REVIEW® of Ophthalmology

June 2016

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GLAUCOMA ISSUE

WHEN TREATING INFLAMMATION AND PAIN
IN YOUR CATARACT SURGERY PATIENTS

#1 Prescribed Branded Ophthalmic NSAID[1]

POTENCY, PRECISELY WHERE YOU NEED IT

ILEVRO® Suspension offers **proven efficacy**, **once-daily postoperative dosing**, and **affordable access** for your patients[2-4]

INFLAMMATION COMPLETELY CLEARED IN **2 OUT OF 3** PATIENTS AT **DAY 14**[2,3*†]

OCULAR PAIN COMPLETELY RESOLVED IN **>80%** OF PATIENTS AT **DAY 14**[3†‡]

1x DAILY POSTOPERATIVE DOSING REGIMEN[3]

- 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[3]
- 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[3]

BROAD COVERAGE[4]

ELIGIBLE COMMERCIAL PATIENTS MAY PAY AS LITTLE AS **$35** OUT OF POCKET[§]

To learn more about treating postoperative inflammation and pain with ILEVRO® Suspension, visit **myalcon.com/ilevro**

INDICATIONS AND USAGE

ILEVRO® (nepafenac ophthalmic suspension) 0.3% is a nonsteroidal, anti-inflammatory prodrug indicated for the treatment of pain and inflammation associated with cataract surgery.

Dosage and Administration

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.

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.

*With ILEVRO® Suspension versus 24% to 32% with vehicle; $P<0.05$.[3]

†Results from 2 randomized, multicenter, controlled, double-masked trials of adult patients undergoing cataract extraction. In Study 1, patients were randomized to receive either ILEVRO® Suspension (n=851), NEVANAC® Suspension (n=845), ILEVRO® Suspension vehicle (n=211), or NEVANAC® Suspension vehicle (n=213). In Study 2, patients were randomized to receive either ILEVRO® Suspension (n=540) or ILEVRO® Suspension vehicle (n=268).[2,3]

‡84% to 86% with ILEVRO® Suspension versus 38% to 46% with vehicle; $P<0.05$.[3]

§This offer is not valid for patients who are enrolled in Medicare Part D, Medicaid, Medigap, VA, DOD, Tricare, or any other government-run or government-sponsored health care program with a pharmacy benefit. Additional eligibility terms apply. See copay savings material for specific details.

References: 1. IMS Health Xponent, January 2015-December 2015. Accessed December 2015. **2.** Data on file. **3.** Ilevro [package insert]. Fort Worth, TX: Alcon Laboratories, Inc; 2014. **4.** Fingertip Formulary, October 2015 (estimate derived from information used under license from Fingertip Formulary, LLC, which expressly reserves all rights, including rights of copying, distribution and republication).

ILEVRO® (nepafenac ophthalmic suspension) 0.3%

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ILEVRO®

(nepafenac ophthalmic suspension) 0.3%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE
ILEVRO® (nepafenac ophthalmic suspension) 0.3% 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. 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 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.

Serious and Otherwise Important Adverse Reactions
The following adverse reactions are discussed in greater detail in other sections of labeling:
- Increased Bleeding Time (Warnings and Precautions)
- Delayed Healing (Warnings and Precautions)
- Corneal Effects (Warnings and Precautions)

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 reactions 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 reactions 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 lens.

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.

Released: February 2014

U.S. Patent Nos. 5,475,034; 6,403,609; and 7,169,767.

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REVIEW NEWS
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U.S. Blindness and Visual Impairment to Double by 2050

With the youngest of the baby boomers hitting 65 by 2029, the number of people with visual impairment or blindness in the United States is expected to double to more than 8 million by 2050, according to projections based on the most recent census data and from studies funded by the National Eye Institute. Another 16.4 million Americans are expected to have difficulty seeing due to correctable refractive errors such as myopia or hyperopia.

The researchers were led by Rohit Varma, MD, director of the University of Southern California's Roski Eye Institute, Los Angeles, and published their analysis May 19th in *JAMA Ophthalmology*. They estimate that 1 million Americans were legally blind (20/200 vision or worse) in 2015. Meanwhile, 3.2 million Americans had visual impairment in 2015—20/40 or worse vision with best possible correction. Another 8.2 million had vision problems due to uncorrected refractive error.

"These findings are an important forewarning of the magnitude of vision loss to come," said NEI Director Paul A. Sieving, MD, PhD. "They suggest that there is a huge opportunity for screening efforts to identify people with correctable vision problems and early signs of eye diseases. Early detection and intervention—possibly as simple as prescribing corrective lenses—could go a long way toward preventing a significant proportion of avoidable vision loss."

Over the next 35 years, Dr. Varma and his colleagues project that the number of people with legal blindness will increase by 21 percent each decade to 2 million by 2050. Likewise, best-corrected visual impairment will grow by 25 percent each decade, doubling to 6.95 million. The greatest burden of visual impairment and blindness will affect those 80 years or older, as advanced age is a key risk factor for diseases such as age-related macular degeneration and cataract.

The researchers analyzed data on visual impairment and blindness from six large studies: the Beaver Dam Eye Study; Baltimore Eye Survey and Salisbury Eye Evaluation Study; the Chinese American Eye Study; Los Angeles Latino Eye Study; and Proyecto VER. They used the 2014 census and population growth projections to estimate the nationwide prevalence of vision impairment and blindness now and in 2050.

In terms of absolute numbers, non-Hispanic whites, particularly white women, represent the largest proportion of people affected by visual impairment and blindness, and their numbers will nearly double. By 2050, 2.15 million non-Hispanic white women are expected to be visually impaired and 610,000 will be blind. "Based on these data, there is a need for increased screening and interventions across all populations, and especially among non-Hispanic white women," Dr. Varma said.

African Americans currently account for the second highest proportion of visual impairment, but that is expected to shift to Hispanics around 2040, as the Hispanic population—and particularly the number of older Hispanics—continues to grow. Hispanics have particularly high rates of diabetes, which is associated with diabetic eye disease, a treatable cause of visual impairment.

African Americans, meanwhile, are expected to continue to account for the second highest proportion of blindness. "African Americans are at disproportionately high risk for developing glaucoma, a potentially blinding eye disease that typically causes the loss of peripheral, but not central vision, so people tend to not realize that they are losing their vision and do not seek treatment," Dr. Varma said.

Avedro Cross-Linking System Gains FDA Nod

Avedro Inc. received approval from the Food and Drug Administration for Photrexa Viscous, Photrexa and the KXL System. Photrexa Viscous and Photrexa are photoenhancers indicated for use with the KXL System in corneal collagen cross-linking for the treatment of progressive keratoconus. Avedro's Photrexa Viscous, Photrexa and the KXL System represent a first-in-class therapeutic treatment for this sight-threatening indication.

"This approval marks a tremendous milestone for the treatment of progressive keratoconus," said Brian Roberts, chief operating and financial officer for

Avedro. "We're excited to provide ophthalmologists in the United States with these tools to treat this orphan disease. We thank the FDA for their diligent efforts as we worked towards approval. We plan to begin taking orders for the KXL System immediately, and plan to begin shipping our Photrexa products in the next few months as we ramp up our drug manufacturing."

Keratoconus is the most common corneal dystrophy in the United States, affecting approximately one in every 2,000 Americans or approximately 170,000 people in the United States.

"This FDA approval has been highly anticipated by the keratoconus community," said Mary Prudden, executive director for the National Keratoconus Foundation. "Corneal cross-linking provides patients a much-needed option to treat this debilitating disease. Patients suffering from progressive keratoconus can now receive a therapeutic treatment that has been rigorously tested and approved."

