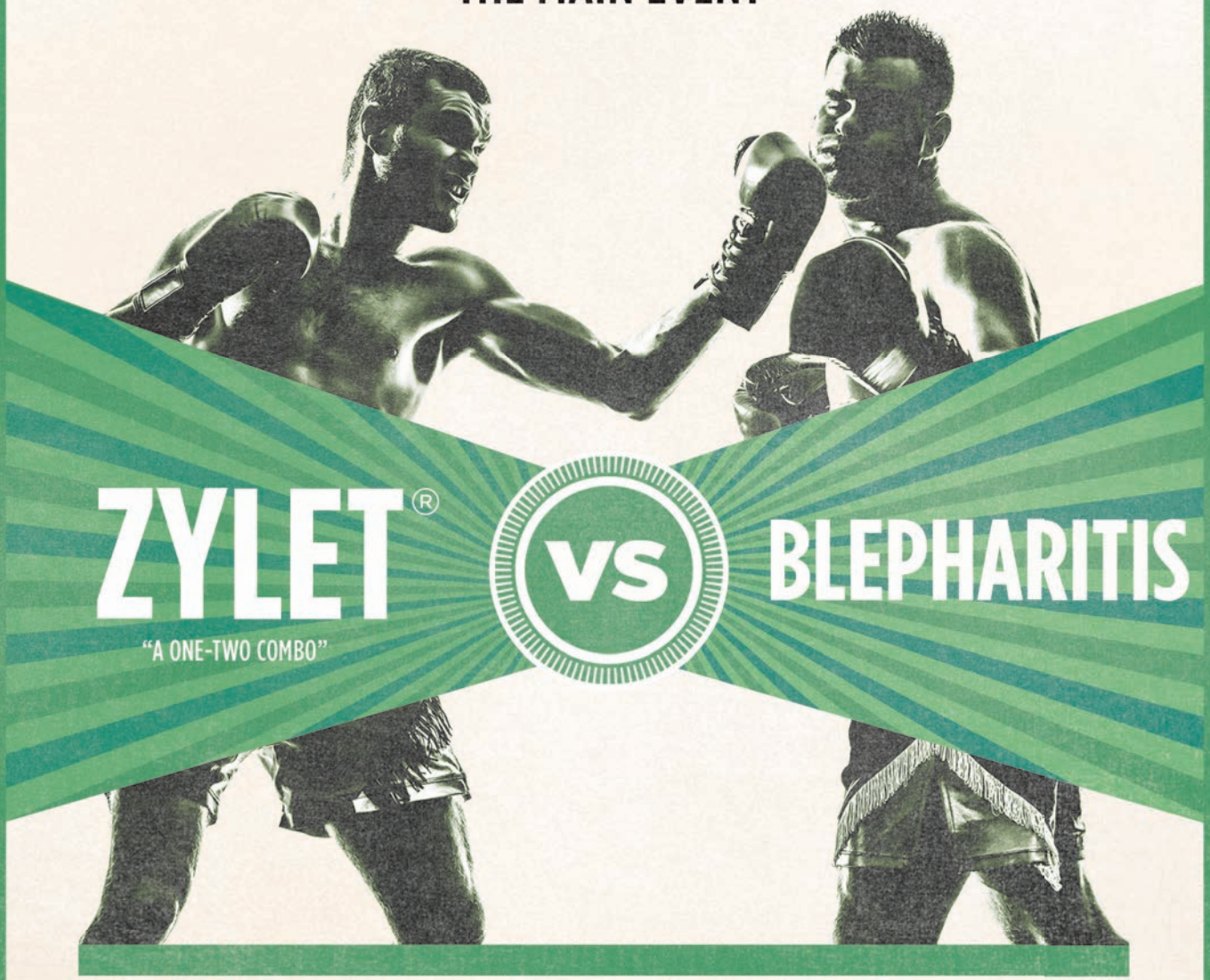

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INDICATIONS AND USAGE

ZYLET® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension) is a topical anti-infective and corticosteroid combination for steroid-responsive inflammatory ocular conditions for which a corticosteroid is indicated and where superficial bacterial ocular infection or a risk of bacterial ocular infection exists.

Please see additional Indications and Usage information on adjacent page, including list of indicated organisms.

INDICATIONS AND USAGE (continued)

Ocular steroids are indicated in inflammatory conditions of the palpebral and bulbar conjunctiva, cornea and anterior segment of the globe such as allergic conjunctivitis, acne rosacea, superficial punctate keratitis, herpes zoster keratitis, iritis, cyclitis, and where the inherent risk of steroid use in certain infective conjunctivitides is accepted to obtain a diminution in edema and inflammation. They are also indicated in chronic anterior uveitis and corneal injury from chemical, radiation or thermal burns, or penetration of foreign bodies.

The use of a combination drug with an anti-infective component is indicated where the risk of superficial ocular infection is high or where there is an expectation that potentially dangerous numbers of bacteria will be present in the eye.

The particular anti-infective drug in this product (tobramycin) is active against the following common bacterial eye pathogens: *Staphylococci*, including *S. aureus* and *S. epidermidis* (coagulase-positive and coagulase-negative), including penicillin-resistant strains. *Streptococci*, including some of the Group A-beta-hemolytic species, some nonhemolytic species, and some *Streptococcus pneumoniae*, *Pseudomonas aeruginosa, Escherichia coli, Klebsiella pneumoniae, Enterobacter aerogenes, Proteus mirabilis, Morganella morganii*, most *Proteus vulgaris* strains, *Haemophilus influenzae*, and *H. aegyptius, Moraxella lacunata, Acinetobacter calcoaceticus* and some *Neisseria* species.

IMPORTANT SAFETY INFORMATION

- ZYLET® 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. 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.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- 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 a slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infections. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Employment of 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.
- Most common adverse reactions reported in patients were injection and superficial punctate keratitis, increased intraocular pressure, burning and stinging upon instillation.

Please see Brief Summary of Prescribing Information on the following page.

With a one-two combo in the treatment of blepharitis and other steroid-responsive ocular conditions with the risk of bacterial infection, PRESCRIBE ZYLET® TODAY.

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Zylet®
loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension

BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use Zylet safely and effectively. See full prescribing information for Zylet.

Zylet® (loteprednol etabonate 0.5% and tobramycin 0.3% ophthalmic suspension)

Initial U.S. Approval: 2004

DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

Apply one or two drops of Zylet into the conjunctival sac of the affected eye every four to six hours. During the initial 24 to 48 hours, the dosing may be increased, to every one to two hours. Frequency should be decreased gradually as warranted by improvement in clinical signs. Care should be taken not to discontinue therapy prematurely.

2.2 Prescription Guideline

Not more than 20 mL should be prescribed initially and the prescription should not be refilled without further evaluation [*see Warnings and Precautions (5.3)*].

CONTRAINDICATIONS

4.1 Nonbacterial Etiology

Zylet, as with other steroid anti-infective ophthalmic combination drugs, 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

5.1 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.

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 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 a slit lamp biomicroscopy and, where appropriate, fluorescein staining.

5.4 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. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

5.5 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).

5.6 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.

5.7 Aminoglycoside Hypersensitivity

Sensitivity to topically applied aminoglycosides may occur in some patients. If hypersensitivity develops with this product, discontinue use and institute appropriate therapy.

ADVERSE REACTIONS

Adverse reactions have occurred with steroid/anti-infective combination drugs which can be attributed to the steroid component, the anti-infective component, or the combination.

Zylet:

In a 42 day safety study comparing Zylet to placebo, ocular adverse reactions included injection (approximately 20%) and superficial punctate keratitis (approximately 15%). Increased intraocular pressure was reported in 10% (Zylet) and 4% (placebo) of subjects. Nine percent (9%) of Zylet subjects reported burning and stinging upon instillation.

Ocular reactions reported with an incidence less than 4% include vision disorders, discharge, itching, lacrimation disorder, photophobia, corneal deposits, ocular discomfort, eyelid disorder, and other unspecified eye disorders.

The incidence of non-ocular reactions reported in approximately 14% of subjects was headache; all other non-ocular reactions had an incidence of less than 5%.

Loteprednol etabonate ophthalmic suspension 0.2% - 0.5%:

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.