"I applaud Avedro's efforts to make this clinically important treatment available to U.S. patients," said Peter Hersh, MD, of The Cornea and Laser Eye Institute, CLEI Center for Keratoconus, and the clinical study medical monitor. Dr. Hersh added, "In the studies, treated eyes showed improvement in Kmax at 12 months, while in untreated eyes Kmax continued to worsen. The Photrexa formulations and the KXL system represent an invaluable new treatment option for corneal surgeons in the treatment of keratoconus patients."

Rajesh Rajpal, MD, chief medical officer for Avedro added, "Avedro and I look forward to working with U.S. ophthalmologists to raise awareness of our new FDA-approved treatment for progressive keratoconus."

The Photrexa formulations and the KXL System are expected to be available for qualifying patients through their ophthalmologists before the end of this year.

RAS Reverses Some Effects of DR In Mouse Model

In a first of its kind report, a study in the *American Journal of Pathology* describes a potential new intraocular treatment based on manipulating the renin angiotensin system (RAS) that both prevents and reverses some characteristics of diabetic retinopathy in a mouse model.

"We are not aware of another study that has demonstrated a therapy capable of reversing this form of retinal pathology, particularly in the presence of persistent untreated hyperglycemia," commented lead investigator Maria B. Grant, MD, of the Eugene and Marilyn Glick Eye Institute of Indiana University, Indianapolis.

"This research is based on the hypothesis that an imbalance between two axes of the RAS is a key initial event that leads to development of diabetic microvascular complications," explained Dr. Grant. The two axes consist of the classic and vasoprotective RAS. The proinflammatory, vasoconstrictive classical RAS component is normally kept in check by a vasoprotective axis that is both anti-inflammatory and vasodilatory. Angiotensin converting enzyme-2 (ACE-2) is the primary enzyme of the vasoprotective component. Administration of AAV-ACE--the therapeutic agent under evaluation—directly into the vitreous cavity of the eye using an adeno-associated virus vector, increases ACE-2 expression.

Investigators used mice, some of which were injected with streptozotocin (STZ) to induce diabetes. The protective effects of AAV-ACE2 were examined by performing two sets of experiments. In one cohort, AAV-ACE2 was administered two weeks prior to STZ injection. In a second cohort, to evaluate whether the enhanced expression of ACE2 could reverse diabetic retinopathy, AAV-ACE2 was administered six months after STZ, when diabetes and retinopathy were already established.

The investigators found that both strategies effectively decreased the numbers of proinflammatory cells present in the diabetic retina. Leukostasis—abnormal aggregation and clumping of white blood cells within blood vessels—was only seen in diabetic animals receiving control injections. In addition, using a histological endpoint of retinal vascular degeneration, called acellular capillaries, the group determined that the AAV-ACE2 injection could reverse the diabetes-induced pathology. "These findings are very exciting because it is traditionally believed that this endpoint of vascular degeneration, acellular capillaries, represents an irreversible lesion," emphasized Dr. Grant.

One strength of this experimental approach is that intravitreal administration eliminates the problem of the blood-retinal barrier interfering with access of systemically administered therapeutic agents. The investigators envision that inducing ACE2 overexpression to improve vascular characteristics and decrease inflammation may be translatable to other vascular diseases such as stroke, kidney disease and heart disease.

ARMOR Again Shows High Levels Of Resistance

Bausch + Lomb announced preliminary 2015 results of the ARMOR (Antibiotic Resistance Monitoring in Ocular MicRoorganisms) surveillance study, the only multicenter, nationwide survey of antibiotic resistance patterns specific to eye care, at the 2016 Association for Research in Vision and Ophthalmology Annual Meeting in Seattle. Researchers also presented data that examined resistance profiles of common bacterial pathogens isolated from the aqueous and vitreous humor to antibiotics routinely used in ophthalmic practice.

In the first study, ARMOR researchers reported comparisons of susceptibility rates available from surveillance in 2015 to results from 2014. At the time of the analysis, a total of 441 isolates of *Staphylococcus aureus*, coagulase-negative staphylococci (CoNS), *Streptococcus pneumoniae*, *Pseudomonas aeruginosa* and *Haemophilus influenzae*, organisms frequently implicated in bacterial eye infections, were collected from 19 sites across the United States. The isolates were then tested for susceptibility to as many as 15 antibiotics.

Similar to previous years, study authors reported that surveillance data continue to show high levels of antibiotic resistance among staphylococcal isolates, especially among methicillin-resistant strains, with many demonstrating multidrug resistance. Resistance among the staphylococci was most notable for azithromycin (54 to 59 percent) oxacillin/methicillin (24 to 45 percent), and ciprofloxacin (22 to 28 percent), while CoNS isolates also exhibited high levels of non-susceptibility to tobramycin (19 percent) and trimethoprim (26 percent). In 2015, 20 percent of *S. aureus* isolates and 39 percent of CoNS isolates were non-susceptible to three or more drug classes, with multidrug resistance remaining prevalent among MR *S. aureus* (67 percent) and MRCoNS (74 percent). Isolates of *S. pneumoniae* remained susceptible to fluoroquinolones and chloramphenicol, while non-susceptibility to azithromycin and penicillin was 50 percent and 38 percent, respectively. Resistance among *P. aeruginosa* isolates continues to be low, while *H. influenzae* isolates were

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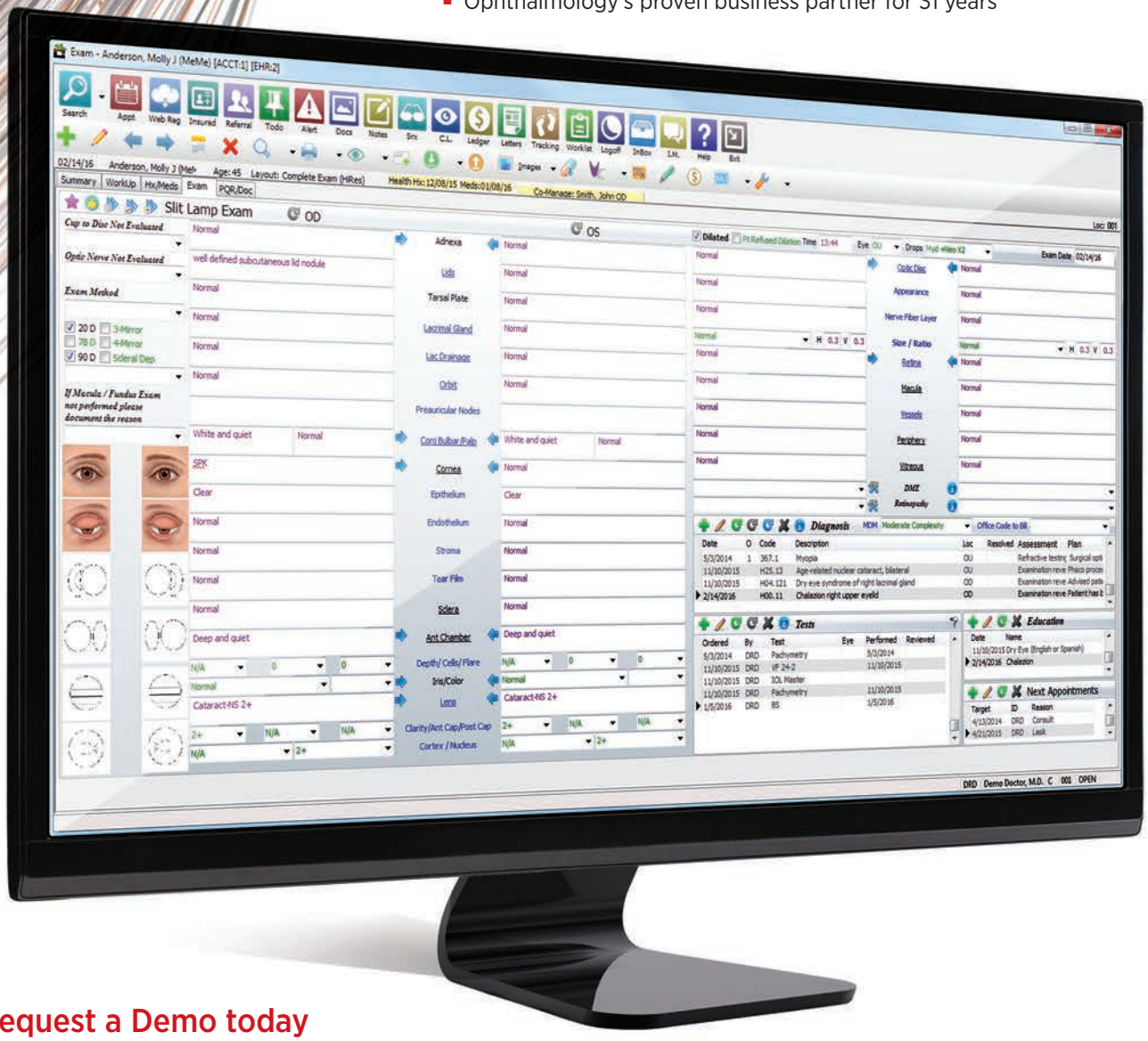

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generally susceptible to all antibiotics tested.

"These latest data demonstrate that resistance of common ocular pathogens to several commonly used antibiotics continues to be a challenge," said Penny Asbell, MD, lead ARMOR study author, professor of ophthalmology at Icahn School of Medicine at Mount Sinai, and director of the Cornea Service and Refractive Surgery Center at the Mount Sinai Hospital. "Understanding antibiotic resistance patterns is critical for the selection of effective agents to treat potentially sight-threatening ocular infections. The ARMOR data allow physicians to select agents that have proven efficacy and a broad spectrum of activity."

In a second study, investigators examined antibiotic resistance profiles of 172 aqueous and vitreous humor isolates collected between 2009 and 2015 through the ARMOR surveillance study, including 30 *S. aureus*, 100 CoNS, 21 *S. pneumoniae*, 10 *P. aeruginosa* and 11 *H. influenzae*. Similar to the preliminary 2015 ARMOR findings, researchers reported that antibiotic resistance was prevalent among staphylococcal isolates, particularly CoNS, with many demonstrating multidrug resistance.

Further Eye Issues Seen in Zika Babies

Researchers studying babies with a Zika virus-related birth defect say they have found previously unreported eye problems possibly linked to the virus that could result in severe visual impairment. In three Brazilian infants with microcephaly, the researchers observed retinal lesions, hemorrhaging and abnormal blood vessel development not noted before in relation to the virus. The findings were published online in *Ophthalmology*.

A prior study of 29 Brazilian babies with presumed congenital Zika infection showed that a third had eye problems. These included ocular lesions, optic nerve abnormalities and chorioretinal atrophy, a withering of the retina and choroid, the latter of which provides oxygen and nutrients to the retina.

For this case study, ophthalmology researchers from Brazil and Stanford University examined the eyes of three infant boys from northern Brazil born in late 2015 with microcephaly. All had mothers with suspected Zika virus infections during the first trimester of pregnancy.

Among the findings, the researchers identified several types of ocular issues not previously observed in relation to Zika virus, some of which could cause visual impairment if untreated. These included: hemorrhagic retinopathy; abnormal vasculature in the retina, including signs of missing blood vessels in the retina where the cells may have died; and torpedo maculopathy. In addition to these observations, the infants in this study also exhibited other ocular symptoms noted in the previous study. Specifically, all three babies in this case study showed signs of pigmentary maculopathy, lesions that appear as speckles of pigment on the macula. Four eyes had symptoms of chorioretinal atrophy marked by a darkly pigmented ring.

The study is small with limited observational data. However, the findings add to a growing body of clinical information about how the Zika virus may affect children's eye development and vision. The authors noted that it remains unclear whether the viral infection itself causes eye abnormalities or if they are a consequence of Zika-induced microcephaly. REVIEW

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

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Down, Boy.

Help Tame Postoperative Ocular Inflammation and Pain With LOTEMAX® GEL

Indication

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

Important Safety Information about LOTEMAX® GEL

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

Please see brief summary of Prescribing Information on adjacent page.

LOTEMAX® GEL
loteprednol etabonate
ophthalmic gel 0.5%

BAUSCH + LOMB

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Lotemax (loteprednol etabonate ophthalmic gel) 0.5%

Rx only
Initial Rx Approval: 1998

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

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

CONTRAINDICATIONS

LOTEMAX, as with other ophthalmic corticosteroids, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

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

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

Bacterial Infections

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

Viral Infections

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

Fungal Infections

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

Contact Lens Wear

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

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

Loteprednol etabonate has been shown to be embryotoxic (delayed ossification) and teratogenic (increased incidence of meningocele, abnormal left common carotid artery, and limb flexures) when administered orally to rabbits during organogenesis at a dose of 3 mg/kg/day (35 times the maximum daily clinical dose), a dose which caused no maternal toxicity. The no-observed-effect-level (NOEL) for these effects was 0.5 mg/kg/day (6 times the maximum daily clinical dose). Oral treatment of rats during organogenesis resulted in teratogenicity (absent innominate artery at ≥5 mg/kg/day doses, and cleft palate and umbilical hernia at ≥50 mg/kg/day) and embryotoxicity (increased post-implantation losses at 100 mg/kg/day and decreased fetal body weight and skeletal ossification with ≥50 mg/kg/day). Treatment of rats with 0.5 mg/kg/day (6 times the maximum clinical dose) during organogenesis did not result in any reproductive toxicity. Loteprednol etabonate was maternally toxic (significantly reduced body weight gain during treatment) when administered to pregnant rats during organogenesis at doses of ≥5 mg/kg/day.

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma tk assay, or in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with up to 50 mg/kg/day and 25 mg/kg/day of loteprednol etabonate, respectively, (600 and 300 times the maximum clinical dose, respectively) prior to and during mating did not impair fertility in either gender.