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.

Tobramycin ophthalmic solution 0.3%:

The most frequent adverse reactions to topical tobramycin are hypersensitivity and localized ocular toxicity, including lid itching and swelling and conjunctival erythema. These reactions occur in less than 4% of patients. Similar reactions may occur with the topical use of other aminoglycoside antibiotics.

Secondary Infection:

The development of secondary infection has occurred after use of combinations containing steroids and antimicrobials. Fungal infections of the cornea are particularly prone to develop coincidentally with long-term applications of steroids.

The possibility of fungal invasion must be considered in any persistent corneal ulceration where steroid treatment has been used.

Secondary bacterial ocular infection following suppression of host responses also occurs.

USE IN SPECIFIC POPULATIONS

8.1 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 fixtures) 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 at 0.5 mg/kg/day (6 times the maximum daily 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.

Reproductive studies have been performed in rats and rabbits with tobramycin at doses up to 100 mg/kg/day parenterally and have revealed no evidence of impaired fertility or harm to the fetus. There are no adequate and well controlled studies in pregnant women. Zylet should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 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 that appear in human milk could suppress growth, interfere with endogenous corticosteroid production, or cause other untoward effects. Caution should be exercised when Zylet is administered to a nursing woman.

8.4 Pediatric Use

Two trials were conducted to evaluate the safety and efficacy of Zylet® (loteprednol etabonate and tobramycin ophthalmic suspension) in pediatric subjects age zero to six years; one was in subjects with lid inflammation and the other was in subjects with blepharoconjunctivitis.

In the lid inflammation trial, Zylet with warm compresses did not demonstrate efficacy compared to vehicle with warm compresses. Patients received warm compress lid treatment plus Zylet or vehicle for 14 days. The majority of patients in both treatment groups showed reduced lid inflammation.

In the blepharoconjunctivitis trial, Zylet did not demonstrate efficacy compared to vehicle, loteprednol etabonate ophthalmic suspension, or tobramycin ophthalmic solution. There was no difference between treatment groups in mean change from baseline blepharoconjunctivitis score at Day 15.

There were no differences in safety assessments between the treatment groups in either trial.

8.5 Geriatric Use

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

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate or tobramycin.

Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma TK assay, a chromosome aberration test in human lymphocytes, or in an *in vivo* mouse micronucleus assay.

Oral treatment of male and female rats at 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (500 and 250 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender. No impairment of fertility was noted in studies of subcutaneous tobramycin in rats at 100 mg/kg/day (1700 times the maximum daily clinical dose).

PATIENT COUNSELING INFORMATION

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 pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using Zylet.

MANUFACTURER INFORMATION

BAUSCH & LOMB INCORPORATED

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Based on 9007705-9004405 Revised 08/2013 US/ZYL/15/0014


Steroids for Glaucoma: Both Friend and Foe

These drugs can be both beneficial and harmful—and their effects can vary from patient to patient.

Ronald L. Fellman, MD, Dallas

There's no question that our medications and surgical procedures have beneficial purposes. However, they also have potential downsides and drawbacks. They can be a friend or foe to our patients—and sometimes they're both.

This is a good way to think about the drugs we prescribe, because we need to know not just the ways in which they can be friendly, but also the ways in which they can cause an adverse event. Steroids, in particular, have a long list of positive and negative effects. That makes it especially important to understand how they work in the eye, so you can make well-informed decisions when using them. Here, I'd like to review some of what we know about how steroids work, and why they are both friend and foe.

The Good and the Bad

The biological changes triggered by corticosteroids are extensive and complex. Generally speaking, a steroid receptor in the nucleus of each cell is stimulated by the drug, causing as many as 6,000 genes to be either expressed or suppressed—in other words, turned on or turned off—all within a few hours of exposure to the steroid. Adding to the complexity of the interaction, the biologic response will depend on the type of cell the steroid reaches. A keratocyte, for example, will respond to a steroid differently than a trabecular meshwork cell. Your job is to try to use the steroid to manipulate the genes and get the result you want to address the patient's problem.

Steroids can have a number of positive effects:

• ***They can be anti-inflammatory.*** In the cell nucleus, steroid-activated glucocorticoid receptors attenuate the DNA-mediated release of proinflammatory cytokines and downregulate arachidonic acid. Glucocorticoids also reduce inflammation at the cellular level by inhibiting leukocytes—their concentration, migration and activity.

• ***They reduce vascular permeability.*** This reduces swelling.

• ***They inhibit phagocytosis and the release of growth factors.*** As a result, they inhibit wound healing and fibrosis.

• ***They inhibit fibroblasts, the cytokines that stimulate fibroblasts, macrophages and other factors that attract blood vessel growth***. This helps to limit the wound-healing response.

• ***They reduce scarring.*** This is a primary reason steroids are used after filtration surgery. This effect is the result of multiple biochemical steps, including reducing the recruitment of monocytes and leukocytes.

For these reasons, among others, steroids help improve outcomes after trabeculectomy; they interrupt the wound-healing cycle, allowing filtration to occur. Today, we're very dependent on steroids in glaucoma surgery, to help ensure that the surgery is successful.

Unfortunately, at the same time, steroids can do some counterproductive things:

• ***They can hasten the formation of posterior subcapsular cataracts.*** This is obviously a serious drawback if the patient is phakic.

• ***They can cause immunosuppression.*** As a result, for example, if someone uses a steroid drop for a long time, a fungal keratitis may develop.

• ***They can cause elevated intraocular pressure.*** Close to 35 per-

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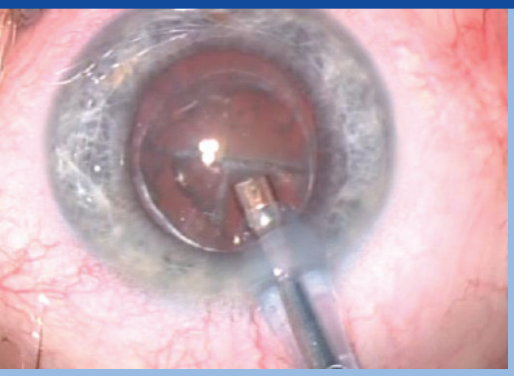

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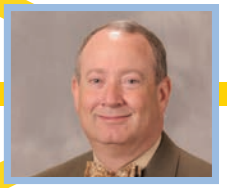

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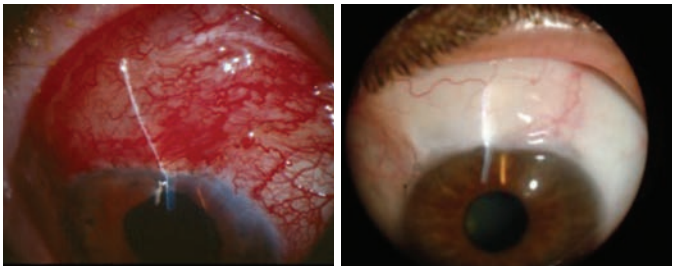
cent of people have a worrisome rise in pressure with topical steroid use. This was studied by Mansour F. Armaly, MD, back in the 1960s. He put steroid drops in one eye of normal volunteers three times a day for a month. He found that there were three levels of responders: In 66 percent of the people the pressure went up by less than 5 mmHg. In about 30 percent, pressure increased by 6 to 15 mmHg. In about 5 percent the pressure went up more than 15 mmHg. These numbers suggest that you need to worry about one out of every three people in the healthy population having a steroid response.



Proper use of steroids can make a huge difference in the way a bleb turns out. Left: A bleb that's injected, red and going to scar down, thanks to insufficient modulation of wound healing. Right: a healthy, functioning bleb resulting from appropriate use of steroids.

Dr. Armaly also noted that in the low-response group, IOP increased for two weeks and leveled off. But in the intermediate and high-response groups, IOP continued to rise for four weeks—and we don't know how long that rise continued. This suggests that checking IOP at two to four weeks may not be adequate to determine how high steroids will push the IOP in individuals who are intermediate- or high-level steroid responders.

What Causes the IOP Increase?