PATIENT COUNSELING INFORMATION

Administration

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

Risk of Contamination

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

Contact Lens Wear

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

Risk of Secondary Infection

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

Bausch & Lomb Incorporated
Tampa, Florida 33637 USA

US Patent No. 5,800,807

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

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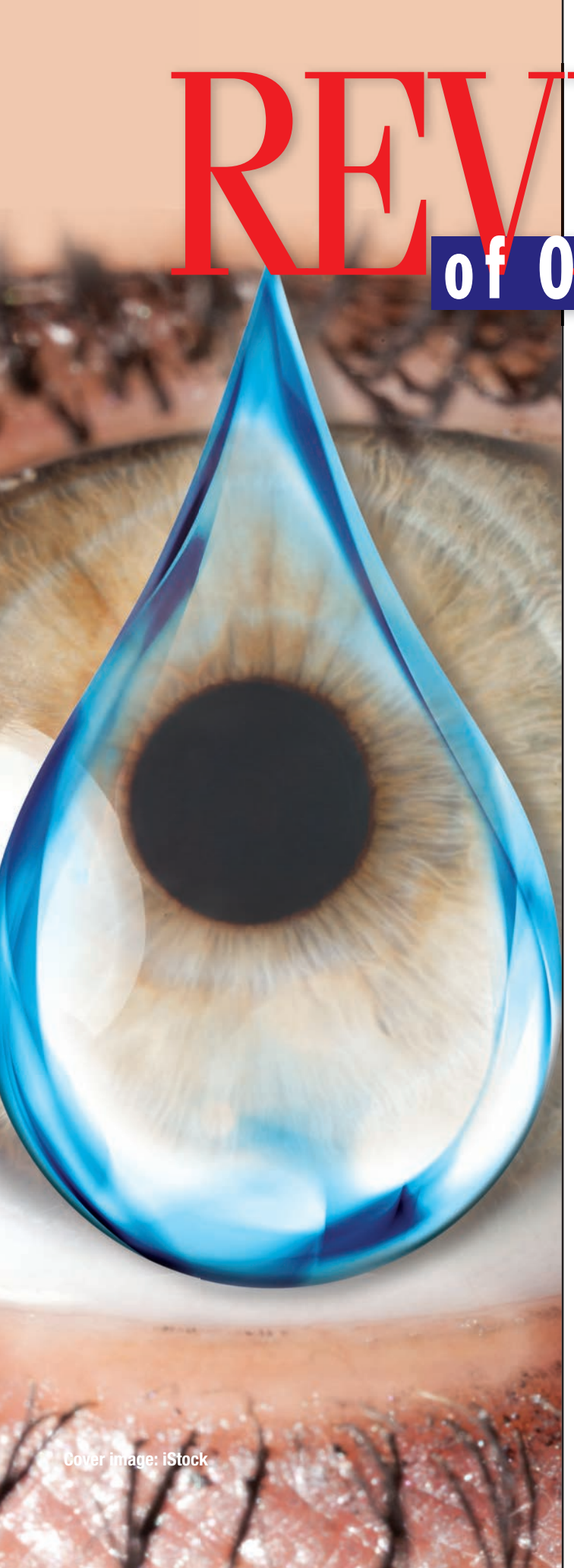

Cover image: iStock

Cover Focus

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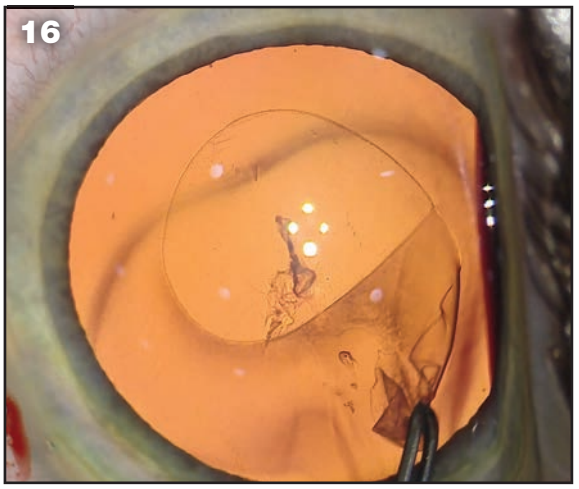

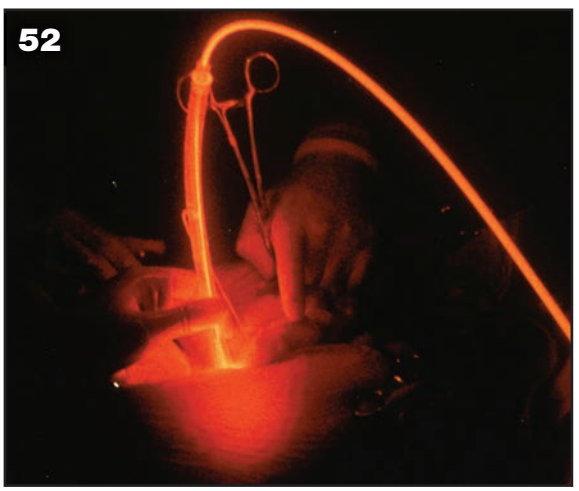

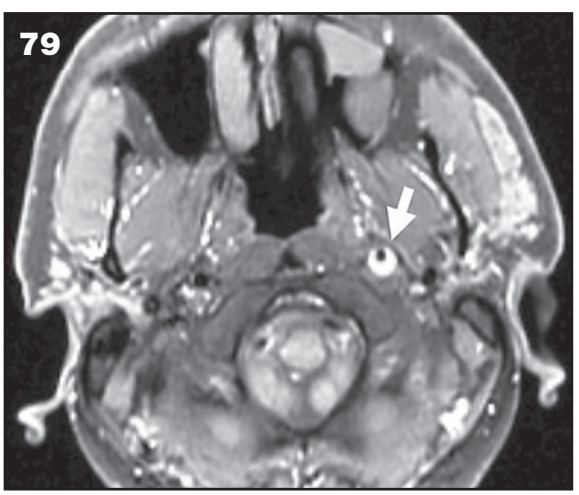

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The Latest in Surgical Microscope Innovations

How recent product introductions might help you operate and share your surgical knowledge more efficiently.

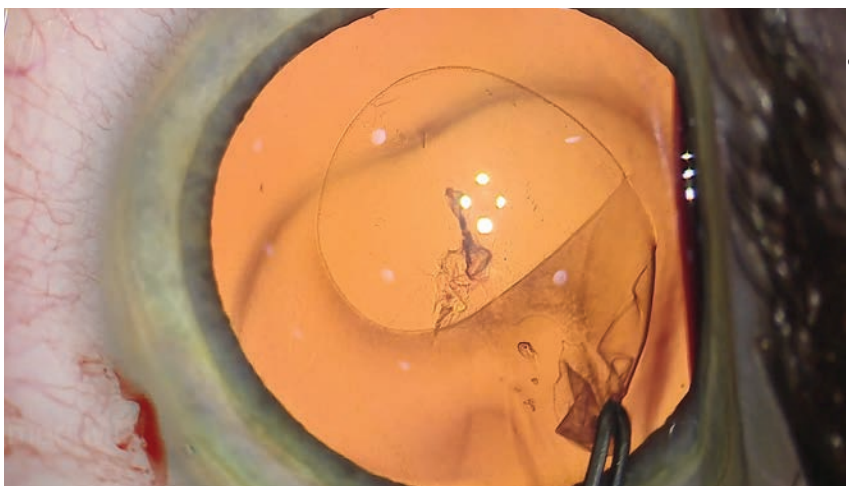
Walter Bethke, Managing Editor

Ophthalmic surgeons and companies are continuously improving their techniques and technology to make surgeries safer and more effective. Unfortunately, all the greatest surgical techniques and instruments in the world don't amount to much if you can't get a well-lit, sharp image of the ocular structures you're working on. Because of this, surgeons rely on their microscopes to be extensions of their eyes while working on their patients or recording cases to share with their colleagues. Here's a look at two recent additions to the microscope market that try to help make surgeons' work a little easier.

Leica's Proveo 8

Leica Microsystems' newest microscope has two features designed to help the surgeon maintain good visualization during a procedure.

The first function is called CoAx 4, and is designed to use four LED light sources to keep the red reflex stable and optimize image contrast. Ike Ahmed, MD, assistant professor at the University of Toronto, has worked with the CoAx 4 system in the Proveo 8 both during its development and in its current form, and says it can be helpful in the OR. "The illumination and the stable red reflex are important features," he says. "The red reflex is consistent throughout the procedure, during such maneuvers as the creation of the capsulorhexis; the red reflex isn't necessarily better than in other microscopes, but it's consistent. The microscope also maintains high-quality images throughout the case. For example, in the past, after hydrodissection, during phaco there's a point at which we might lose the red reflex. With this system, however, we maintain good visualization throughout the steps of the procedure. I think this consistent visualization has to do with the way the coaxial light is delivered using the microscope's four LEDs—there are no fiber optics involved in the system. By being a full-LED system, I think that leads to enhanced



All images: Ike Ahmed, MD

Some surgeons may have experienced instances in which the illumination gets dim during their surgeries and then brightens again. The idea behind using four LEDs to provide the illumination in the Proveo system is to avoid such fluctuations.

This article has no commercial sponsorship.

The Proveo 8 system tries to provide a red reflex that remains consistent throughout the various phases of the procedure.

illumination when combined with the system's optics. In the past, with some other scopes I might get great images at certain phases of the procedure but then lose them a bit, or I'd get unusual reflections that led to a loss of quality." The system also allows the surgeon to adjust the diameter of the illumination from 4 to 23 mm, so he can illuminate just the iris or the entire eye. The idea is that a small diameter avoids scleral reflections and improves the contrast, while a larger diameter negates the negative effect of patient movement by keeping the diameter of light larger.

The other challenge faced by surgeons when using microscopes is the trade-off between depth of field and the amount of resolution of the image. To address this, the microscope uses a different aperture in each of the microscope's ocular pathways. One aperture is larger and is designed for high-resolution imaging, while the other is smaller and geared toward providing a greater depth of field. The system then relies on the brain of the observer to fuse the disparate images into one that has both a high resolution and a good depth of field. "The enhanced depth of field, made possible by the asymmetrical apertures between the two oculars, is also really helpful," says Dr. Ahmed. "This approach allows more things to be in focus at one time, which means less refocusing by the surgeon and better visualization across the various depths at which he's working. During phaco, for instance, this comes into play when you're bringing pieces of the nucleus up and down from the capsular bag to the iris plane. You go back and forth, sometimes in the anterior chamber, and you often need to perform frequent refocusing to get the images into focus. The nice thing with having increased depth of field is there's less of a need to manipulate the foot pedals to change the focus because there are more things in focus at once. It's such a subtle difference between the eyes that the surgeon really doesn't perceive it."

For information, call 1 (800) 248-0123, or visit leica-microsystems.com.

Topcon HD Video System

Topcon has released a modular high-definition video system to let surgeons capture procedures in higher detail.

"Recording in higher resolution lets the surgeon capture very small details," says Topcon's Ricardo Almiron. "The details are important when you're dealing with sutures, IOL haptics or when a surgeon is performing retinal procedures such as peeling a subretinal membrane. Having these details is helpful when teaching or projecting an image for the surgeon's assistants or out to an operating room theater."

The base HD video system, which is a Panasonic product, has four components: a camera; camera control unit; cable; and a power supply. The camera attaches to the surgical microscope's beam splitter. The system is described as fitting Topcon microscopes; however Mr. Almiron says it can fit most microscopes. Though the camera is Panasonic, Topcon provides the video adaptor that connects it to the microscope, and optimizes the color balance for ocular surgery.

Since various facilities may already have complementary components such as HD recorders and monitors, those are sold separately. "Facilities such as hospitals already have video monitors attached to booms affixed to the ceiling or the wall," Mr. Almiron explains. "But if a facility needs it, we also sell a 26-inch HD monitor. We also make available a recorder that records to an SD card. It comes with 32 GB of memory, but that can be expanded to 64 GB, and it will allow up to 12 hours of recording depending on the resolution the surgeon chooses."

The price for the HD video system is $7,675, though a discount is available for Veterans Administration facilities. The optional HD monitor is $7,995 and the recorder sells for $5,970. For information, call 1 (800) 223-1130, or visit topconmedical.com. REVIEW

Dr. Ahmed is a consultant for Leica.

TrueVision Patents Its Tech

Recently, the U.S. Patent and Trademark Office awarded TrueVision 3D Surgical patents for digital surgical guidance as well as low-light imaging of surgical procedures.

TrueVision's surgical guidance and visualization patent describes a visualization platform that uses computer-guidance for different steps of ocular surgery, including aiding with the creation of a capsulorhexis and the centering of a corneal inlay for presbyopia treatment. The surgeon can make real-time adjustments to his inputs, such as changing the selected lens, and the system will change its guidance to allow him to reach the postop target refraction.

The low-light imaging patent describes a system that would enable surgeons to visualize target tissues and structures accurately with the use of very little illumination. The company says surgeons may be able to dramatically reduce the use of the microscope light during procedures, which can be especially useful in vitreoretinal work.

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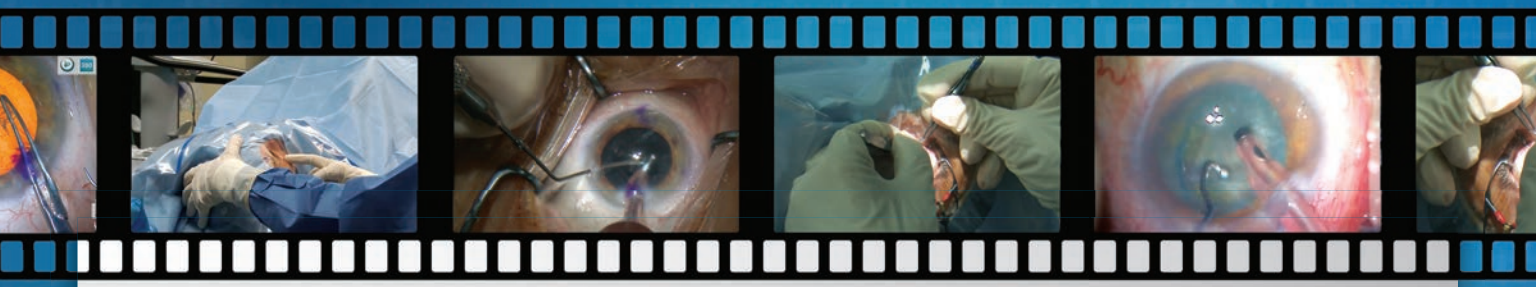

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Episode 6: "Phacoaspiration of a Nuclear Cataract in a 78 Year Old Patient"

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Richard J. Mackool, MD

Video Overview:
Utilizing high vacuum, removal of a 2+ nuclear cataract is accomplished without ultrasound.

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Richard J. Mackool, MD

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

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

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

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

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

Learning Objective:
After viewing the video, participants should be able to demonstrate a method to minimize the use of ultrasonic energy during phacoemulsification.

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

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How to Document and Code Lesion Removal

The number, histology, location, removal method—a host of factors can come into play when billing these procedures.

Q Is there a method to determine the best CPT code for lesion removals?

A Yes. From an anatomical perspective, lesions can exist on various ocular structures. For example, they may be corneal, conjunctival, lacrimal or located on the eyelid. Once you determine the location, the next step is to determine the histology, whether the lesion is benign, malignant or uncertain, and method of removal—cut, scrape, excise, cauterize, incise or drain. Was closure necessary and, if so, was it simple or complex? Once you have answered these questions, you will have narrowed the choice of CPT codes to match your documentation.

Q Do lesion removal codes have a global period, and may we file for an office visit on the day of the removal?

A Lesion removals are minor procedures and have either zero or 10 postop days. Because these are minor procedures, the office visit is usually bundled with the lesion removal unless your documentation includes a separately identifiable service supporting the use of modifier -25 for the office visit.

Q What is the best way to document the procedure?

A Best practices would be to have a separate operative report for the procedure. It should contain the indications for the procedure, a description of the procedure and discharge instructions. A clearly documented consent, either written or verbal, for the procedure should also be in the medical record.

Q What is the difference between the three CPT codes that describe a chalazion removal?