The problem of steroids causing an increase in IOP has been known to be an issue for about 65 years. Studies have demonstrated that the reason the pressure goes up when steroids are being used is increased resistance to outflow.[1]

As noted earlier, generally speaking, a steroid receptor in the nucleus of each cell is stimulated by the drug. In a normal trabecular meshwork cell, the glucocorticoid receptors in the nucleus come in two types: alpha and beta. The beta receptor is believed to inhibit the alpha receptor, whose job is to manufacture extracellular matrix, or ECM, which can clog up your drainage system by forming a kind of soup around the cell. Normally the beta receptors modulate the degree of alpha expressivity, ensuring that the alpha receptors don't make too much ECM, thus striking a balance that tends to maintain good outflow. However, in trabecular meshwork cells from glaucoma patients, there is an imbalance of the two receptors—a lack of expressivity of the beta cells. Therefore, the alpha receptors are left unchecked, leading to an excess of ECM that clogs up the outflow system.[2] The bottom line is that the outflow system in patients who are high and moderate steroid responders becomes constipated. The pressure builds, and the patient ends up with steroid glaucoma.

It's worth noting that steroid glaucoma and open-angle glaucoma look very similar. It's certainly possible that non-steroid-related glaucoma has something to do with the alpha and beta receptors. Some people may simply be born with fewer beta receptors or receptors with less expressivity, making the person more susceptible to glaucoma because of excess ECM production by the less-inhibited alpha receptors. (This would also make these individuals more likely to be steroid responders.)

Steroids also have other negative effects on outflow that probably contribute to elevating the IOP:

• In addition to causing cells to make more ECM, steroids also inhibit the mechanisms that degrade ECM that help to keep the channels open. That results in increased accumulation of ECM and debris in the trabecular meshwork.

• Steroids cause cross-linking of actin, which alters the trabecular cytoskeleton. Cross-linking the actin makes any blockage stronger and less permeable to flow.

• Steroids inhibit phagocytosis by trabecular meshwork cells, reducing the elimination of blockages.

• Steroids increase cell adhesion in the tight junctions. This may be the reason steroids inhibit blood vessel leakage, but you don't want this in glaucoma. If the cells are more tightly bound together in the meshwork, they're less likely to let fluid pass.

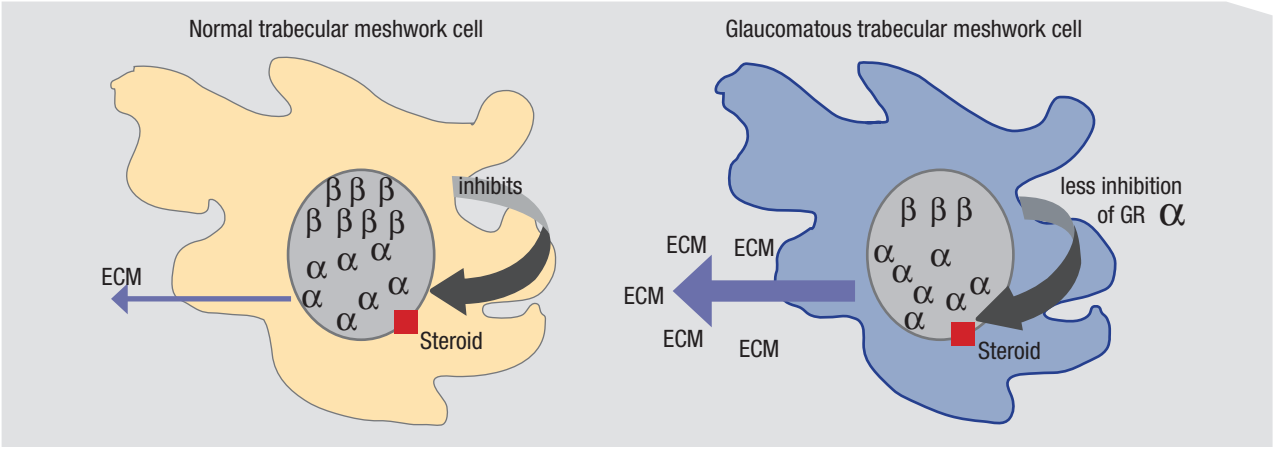
Of course, these changes are unlikely to lead to increased pressure if the patient has a functioning tube or trabeculectomy; those allow fluid to escape the eye regardless of any blockage in the trabecular meshwork.[3]

Other Considerations

Because the negative effects of steroids can be serious, it's important to remember a few other things:

• ***Systemic absorption from topical drops is significant because it avoids first-pass hepatic metabolism normally seen with a pill.*** The steroid in topical drops is systemically absorbed through the nasal mucosa, just as happens with glaucoma drops such as beta blockers, allowing them into the bloodstream. One reason this is problematic is that it bypasses what is called "first-pass hepatic metabolism." When you take a steroid in pill form, it goes into your gastrointestinal tract and ends up being partially detoxified by your

Glucocorticoid Receptors in Glaucoma vs. Healthy Trabecular Meshwork Cell Nuclei



A normal trabecular meshwork cell nucleus contains both alpha and beta glucocorticoid receptors. The beta receptors are believed to inhibit the alpha receptors, whose job is to manufacture extracellular matrix, which can clog up your drainage system. Glaucoma patients' cells have fewer beta receptors, causing the alpha receptor to overproduce ECM, clogging the outflow system.

liver before it enters the bloodstream. In contrast, when a drug is absorbed through the nasal mucosa, it's like giving it intravenously. That's why topical drops can have so many side effects; they're not detoxified in their first pass through the body.

• ***Steroids in the vitreous can remain there for months.*** Kenalog or triamcinolone injected intravitreally can stay in the eye and have both positive and negative effects for months. They may provide significant help in addressing disease processes, but at the same time, they can make intraocular pressure increase.

• ***Once a steroid has been systemically absorbed, it can affect both eyes.*** No matter how a steroid is used in the eye or in the body, it will get into your bloodstream. One of the consequences of this is that using a topical steroid in one eye can cause an IOP rise in the fellow untreated eye. You can see this effect with other drugs as well; if you put an aqueous suppressant like timolol in one eye to lower the pressure, it gets into your bloodstream and the pressure in the other eye goes down a little bit. Since steroids may cause a pressure increase, this unintended effect on the fellow eye is of more concern.

Strategies for Success

Given the pros and cons of steroid use, it's crucial to be on the lookout for trouble and take steps to protect your patient. These strategies can help:

• ***Be aware of which patients are most likely to have a steroid-induced IOP increase.*** People falling into this category include:

— *Glaucoma suspects, primary open-angle glaucoma patients and low-tension glaucoma patients.* Studies show that if you have POAG, it's almost a guarantee that steroids will cause your pressure to go up. Dr. Armaly found that 95 percent of POAG patients have a significant rise in pressure when treated with steroids. In one of his POAG studies, glaucoma patients who were off of their drops had an average IOP of 26 mmHg; with steroid drops, 50 percent of POAG patients had an IOP above 40 mmHg at two weeks.[1] (I've seen pressure double in four or five days in a glaucoma patient on a q.i.d. steroid.) Likewise, almost 100 percent of low-tension glaucoma patients are steroid responders. Even glaucoma suspects have a much higher risk of a pressure rise than the general population.

— *Kids 4 to 6 years old.* They can have a significant pressure rise.

— *First degree relatives of patients with POAG.*

— *Patients with myopia.* This is especially likely in people with more than 5 D of myopia.

— *Type I diabetics.*

— *Previous steroid responders.*

— *Anyone suffering from traumatic glaucoma.* The reason for this is not yet clear.

— *Patients with Fuchs' dystrophy or keratoconus who have had penetrating keratoplasty.*

Interestingly, if you have pseudoexfoliation glaucoma or narrow-angle glaucoma, you're not at increased risk of being a steroid responder. The reason isn't clear, but whatever the genetic issue is in POAG patients, it doesn't appear to be present in narrow-angle patients.

This list of likely steroid responders should always be in the back of your mind if you're prescribing steroids for any reason.

• ***If a patient is on the list of likely steroid responders, adjust your treatment accordingly.*** Try prescribing a weaker steroid. For example, switch from Pred Forte to milder prednisolone acetate. Reduce the frequency of administration.

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Consider switching to an NSAID.

Also, check the patient's pressure frequently. If you're starting an at-risk patient on a steroid via any route—intravitreal, drops, periocular or oral—check IOP every two weeks, then monthly for two or three months; then every three to six months, depending on the type of risk factor the patient has.