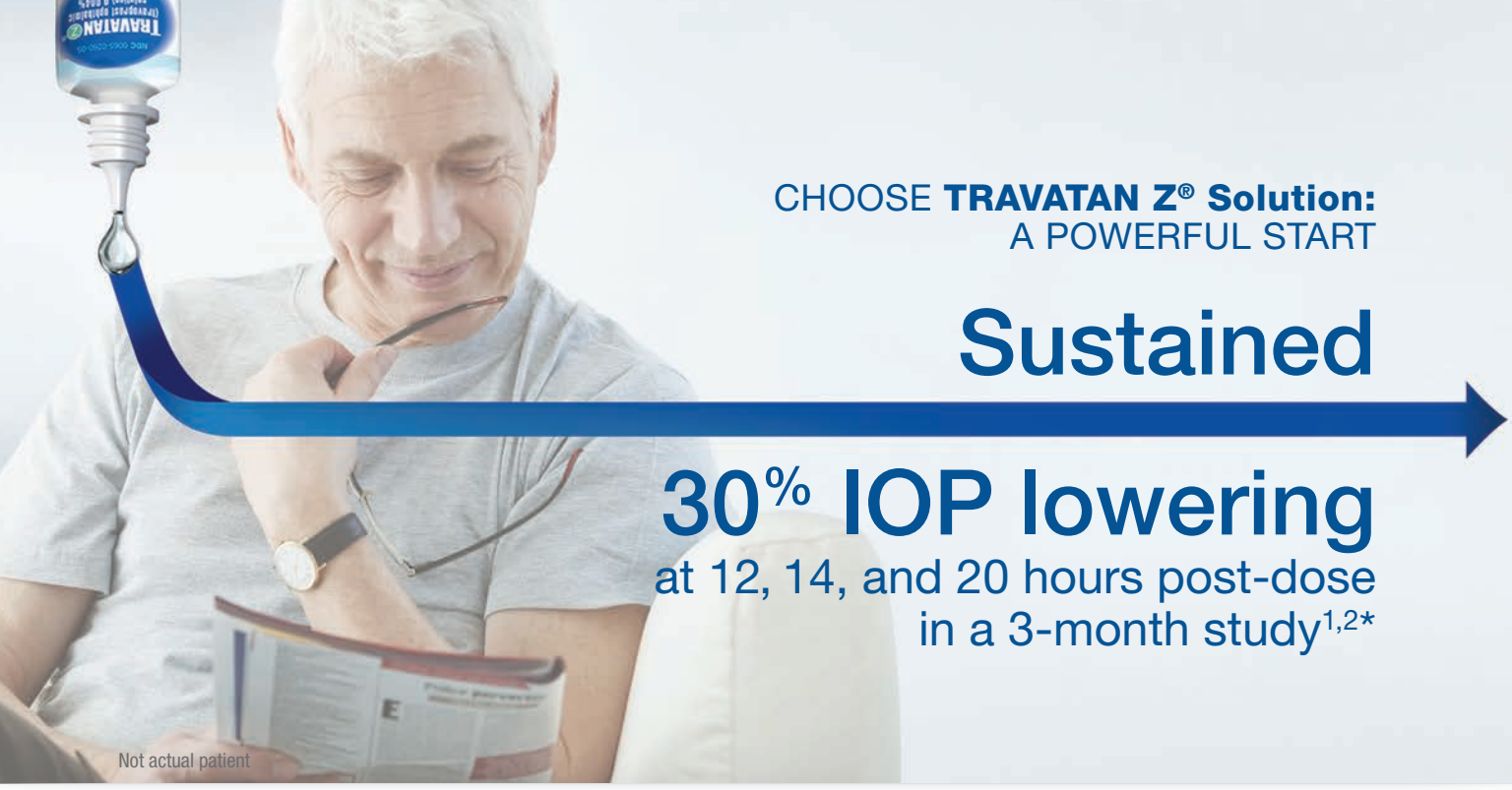
A The various codes differentiate between the number of removals, location of chalazia and whether general anesthesia or hospitalization is required. For a single chalazion, code as CPT 67800; if more than one is removed on the same eyelid, use CPT 67801; if there are multiple located on different eyelids, use 67805. CPT 67808 is reserved for an excision under general anesthesia and/or requiring hospitalization, and is used whether a single or multiple chalazia are removed under these conditions. This is more commonly used for pediatric patients.

Q Is it appropriate to use CPT 67840, *excision of lesion of eyelid (except chalazion) without closure or with simple direct closure*, for all eyelid lesions?

A No. The CPT manual contains instructions at the beginning of the section for Excisions / Destructions just above CPT 67800. It states: *"Codes for removal of lesions include more than skin (ie., involving lid margin, tarsus, and/or palpebral conjunctiva."* The procedure note describing the surgery should describe removal of more than just skin to support the use of this code.

Q If 67840 is not appropriate and the lesion removal is only skin, what codes should be considered?

A The 11xxx series of codes relates to the integumentary system. More specifically, 1144x addresses benign lesions of face, ears, eyelids, nose and



Not actual patient

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in a 3-month study[1,2]*

TRAVATAN Z® Solution has no FDA-approved therapeutic equivalent available

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INDICATIONS AND USAGE

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

Dosage and Administration

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

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

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

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

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

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

Adverse Reactions

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

Use in Specific Populations

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

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

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

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

TRAVATAN Z®
(travoprost ophthalmic solution) 0.004%

Alcon®
a Novartis company

TRAVATAN Z®

(travoprost ophthalmic solution) 0.004%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

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

CONTRAINDICATIONS
None

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Alcon®

ALCON LABORATORIES, INC.
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10/15 US-TRZ-15-E-0278

lips. CPT 1164x codes are used for malignant lesions of those same areas. The range of codes from 11440 to 11446 and 11640 to 11646 are distinguished based on the size of the removal. The CPT descriptors contain measurements using centimeters. For example, CPT 11441 describes a lesion that is 0.6 to 1.0 cm.

Q How is the size of the excision calculated?

A When measuring the removal to select the appropriate CPT code, measure the lesion itself at its greatest clinical diameter and the margin required to accomplish a complete excision. Document the size in the procedure note.

Q If the surgeon is unsure of the histology of the skin lesion and submits the specimen to pathology, can this be coded and filed on the date of service?

A We don't recommend it. Without the pathology report, you are unable to accurately select a CPT code for the removal. These claims should be set aside until the pathology report has been returned and a code can be selected from the 1144x series or the 1164x series.

Q What is the difference between an excisional biopsy and a biopsy?

A Typically a biopsy indicates that a portion of the lesion is removed and sent to pathology for evaluation. These are coded as 67810 if it is more than just skin. However, if the entire lesion is removed and sent for pathology, and it is more than just skin, you have met the criteria for lesion removal, 67840.

Q Does Medicare reimburse removal of benign lesions?

A Maybe. Few Medicare contractors publish local policies on lesion removals to provide coverage guidance. WPS, Medicare contractor for several Midwest states, publishes a local coverage determination that states:

"Medical Indications – There may be instances in which the removal of non-malignant skin lesions is medically appropriate. Medicare will, therefore, consider their removal as medically necessary and not cosmetic, if one or more of the following conditions are present and clearly documented in the medical record:

The lesion has one or more of the following characteristics: bleeding, itching, pain; change in physical appearance (reddening or pigmentary change), recent enlargement, increase in number; or

1. The lesion has physical evidence of inflammation, e.g., purulence, edema, erythema; or

2. The lesion obstructs an orifice; or

3. The lesion clinically restricts vision; or

4. There is clinical uncertainty as to the likely diagnosis, particularly where malignancy is a realistic consideration based on the lesion appearance; or

5. A prior biopsy suggests or is indicative of lesion malignancy; or

6. The lesion is in an anatomical region subject to recurrent trauma, and there is documentation of such trauma."

It further states: *"A medical record statement of 'irritated skin lesion' is insufficient justification for lesion removal when solely used to reference a patient's complaint or a physician's physical findings."*

Q Is closure of the wound or an adjacent tissue transfer separately billable?

A Simple closure is included with the excision codes. Intermediate or complex closure might be separately billed. CPT instructs to use only the adjacent tissue transfer code (14000 to 14302) if performed in conjunction with the lesion removal. The removal is included.

Q Do third-party payers reimburse for the removal of skin tags?

A Rarely. Skin tag removal, CPT 11200, is usually considered cosmetic and the patient is financially responsible. For regular Medicare, practices should secure an Advance Beneficiary Notice of Noncoverage (ABN) informing the patient of noncoverage and patient liability. If coverage is uncertain, the claim can be filed with modifier -GA; if cosmetic, the claim may be filed with modifier -GY. A financial waiver is also required for Medicare Advantage plans and commercial insurance, but check with the payer for its process and requirements.

Q Are there additional ophthalmic surgical codes to consider?

A Yes. Depending on the complexity of the removal and repair, codes in the 67930 to 67975 section may apply.

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

Making Allergic Conjunctivitis Treatment a Priority

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

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

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

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

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

BY NO MEANS BENIGN

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

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

IMPACT ON SURGERY

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

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

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

DIAGNOSIS

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

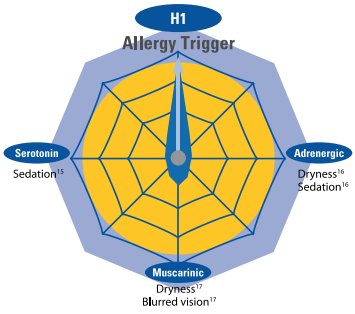
Patients can have a variety of signs, such as injection, chemosis, conjunctival chalasis, lid droop, and red, thickened lids. There is a wealth of information on examination of the everted upper tarsus: conjunctival hyperemia, papillae in the acute phase, follicles in the chronic phase, conjunctival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

extreme cases, and conjunctival scarring in chronic cases.

RELIEF OF SEVERE OCULAR ITCH

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

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



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

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

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

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

MULTISYMPTOM RELIEF

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

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

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

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

ACCESSIBILITY

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

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

REFERENCES

1. Rosario N, Bielory L. Epidemiology of allergic conjunctivitis. *Curr Opin Allergy Clin Immunol*. 2011;11:471-6.
2. Bielory L, Katelaris CH, Lightman S, et al. Treating the ocular component of allergic rhinoconjunctivitis and related eye disorders. *MedGenMed*. 2007;9(3):35.
3. Blaiss MS. Allergic rhinoconjunctivitis: burden of disease. *Allergy Asthma Proc*. 2007 Jul-Aug; 28(4):393-7.
4. Yang HY, Fujishima H, Toda I, et al. Allergic conjunctivitis as a risk factor for regression and haze after photorefractive keratectomy. *Am J Ophthalmol*. 1998 Jan;125(1):54-8.
5. Bielory BP, O'Brien TP. Allergic complications with laser-assisted in-situ keratomileusis. *Curr Opin Allergy Clin Immunol*. 2011 Oct;11(5):483-91.
6. Montes-Mico R. Role of the tear film in the optical quality of the human eye. *J Cataract Refract Surg*. 2007;33:1631-5.
7. Padmanabhan P, Aiswaryah R, Abinaya Priya V. Post-LASIK keratectasia triggered by eye rubbing and treated with topography-guided ablation and collagen cross-linking — a case report. *Cornea*. 2012;31(5):575-80.
8. Boorstein SM, Henk HJ, Elner VM. Atopy: a patient-specific risk factor for diffuse lamellar keratitis. *Ophthalmology*. 2003 Jan;110(1):131-7.
9. BEPREVE [package insert]. Tampa, FL: Bausch & Lomb Incorporated; 2012.
10. Meier EJ, Torkildsen GL, Gow JA, et al; for Bepotastine Besilate Ophthalmic Solutions Study Group. Integrated phase III trials of bepotastine besilate ophthalmic solution 1.5% for ocular itching associated with allergic conjunctivitis. *Allergy Asthma Proc*. 2012;33:265-274.
11. Data on file. Clinical study report CL-SAF 04-0507-P. NDA 22-288. Ista Pharmaceuticals, Inc. October 27, 2008.
12. ALREX [package insert]. Tampa, FL: Bausch & Lomb Incorporated; 2013.
13. Dell SJ, Lowry GM, Northcutt JA, et al. A randomized, double-masked, placebo-controlled parallel study of 0.2% loteprednol etabonate in patients with seasonal allergic conjunctivitis. *J Allergy Clin Immunol*. 1998 Aug;102(2):251-5.
14. Shulman DG, Lothringer LL, Rubin JM, et al. A randomized, double- masked, placebo-controlled parallel study of loteprednol etabonate 0.2% in patients with seasonal allergic conjunctivitis. *Ophthalmology*. 1999;106(2):362-369.
15. Kato M, Nishida A, Aga Y, et al. Pharmacokinetic and pharmacodynamic evaluation of central effect of the novel antiallergic agent betotastine besilate. *Arzneimittelforschung*. 1997;47(10):1116-1124.
16. Hawkins DW, Bussey HI, Trisant LM. Hypertension. In: Dipiro T, ed. *Pharmacotherapy: A Pathophysiologic Approach*. Stamford, CT: Appleton & Lange; 1997:195-218.
17. Crismon ML, Dorson PG. Schizophrenia. In: Dipiro T, ed. *Pharmacotherapy: A Pathophysiologic Approach*. Stamford, CT: Appleton & Lange; 1997:1367-1394.
18. Data on file. Bepreve® Integrated Summary of Safety. NDA 22-288. ISTA Pharmaceuticals, Inc. October 18, 2008.

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

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Alrex®

loteprednol etabonate
ophthalmic suspension 0.2%

Sterile Ophthalmic Suspension

Rx only

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Revised: August 2013.

Bausch & Lomb Incorporated, Tampa, Florida 33637

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

BEPREVE® (bepotastine besilate ophthalmic solution) 1.5%

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

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

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

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

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

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

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

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

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

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

Revised: 10/2012

FULL PRESCRIBING INFORMATION: CONTENTS*

*Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

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

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

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

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

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

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

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

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

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

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

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

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

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

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

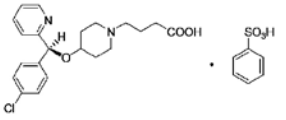
8.3 Nursing Mothers
Following a single 3 mg/kg oral dose of radiolabeled bepotastine besilate to nursing rats 11 days after delivery, the maximum concentration of radioactivity in milk was 0.40 mcg-eq/mL 1 hour after administration; at 48 hours after administration the concentration was below detection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

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

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

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

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



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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

US/BEP/13/0028 4/13

Prostaglandin Drops: First-line Forever?

Christopher Kent, Senior Editor

Alternate choices may soon challenge the current favorite's status as the best first option.

When an ophthalmologist treating glaucoma decides that a new patient needs therapy, odds are good that the first treatment choice will be a daily drop of one of the prostaglandins. There are plenty of logical reasons for that choice, given their efficacy—typically lowering intraocular pressure by 25 to 30 percent—along with their once-a-day dosing and minimal side effects. But with new developments and treatment options appearing every few years, it's reasonable to wonder how long prostaglandins will be the favorite first-line choice.

"The prostaglandin class of drugs represents the most efficacious, safest and most conveniently dosed drugs that we have currently to treat glaucoma," notes Tony Realini, MD, MPH, professor of ophthalmology at West Virginia University Eye Institute in Morgantown, W.Va. "They don't have many downsides. There is an issue with hyperemia, although for most patients it's a non-issue or a tolerable one. There are some concerns about eyelash growth, which may be spurred by using a prostaglandin. For some patients that's a problem, but for others it's a blessing. There is also the much-discussed prostaglandin-associated orbitopathy. I've seen a handful of patients with it, but I've never had a single patient complain about it, so I don't know how significant that is. I put it up there with iris color change. In the 20 years we've had prostaglandins, I've had two patients who declined to use a prostaglandin on the grounds that it might change their eye color. No patients have ever reported to me that their eye color changed, and I've never objectively observed a color change in any patient's iris."