• ***Consider having the patient use eyelid closure to minimize systemic steroid exposure from topical drops.*** When you put a drop in your eye and blink, that pumps some of the drug into your nose; from there, some is absorbed into your bloodstream. Simply keeping your eye closed for two or three minutes after putting in the drop prevents this from happening, increasing the absorption of the drug into your eye and decreasing the systemic absorption. Studies have shown that this can reduce systemic absorption by 60 percent.[4,5]

Another strategy people sometimes use to restrict the flow of drug into the nose is pressing a finger on the punctum. I don't use this approach simply because I don't like having patients put their fingers near their eyes. People don't wash their hands that often, so this is riskier than simply closing the eye. Also, studies have found that nasal lacrimal occlusion and eyelid closure have similar success in reducing the systemic level of topically applied eye drops.[5]

It's very common that the fellow eye's pressure goes up after we do a filter. This almost certainly is the result of systemic absorption of the steroids used after surgery. If a patient has this problem, you may want to have the patient try eyelid closure; this simple strategy may bring the pressure back down in the other eye.

• ***If a problem persists and causes glaucomatous or optic neuropathy, consider glaucoma surgery.*** Trabeculectomy and tube surgery allow the fluid an escape that doesn't depend on getting through a blocked trabecular meshwork. Most patients who don't have preexisting glaucoma who get a pressure rise with steroids are very responsive to glaucoma drops. However, glaucoma patients who are already on several drops and then get a pressure rise in response to a steroid may need to have surgery in order to control the pressure.

• ***Be alert for systemic steroid problems caused by absorption of the topical drops.*** As already noted, a steroid drop placed on the eye will be at least partly absorbed systemically. In addition to possibly causing the pressure to rise in the fellow eye, systemic absorption can cause problems such as gastrointestinal ulcers. (I've seen this happen in patients taking a lot of steroid drops.)

• ***Be aware of the condition of the optic nerve.*** How much more pressure can it handle without further damage? Obviously it won't handle much if the eye already has glaucomatous damage. In that situation, be especially conservative with your use of steroids and generous in your follow-up schedule.

• ***Remember that MIGS may not protect the patient from a steroid-related pressure rise.*** Minimally invasive glaucoma surgeries are getting a lot of attention these days. However, we've learned the hard way that MIGS won't always protect you from a pressure rise related to steroids—unlike a trabeculectomy, where you've created an artificial external drain that keeps the pressure low.

Most MIGS surgeries, such as a stent or some kind of trabecular bypass or trabeculotomy, are designed to get the trabecular meshwork to flow better. If you use a lot of steroids in those people, the pressure can still go up. This may seem odd, but a recent study by Darryl R. Overby, PhD, may provide an explanation. We always used to think that steroids only clogged the upstream collector systems, like the trabecular meshwork. Now we're learning that they can also clog things downstream, past the point at which you've opened up the outflow system with your MIGS. Dr. Overby's study, using a mouse model, showed that fibroblasts in the downstream collector channels can turn into myofibroblasts, making excess ECM and clogging up the downstream collectors.[6] The bottom line is that even though you've successfully done MIGS, it may not be as protective in steroid-responsive patients.

Striking a Balance

When it comes to prescribing

Patients Most Likely to Have a Steroid-induced IOP Increase

- Primary open-angle glaucoma patients
- Low-tension glaucoma patients
- Glaucoma suspects
- Kids four to six years old
- First degree relatives of patients with POAG
- Patients with myopia
- Type I diabetics
- Previous steroid responders
- Anyone suffering from traumatic glaucoma
- Patients with Fuchs' or keratoconus who have had penetrating keratoplasty

Note: Among healthy patients, about one in three will have a significant steroid-related pressure increase.[1] Patients with pseudoexfoliation glaucoma or narrow-angle glaucoma are generally not at increased risk of being a steroid responder.

drugs, the physician's job is to balance the friend with the foe. This is particularly challenging with steroids. For this reason we have to be very careful when we give our patients steroids. Clearly we use them for specific positive purposes, but we have to make sure we find the best drug, the best concentration, the best frequency, the best route of delivery—which might be topical, peribulbar, intravitreal or systemic—and only have the patient use it as long as necessary. We have to know which patients are at the greatest risk of suffering an adverse effect from the steroid. We need to consider eyelid closure in susceptible patients to prevent the systemic side effects—especially pressure rise in the fellow eye. And we need to remember that having a glaucoma surgery such as MIGS is not an assurance that the patient won't experience a rise in pressure from corticosteroids.

All of this is very different from our concerns when prescribing a typical glaucoma drop; there's usually just one route to administer it. Of course, even glaucoma drops may occasionally become both friend and foe, causing cystoid macular edema, uveitis, follicular conjunctivitis, dry mouth, dry eye, hypotension, kidney stones, etc. But steroids are particularly potent as both friend and foe. Our practice in Dallas sees glaucoma patients exclusively, making us acutely aware of these issues. But the general ophthalmologist has an even tougher job because it's more difficult to target the steroid responder while treating other diseases that may need steroid intervention. All eye-care providers need to keep the complete steroid picture in the back of their mind, to provide optimal patient care. REVIEW

Dr. Fellman is a clinical associate professor emeritus at the University of Texas Southwestern Medical Center in Dallas, and president of Glaucoma Associates of Texas. He has no financial conflicts with any product discussed in this article.

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Biometry Is the Key to Phakic IOL Success

The more accurate you are at the beginning of the process, surgeons say, the more accurate your result will be at the end.

Walter Bethke, Managing Editor

As the old saying goes, "Use the right tool for the job," and for high myopes many refractive surgeons are grateful to have phakic intraocular lenses in their toolbox. However, even though phakic IOLs are well-suited for these patients, surgeons emphasize they have to be used the right way. In this article, experts well-versed with phakic IOL implantation share the techniques that will help you get the best results with these lenses.

The AMO Verisyse

A common theme with both phakic lenses approved in the United States is the importance of preop biometry.

Jeffersonville, Ind., surgeon Asim Piracha says the first things surgeons should focus on are endothelial cell counts, anterior chamber depth and iris anatomy.

"The new FDA guidelines are strict regarding cell counts," Dr. Piracha says. "The minimum density, based on patient age, is listed on the Verisyse product insert. You want to see a good, dense cell pattern with no guttata.

The second consideration is anterior chamber depth," he continues. "For the Verisyse, you want at least 3.2 mm from the endothelium to the anterior lens capsule. If your device calculates anterior chamber depth and includes the epithelial surface, you have to subtract that corneal thickness amount from the measurement."

The third factor to consider is the iris anatomy. "If the patient has a flat or concave iris, I feel better about implanting the lens," Dr. Piracha says. "If, however, it's convex, raised up anteriorly or has a little elevation to it, there's more risk for posterior synechiae. You can evaluate the iris using a Pentacam or an OCT. Undesirable iris anatomy is more of an issue for hyperopes, however; you hardly ever see convexity in high myopes."

Two unique aspects of the actual surgery are that the Verisyse, which is non-foldable, requires a relatively large incision and is fixated using a special iris enclavation technique that is as much art as it is science. "You make an incision that's a little bigger than 6 mm so you're not squeezing the lens into the wound," Dr. Piracha explains. "If you squeeze it in, you can inadvertently pop it in and ding the capsule. The sideport incisions are about 10 mm apart, which means they're about 2 mm from the lateral edge of the main incision on each side. The key to creating the sideports is to point your blade toward the enclavation site. This is different from the way surgeons usually do it, which is to point the blade toward the pupillary center."

The enclavation of the Verisyse, which roots it in place, involves using special claws on either side of the lens to grab a small piece of iris. "After inserting the lens I rotate it 90 degrees and enclavate the nasal haptic first, because it's a tighter space," Dr. Piracha explains. "There's something of an art to enclavation. First, you grab the IOL. For this step I recommend using an Artisan/Verisyse forceps because it has a kind of platform to it that prevents the lens from flipping like a tiddlywink. Next, I use an enclavation needle on the iris with a motion similar to the rubbing motion you'd use to bunch up a piece of rug. If you're enclavating at 3 and 9 o'clock, start a little superior with the needle then push it inferiorly. This causes a wrinkle in the iris that you then use to enclavate. As to how much iris to enclavate, taking too much will cause ovalization of the pupil, but

taking just a little wisp can result in the lens being dislocated with any trauma. The ideal amount is probably about 1 mm; you want it just overlapping the claw port. As in the story of Goldilocks, the best amount is not too much and not too little."

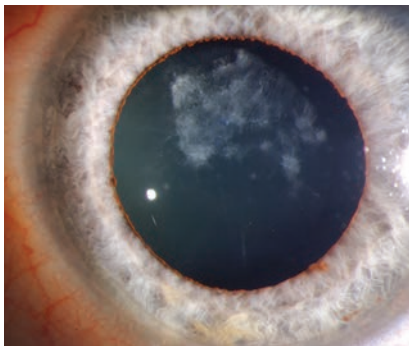
The Staar Visian ICL

As with the Verisyse, preop measurements are crucial to the success of Visian ICL implantation.

"Once you've decided to implant a Visian ICL in a patient, the sizing of the lens will make you or break you," avers Majid Moshirfar, MD, co-director of the cornea and refractive surgery division and professor of ophthalmology at the University of California, San Francisco Medical Center. "There are three keys to determining the proper lens size: the sulcus-to-sulcus measurement; the rise of the anterior capsule; and the amount of myopia."

The problem with inaccurate sizing is it can lead to postoperative issues. "I like the space between the anterior crystalline lens capsule and the Visian ICL to be between 100 and 400 µm," says Dr. Moshirfar. "If you undersize, the vault will be less, and the space between the lens and the ICL will be small, around 50 to 90 µm. If you oversize it, however, it creates a huge vault and, as a result, the space can be 700 to 1,000 µm. In this condition, the iris is pushed forward and the patient can go into a form of angle-closure glaucoma that can cause pressure spikes, corneal edema, atonic pupil and, in some cases, optic nerve damage if the pressure is high for several weeks."

The first aspect, the width measurement, is best done using ultrasound. "We concluded that calipers and a white-to-white measurement wasn't the best way to do it," says Dr. Moshirfar. "Now, the standard is ultrasound biomicroscopy. The Sonomed machine, which scans between 35 and 50 MHz, gives a good sulcus-to-sulcus measurement. It's OK for a tech to measure it, but either you or someone else who's competent in reading ultrasound should interpret it.



Though it's uncommon, anterior subcapsular cataract can occur in an ICL that has an incorrect vault.

"Over the past four years," Dr. Moshirfar continues, "I've also learned that it's not just the sulcus-to-sulcus measurement that's important, but also the shape of the anterior curvature of the crystalline lens. I've seen some eyes in which the curvature of the anterior surface of the crystalline lens has a high rise to it, and they look almost spherical. Then, in other cases, you have myopes in whom the crystalline lens's anterior capsule is instead very flat-looking. Ultrasound or even the Visante OCT can show you the curvature of the anterior surface of the lens to some degree, with UBM being the better choice. Based on the sulcus-to-sulcus measurement and the rise of the anterior capsule, every Visian ICL surgeon has developed a nomogram that gives us less risk of being surprised after surgery. If the rise is steep, I will usually oversize the lens. If it's flat then I will undersize it."

The third aspect of sizing to take into account is the amount of myopia being corrected. "If the power of the ICL is 7 D or less—such as in a forme fruste keratoconus patient on whom I don't want to perform PRK—I usually try to oversize my ICL. So, if my nomogram says to put in a 12.1-mm lens, I put in a 12.6. On the other hand, if I have a correction that's greater than -10 D, I usually try to undersize my ICL; if my nomogram says to implant a 12.6-mm lens, for example, I'll put in the 12.1-mm lens. If someone were to ask which of the factors was most important, I'd say the number one is the sulcus-to-sulcus measurement, as it comprises 90 percent of my decision. Next in importance is the rise of the anterior capsule. Following that, the refractive error would be weighted a few percentage points."

In terms of handling the procedure, Dr. Moshirfar says, for one, he doesn't think the size of the peripheral iridectomy is important, but the location is. "I've had patients do perfectly fine with small peripheral iridectomies," he says. "I think the ones who end up needing a large PI are the patients in whom the sizing wasn't done properly; their vault is too much so the surgeon has to go back and do additional PIs or try to increase the PI's size. I create two YAG PIs two weeks before the surgery. I'm meticulous about the PIs being peripheral and not mid-peripheral. Two weeks later, when I'm in the OR and have completed the lens implantation, I'll bring down the pupil and use an angled Sinksey hook to gently stretch each PI to ensure patency."

Managing the viscoelastic is another step during which surgeons can get into trouble. "I use OcuCoat and don't try to overinflate the anterior chamber, because the more it's inflated, the more I have to take out afterward," Dr. Moshirfar says. "At the end, I remove the viscoelastic with passive irrigation. If you use a coaxial or bimanual I/A system, and the pupil is still dilated, you can cause transient capsular opacification."

Dr. Moshirfar feels that if there are no problems early on with the ICL, that's a good sign. "I'd say if you can properly figure out the lens sizing and the patient doesn't have an issue in the first two weeks postop, you're home free," he says. REVIEW

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- Bacterial infections—Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- 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).
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For additional information about DUREZOL® Emulsion, please refer to the brief summary of Prescribing Information on adjacent page.

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References: 1. DUREZOL (difluprednate ophthalmic emulsion) [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; Revised May 2013. **2.** Korenfeld MS, Silverstein SM, Cooke DL, Vogel R, Crockett RS; Difluprednate Ophthalmic Emulsion 0.05% (Durezol) Study Group. Difluprednate ophthalmic emulsion 0.05% for postoperative inflammation and pain. *J Cataract Refract Surg.* 2009;35(1):26-34. **3.** Fingertip Formulary, November 2014 (estimate derived from information used under license from Fingertip Formulary, LLC, which expressly reserves all rights, including rights of copying, distribution and republication). **4.** WellCare. Medication Guide: 2014 WellCare Classic. WellCare website. https://www.wellcarepdp.com/medication_guide/default. Accessed November 14, 2014. **5.** WellCare. Medication Guide: 2015 WellCare Classic and Simple. WellCare website. https://www.wellcarepdp.com/medication_guide/default. Accessed November 14, 2014. **6.** Humana. Drug guides for Medicare plans 2014. Humana website. https://www.humana.com/medicare/products-and-services/pharmacy/rx-tools/medicare-drug-list/2014-print. Updated October 30, 2014. Accessed November 14, 2014. **7.** Humana. Drug guides for Medicare plans 2015. https://www.humana.com/medicare/products-and-services/pharmacy/rx-tools/medicare-drug-list/2015-print. Updated September 5, 2014. Accessed November 14, 2014.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
Ocular Surgery
DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.
Endogenous Anterior Uveitis
DUREZOL® Emulsion is also indicated for the treatment of endogenous anterior uveitis.

DOSAGE AND ADMINISTRATION
Ocular Surgery
Instill one drop into the conjunctival sac of the affected eye 4 times daily beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.

Endogenous Anterior Uveitis
Instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

DOSAGE FORMS AND STRENGTHS
DUREZOL® Emulsion contains 0.05% difluprednate as a sterile preserved emulsion for topical ophthalmic administration.

CONTRAINDICATIONS
The use of DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active 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 disease of ocular structures.

WARNINGS AND PRECAUTIONS
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 beyond 28 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.

Bacterial Infections
Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.

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 culture should be taken when appropriate.

Topical Ophthalmic Use Only
DUREZOL® Emulsion is not indicated for intraocular administration.

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

ADVERSE REACTIONS
Adverse 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 Surgery
Ocular adverse reactions occurring in 5-15% of subjects in clinical studies with DUREZOL® Emulsion included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in 1-5% of subjects included reduced visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in < 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritus, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.

Endogenous Anterior Uveitis
A total of 200 subjects participated in the clinical trials for endogenous anterior uveitis, of which 106 were exposed to DUREZOL® Emulsion. The most common adverse reactions of those exposed to DUREZOL® Emulsion occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis. Adverse reactions occurring in 2-5% of subjects included anterior chamber flare, corneal edema, dry eye, iridocyclitis, photophobia, and reduced visual acuity.

USE IN SPECIFIC POPULATIONS
Pregnancy
Teratogenic Effects
Pregnancy Category C. Difluprednate has been shown to be embryotoxic (decrease in embryonic body weight and a delay in embryonic ossification) and teratogenic (cleft palate and skeletal) anomalies when administered subcutaneously to rabbits during organogenesis at a dose of 1–10 mcg/kg/day. The no-observed-effect-level (NOEL) for these effects was 1 mcg/kg/day, and 10 mcg/kg/day was considered to be a teratogenic dose that was concurrently found in the toxic dose range for fetuses and pregnant females. Treatment of rats with 10 mcg/kg/day subcutaneously during organogenesis did not result in any reproductive toxicity, nor was it maternally toxic. At 100 mcg/kg/day after subcutaneous administration in rats, there was a decrease in fetal weights and delay in ossification, and effects on weight gain in the pregnant females. It is difficult to extrapolate these doses of difluprednate to maximum daily human doses of DUREZOL® Emulsion, since DUREZOL® Emulsion is administered topically with minimal systemic absorption, and difluprednate blood levels were not measured in the reproductive animal studies. However, since use of difluprednate during human pregnancy has not been evaluated and cannot rule out the possibility of harm, DUREZOL® Emulsion should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

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

Pediatric Use
DUREZOL® Emulsion was evaluated in a 3-month, multicenter, double-masked, trial in 79 pediatric patients (39 DUREZOL® Emulsion; 40 prednisolone acetate) 0 to 3 years of age for the treatment of inflammation following cataract surgery. A similar safety profile was observed in pediatric patients comparing DUREZOL® Emulsion to prednisolone acetate ophthalmic suspension, 1%.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, and Impairment of Fertility
Difluprednate was not genotoxic *in vitro* in the Ames test, and in cultured mammalian cells CHL/IU (a fibroblastic cell line derived from the lungs of newborn female Chinese hamsters). An *in vivo* micronucleus test of difluprednate in mice was also negative. Treatment of male and female rats with subcutaneous difluprednate up to 10 mcg/kg/day prior to and during mating did not impair fertility in either gender. Long term studies have not been conducted to evaluate the carcinogenic potential of difluprednate.

Animal Toxicology and/or Pharmacology
In multiple studies performed in rodents and non-rodents, subchronic and chronic toxicity tests of difluprednate showed systemic effects such as suppression of body weight gain; a decrease in lymphocyte count; atrophy of the lymphatic glands and adrenal gland; and for local effects, thinning of the skin; all of which were due to the pharmacologic action of the molecule and are well known glucocorticosteroid effects. Most, if not all of these effects were reversible after drug withdrawal. The NOEL for the subchronic and chronic toxicity tests were consistent between species and ranged from 1–1.25 mcg/kg/day.

PATIENT COUNSELING INFORMATION
Risk of Contamination
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 emulsion.
Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

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

Contact Lens Wear
DUREZOL® Emulsion should not be instilled while wearing contact lenses. Patients should be advised to remove contact lenses prior to instillation of DUREZOL® Emulsion. The preservative in DUREZOL® Emulsion may be absorbed by soft contact lenses. Lenses may be reinserted after 10 minutes following administration of DUREZOL® Emulsion.

Revised: May 2013
U.S. Patent 6,114,319

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Conventional vs. Accelerated CXL

By studying the effects of different protocols of corneal collagen cross-linking on visual, refractive and tomographic parameters in patients with progressive keratoconus, researchers determined that patients who received accelerated cross-linking with irradiations of 30 mW/cm² for three minutes fared worse at the end of 12 months than conventional cross-linking or accelerated cross-linking of 9 mW/cm² for 10 minutes or 18 mW/cm² for five minutes.

In the study, 138 eyes of 138 patients with progressive keratoconus underwent corneal collagen cross-linking. Following detailed preoperative examination, Group I (n=36) underwent conventional cross-linking (3 mW/cm² for 30 minutes); Group II (n=36), Group III (n=33) and Group IV (n=33) each underwent accelerated cross-linking (Group II: 9 mW/cm² for 10 minutes; Group III: 18 mW/cm² for five minutes; Group IV: 30 mW/cm² for three minutes). Changes in corrected distance visual acuity, spherical equivalent, flat keratometry, steep keratometry, thinnest pachymetry, specular microscopy and demarcation line were studied at six and 12 months.

Improvement in the mean CDVA and SE was seen in all groups at the one-year follow-up period. However, the improvement seen in Group IV (p=0.15 at six months; p=0.17 at 12 months) was not statistically significant when compared with the other groups. Likewise, Group III (p=0.01 at six and 12 months) showed the best results among all groups. Flattening of steep and flat keratometry was significant in Groups I (p=0.01) and II (p=0.01) as compared to the other groups. There was no significant difference in the pachymetry or specular microscopy in any of the groups. Groups I and II demonstrated a good demarcation line when compared to other groups. Groups I, II and III showed better visual, refractive and tomographic improvements at the end of the 12 months.

Am J Ophthalmol 2015;160:243-249.

Shetty R, Pahuja N, Nuijts R, Ajani A, et al.

Refractive Outcomes of Triple DMEK with Cataract Surgery

A retrospective case series including patients with Fuchs' endothelial dystrophy and cataract without coincident pathology found that triple Descemet's membrane endothelial keratoplasty safely achieved excellent corrected distance visual acuity.

Researchers evaluated the outcomes of 108 sequential triple DMEK procedures, including the use of toric IOLs in select cases. Within the mean follow-up of 11.9 months, the median CDVA was 20/20 (range: 20/15 to 20/40) and the median uncorrected distance visual acuity in eyes with a distance target (n=84) was 20/40 (r: 20/20 to 20/200). Additionally, 45 percent of patients gained three or more lines of CDVA.

The median refractive error was +0.43 D (interquartile range: -0.34 to +1.17 D). Aspheric intraocular lenses (n=91) did not significantly change refractive astigmatism (mean: preoperative +0.926 ±0.144 D [SD]; postoperative +0.945 ±0.129 D; p=0.83), while toric IOLs (n=9) did (mean: preoperative +2.47 ±0.36 D; postoperative: +0.94 ±0.90 D; p=0.0015). The anterior curvature measured by Scheimpflug imaging (Pentacam) did not significantly change (mean: -0.06 ±0.47 D; p=0.41); however, keratometry by partial coherence interferometry (IOLMaster) did (mean -0.6 ±0.9 D; p<0.0001).

The selection of the optimum IOL power is complicated by several factors. Because Fuchs' dystrophy induces changes predominately in the central cornea, measurements averaging curvature over a larger area might underreport significant refractive deviations. In the absence of an algorithm to more precisely individualize IOL calculations, a refractive target of -0.75 to -1 D will help reduce the proportion of eyes left hyperopic.

J Cataract Refract Surg 2015; 41:1182-1189.

Schoenberg E, Price Jr. F, Miller J, McKee Y, Price M.

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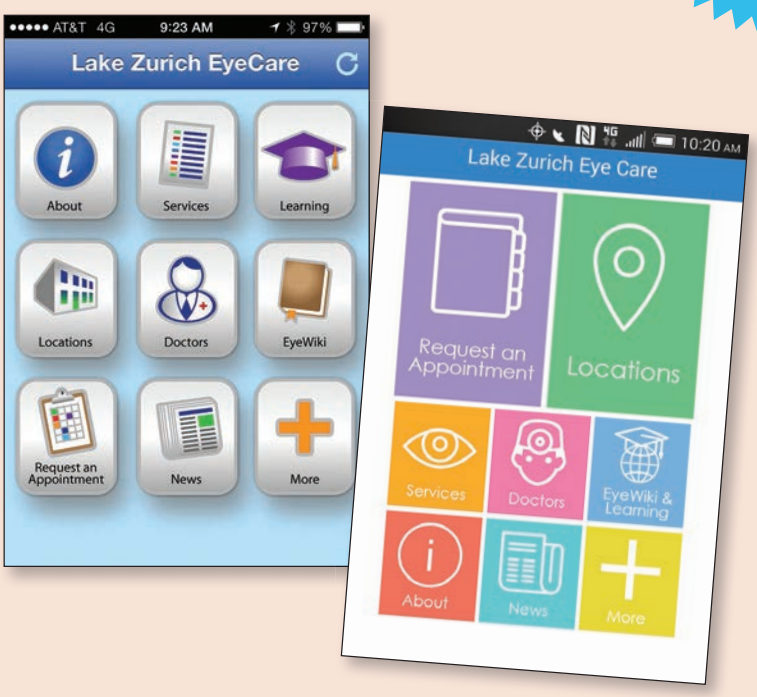

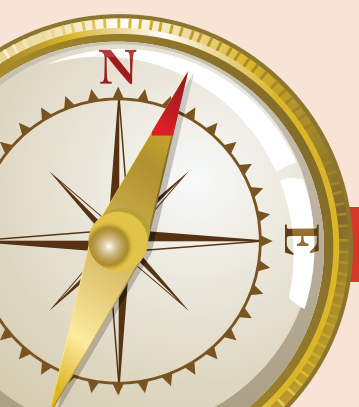

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Progressively worsening monocular blurred vision leads a 60-year-old woman to seek an evaluation at Wills.

Brenton Finklea, MD, Marta McKeague, MD, and James P. Dunn, MD

Presentation

A 60-year-old Indian woman presented with two to three weeks of slowly progressive vision loss in her right eye. She denied redness, irritation, pain, photosensitivity, photopsias or floaters. There were no co-existing headaches, scalp pain or jaw claudication. She noted no prior ocular history, trauma or recent illnesses. Further systemic review of systems was negative.

Medical History

The patient's past medical history was significant for type 2 diabetes mellitus and hypertension. Her most recent eye examination was greater than five years prior. Medications included sitagliptin and metformin for diabetes and lisinopril for hypertension. She reported no allergies.

Our patient moved at age 26 from India to the United States, where she currently resides. While in India she received routine medical care, including the Bacillus Calmette–Guérin (BCG) vaccine. She had no history of tobacco or alcohol use.

Examination

On initial presentation, the patient was afebrile and had stable vital signs. Her uncorrected visual acuity was 20/200 OD and 20/50¬-2 OS with no improvement on pinhole in the right eye, and improvement to 20/40 in the left eye. Pupils were equal, round and reactive to light without afferent pupillary defect, and intraocular pressures were 11 mmHg OU. Confrontational visual field testing was full to finger counting bilaterally, and extraocular muscle movements were full. Anterior segment examination revealed diffuse fine keratic precipitates in both eyes, more prominent in the right eye. The anterior chambers were deep with 2+ cell OD and 1+ cell OS. The right iris had Koeppe nodules at the iris margin; no Busacca nodules were identified. Nuclear sclerosis was moderate in the right and mild in the left eye.

Dilated funduscopic exam revealed moderate vitreous debris OD with 1+ anterior vitreous cell and mild vitreous debris OS with no vitreous cell. Active retinitis was noted within the macula of both eyes with macular edema OD *(See Figure 1)*. There was no optic nerve edema. Peripheral retinal examination was within normal limits.

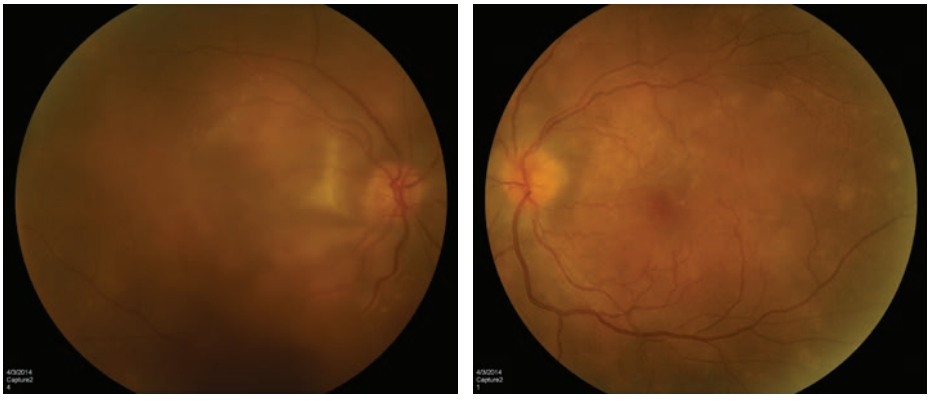

Figure 1. Fundus photos of posterior segment on presentation.

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

Diagnosis, Workup and Treatment

In the setting of extensive panuveitis in both eyes, the differential diagnosis for this individual was broad, including infection (tuberculosis, syphilis, Lyme disease, progressive outer retinal necrosis (PORN), and toxoplasmosis); inflammatory disease (serpiginous choroidopathy, multifocal choroiditis with panuveitis (MCP) and sarcoidosis); and neoplastic disorders such as primary intraocular lymphoma. Vascular causes, such as polypoidal choroidal vasculopathy and exudative age-related macular degeneration were considered less likely. Fluorescein angiography *(See Figure 2)* and optical coherence tomography *(See Figure 3)* were performed to assist in differentiating between clinical entities.

Despite having lived in the United States for 34 years, with her most recent trip to India 14 years ago, tuberculosis was high on our differential. She was started on prednisolone acetate 1% eye drops every hour in both eyes, and a uveitis workup was performed including complete blood count; comprehensive metabolic panel; QuantiFERON-TB Gold (QFT) assay (Qiagen, Germantown, Md.); and chest X-ray. The workup was negative, including chest X-ray, except for a positive QFT, consistent with tuberculosis.

Our patient was kept on frequent topical corticosteroid drops and it was recommended that she start a four-drug, anti-tuberculosis therapy (ATT) regimen of isoniazid, pyrazinamide, ethambutol and rifampin. She was referred to an infectious disease specialist for close management. The patient initially declined the ATT, wanting a second opinion for the diagnosis of TB chorioretinitis. She ultimately began taking the ATT once the vision in her left, better-seeing eye, declined to 20/200. One month after initiation of therapy her inflammation had begun to improve and visual acuity improved to 20/60 OS. Two months after starting ATT her vision OS improved to 20/30. Vision OD remained a constant 20/200 throughout therapy and after.

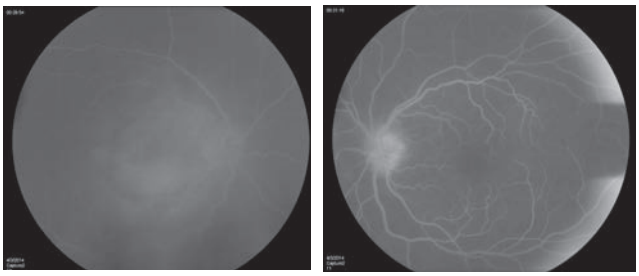

Figure 2. Fluorescein angiogram of the posterior segment on presentation.

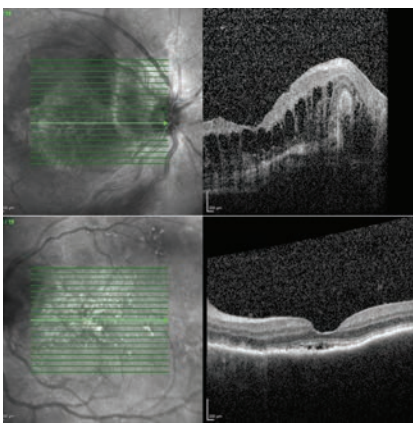

Figure 3. Optical coherence tomography of the posterior segment on presentation.

Oral corticosteroids were never started in this patient due to a new diagnosis of endometrial cancer, which was made in the first month after initiating ATT, and for which she underwent a hysterectomy. Her course was further complicated by development of a choroidal neovascular membrane OS for which she received an intraocular injection of bevacizumab with good response *(See Figure 4)*.

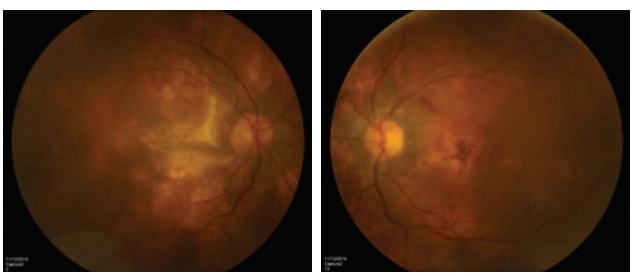

Figure 4. Fundus photos of posterior segment on six-month follow-up.

Discussion

Infection by *Mycobacterium* tuberculosis can have manifestations in both the anterior and posterior segments of the eye. The most common ophthalmic manifestations of tuberculosis are uveitis (anterior, posterior or pan-uveitis), while posterior segment presentations include retinal vasculitis (primarily venous), optic neuritis, serpiginous-like choroiditis, and resulting choroidal and subretinal neovascularization.[1] The anterior uveitis is typically "sticky," with extensive posterior and peripheral anterior synechiae.[2] Conjunctival granulomas are more common than lacrimal gland or orbital granulomas. Nodular scleritis and interstitial keratitis may occur. Choroidal granulomas or "tubercles" may be present as focal, elevated, dome-shaped lesions if direct invasion with bacteria occurs, and are especially prevalent in immunocompromised patients. Most

diagnoses of TB-associated uveitis are presumptive, as the organism is difficult to directly isolate. Clinical criteria are used to make the diagnosis of TB-associated uveitis. The clinical criteria include a positive tuberculosis test (PPD or interferon gamma release assay such as QuantiFERON-TB Gold), clinical picture compatible with tuberculosis, response to treatment with ATT, or thorough complete diagnostic evaluation including microbiological isolation, X-ray, CT scan and/or MRI.[3,4] It is essential to realize, however, that a majority of cases of ocular tuberculosis occur in the absence of any radiographic or symptomatic evidence of TB elsewhere.[5]

It has been estimated that nearly 2 billion people in the world are infected with *Mycobacterium* tuberculosis, 10 percent of whom will develop active TB at some point in their lifetime.[6] Most cases of active tuberculosis, around 80 percent in the United States, are the result of reactivated latent infections.[7] The incidence of latent tuberculosis in foreign-born persons living in the United States may be as high as 18.7 percent.[8] In one study looking at all cases of presumed tuberculosis-induced scleritis and uveitis with positive QuantiFERON-TB Gold studies, 85 percent of patients had spent at least six months living in tuberculosis-endemic regions.[9]

Due to the high prevalence of disease in at-risk populations (e.g., immigrants from endemic areas, HIV-positive patients and people with prolonged exposure to prisons and homeless shelters), it is important to have a high index of suspicion in early cases of intraocular inflammation. A delay in the diagnosis of tuberculous eye disease is one of factors most associated with poor visual outcomes.[5]

The interferon gamma release assay (IGRA) demonstrates comparable sensitivity to the classic tuberculin skin test (TST) but is more specific in individuals who have previously received the BCG vaccine. Furthermore, IGRA tests do not require the patient to return for interpretation, making it more convenient. However, the IGRA tests are more expensive, and are not recommended for serial screening in patients with possible workplace exposure (e.g., health-care workers) because of a high rate of false-positive tests.

Two versions of this test are currently available: the QuantiFERON-TB Gold and T-SPOT TB tests.[10] However, neither the IGRA nor TB skin testing will distinguish between latent TB infection and active TB. This test measures the response of a patient's immune system to tuberculosis antigens. It is dependent on the patient's immunologic status and may be falsely negative in patients with HIV infection, malignancy or iatrogenic immmunosuppression. There is no association between IGRA level and clinical disease severity, so the test is not useful for clinical monitoring or treatment response.[9]

Uveitis due to tuberculosis responds favorably to anti-tuberculosis therapy with complete remission rates reported as high as 91 percent.[9] The initiation of therapy often includes a four-drug regimen of isoniazid, rifampicin, pyrazinamide and ethambutol, followed by a choice of medication combinations over the following four to seven months, which should be directed by an internist or infectious disease specialist.[2] Following the initiation of ATT, a paradoxical worsening of uveitis and fundus appearance may occur. This clinical deterioration may represent a Jarisch-Herxheimer reaction, which has been speculated to derive from endotoxin release, delayed hypersensitivity or decreased suppressor mechanisms.[11] The same phenomenon can be observed in systemic manifestations of tuberculosis. The possibility of a JHR emphasizes the utility of topical and/or systemic steroids on initiation of ATT.[2] The use of corticosteroids in the treatment of ocular TB is unclear, with some authors reporting better outcomes while others report a higher risk of relapse.[2,5]

The diagnosis and treatment of TB-associated intraocular inflammation continues to be an evolving field as we understand more about the pathogenesis of the disease and concurrently improve accuracy of diagnosis. Practitioners should continue to be vigilant in considering tuberculosis in the differential diagnosis of uveitis and retinal vasculitis to ensure prompt initiation of therapy and to improve visual outcomes. REVIEW

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REVIEW

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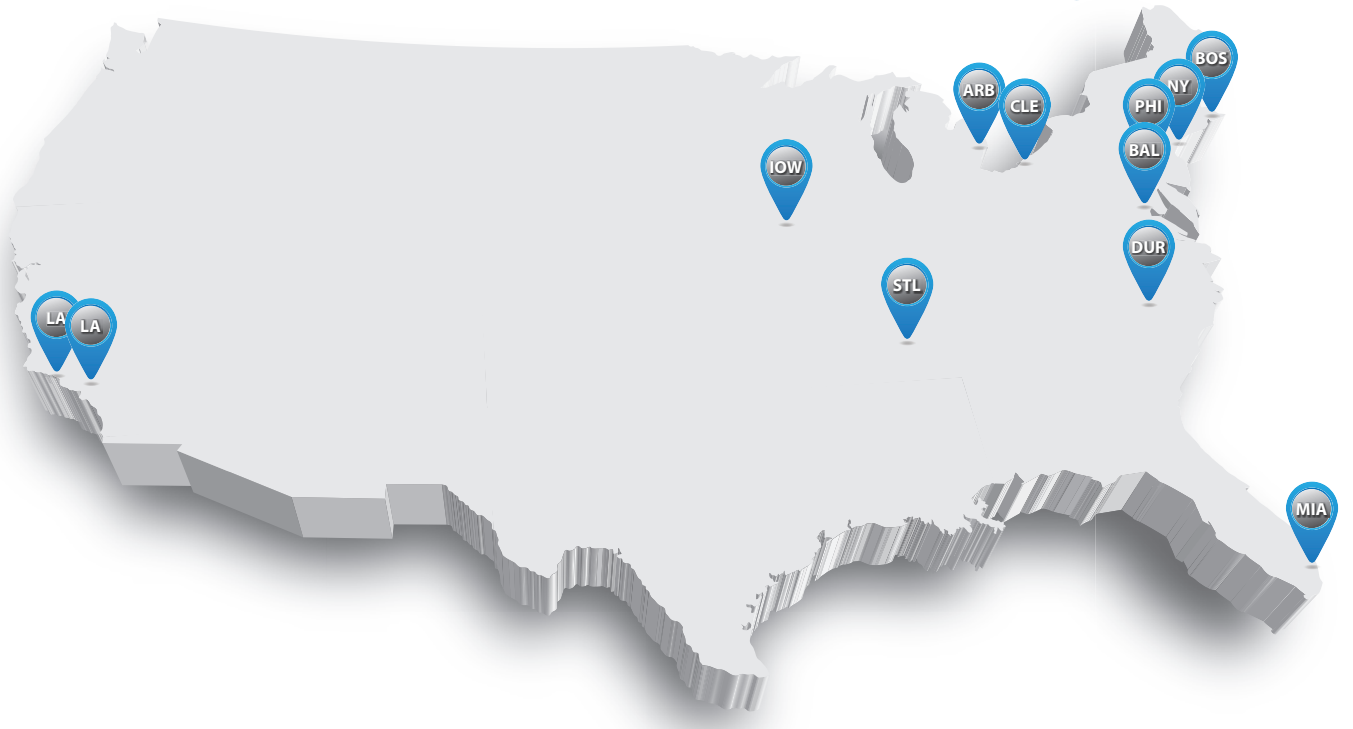

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Increased tear production was seen at 6 months.[1]

Indication and Usage

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

Important Safety Information

Contraindications

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

Warnings and Precautions

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

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

Adverse Reactions

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

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

Reference: 1. RESTASIS® Prescribing Information.

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