Despite prostaglandins' popularity as a first-line treatment, Dr. Realini says there are a few circumstances in which he might not choose a prostaglandin as the first choice for therapy, such as when a patient has uveitis. "Prostaglandin molecules are important mediators of inflammation, so a prostaglandin might increase the risk of inflammation in someone who is prone to uveitis," he says. "However, the level of evidence for this is on the order of small case reports and case series, so it's not a strong association. In fact, I've used prostaglandins in patients with uveitis, not as a first choice, but as a last choice before surgery. In that situation I'd much rather take the small risk of aggravating uveitis and give the prostaglandin a try than go to the operating room and take on all of the known risks of surgery."

Clearly, in order to replace prostaglandin drops as the first-line option

This article has no commercial sponsorship.

for most patients an alternative will have to offer some significant advantages. Treatment options that could conceivably fit the bill—many still in the pipeline—include new drugs; new drops that combine drugs; selective laser trabeculoplasty; and long-term delivery devices. Here, doctors familiar with the latest developments in these areas share their thoughts regarding whether or not one of these options are likely to eventually become the next first-line treatment choice.

ROCK Inhibitors

One new class of drugs showing great promise is Rho kinase inhibitors. Savak Teymoorian, MD, MBA, a cataract and glaucoma specialist at Harvard Eye Associates in Laguna Hills, Calif., has participated in the trials of Rhopressa (Aerie Pharmaceuticals), a ROCK inhibitor likely to be the first drug in this class to be approved. "The reason prostaglandins work so well is that they're dosed once a day, they provide good pressure reduction and the major side effects are all related to the eye, mostly hyperemia issues," he says. "For any alternative to take over as first-line therapy, it has to be comparable—if not better—in those respects. I think some of the Rho kinase inhibitor products in the pipeline might fit that description, in particular Rhopressa and Roclatan, the latter being a fixed combination of Rhopressa and latanoprost. Both Rhopressa and Roclatan are dosed once a day, and they don't appear to have any major systemic side effects; just ocular side effects comparable to what we see with the prostaglandins.

"They may provide a couple of other benefits as well," he continues. "Rhopressa is currently believed to have three mechanisms that lower IOP—via enhancement of the conventional trabecular meshwork pathway; through the reduction of aqueous production; and also through the novel method of decreasing episcleral venous pressure. Notably, all three are different from the mechanism used by prostaglandins: increasing uveoscleral flow. So if you combine Rhopressa and a prostaglandin, you're lowering pressure through four mechanisms."

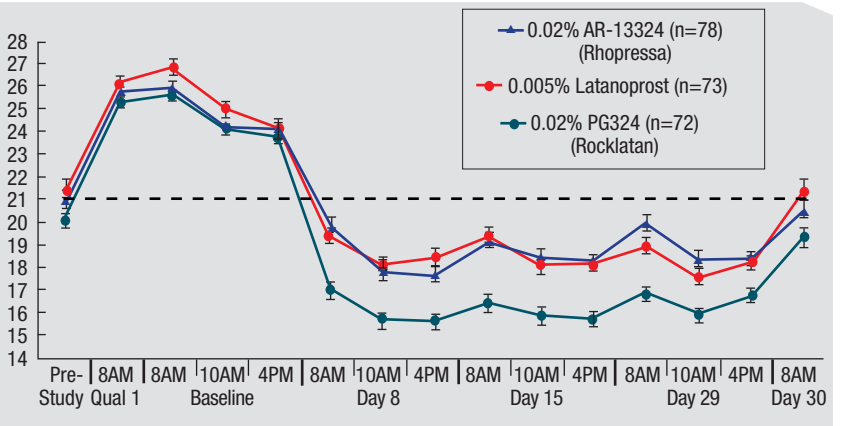
Dr. Teymoorian notes that a ROCK inhibitor has the potential to be an effective tool when treating low-tension glaucoma. "This is one of the hardest types of glaucoma to take care of because the IOP is already low, but you need to get it down even further," he says. "ROCK inhibitors are relevant here because episcleral venous pressure is a factor in Goldmann's equation for determining IOP, and none of the current medications really addresses that. The ROCK inhibitors, at least in animal models, have been shown to bring episcleral venous pressure down. Essentially, there's a certain level of IOP you can't get below [without creating hypotony] because episcleral venous pressure is always present. No matter how much you reduce aqueous production, or how much you enhance aqueous outflow, you still have to deal with that factor. So in special cases like low-tension glaucoma, ROCK inhibitors may work well, simply because they appear to address that aspect of the pressure equation.

Dr. Teymoorian says another possible advantage of ROCK inhibitors that remains to be confirmed is antifibrogenic properties seen in cultures of human trabecular meshwork cells. "There is some evidence that ROCK inhibitors may help to regenerate or rejuvenate a diseased trabecular meshwork," he says. "That might explain why these drugs appear to increase flow through that pathway."

Even with these potential selling points, Dr. Realini is skeptical that Rhopressa will become a first-line alternative to PGAs. "The problem is that it doesn't appear to lower intraocular pressure enough when a patient starts with very high pressure, even though it did a good job if the starting pressure was below the mid-20s," he says. "This is a perfect example of why we haven't had a new class of drugs in 20 years. The PGAs set the bar really high. For a new drug to become the preferred first-line agent, it would have to lower IOP significantly more than PGAs to justify the cost of a new branded product over a generic PGA."

Dr. Teymoorian agrees that the reduced efficacy of Rhopressa when the starting pressure is higher than the mid 20s was one of the important

IOP Reduction: Rho Kinase vs. Prostaglandin vs. Combination



A recent double-masked, randomized, controlled 28-day study in patients with open-angle glaucoma or ocular hypertension suggests that the Rho kinase inhibitor Rhopressa can be about as effective as latanoprost; combining them may be even more effective.[8]

Sustained-delivery systems are another potential contender for first-line glaucoma treatment. One option under investigation is the bimatoprost ring (ForSight Vision5), which provides sustained delivery of glaucoma medication for six months. It is first placed by the physician under the upper eyelid, then under the lower lid. After placement it is barely visible at the medial edge of the eye.

findings to come out of the ROCKET study. "This may be a result of the fact that Rhopressa appears to reduce the episcleral venous pressure," he explains. "EVP is a constant number, whether the patient's intraocular pressure is 22 or 42 mmHg, so reducing episcleral venous pressure will have a much smaller impact if the patient's starting pressure is high. For example, if your IOP is 24 mmHg and your episcleral venous pressure is 8 mmHg, you could theoretically lower the pressure by a third by addressing EVP. If your pressure is 40, the EVP only represents one-fifth of that, so reducing it won't have as big an impact.

"It's important to keep the practical side of this in mind," he adds. "If you look at the Baltimore Eye Study, 80 percent of the glaucoma patients had a pressure lower than 26 mmHg. As a glaucoma specialist, I see this all the time; most of our patients come in with pressures in the upper teens and low 20s. So even though Rhopressa wouldn't work as well on patients with pressures above 26 mmHg, it could be a valid first-line drug for most of my patients. In addition, it could be a major player in the patients who do have higher pressures, because most eyes above 26 mmHg will need more than one mechanism of therapy. If the patient comes in at 30 mmHg, a 25-percent reduction from a prostaglandin will get you down to 21 or 22 mmHg. Chances are, that's still too high; you're going to need an adjunctive therapy. In that case, you might very well end up prescribing both a prostaglandin and a ROCK inhibitor."

Other New Drugs

Other drugs in the pipeline may offer advantages over prostaglandins, although it's not clear yet whether those advantages will be sufficient to cause them to replace prostaglandins as the first-choice option.

Trabodenoson (Inotek Pharmaceuticals) is a first-in-class selective adenosine mimetic designed to lower IOP by restoring the function of the trabecular meshwork, currently in Phase III development. A Phase II, randomized, double-masked, placebo-controlled study tested four different dosages of the drug administered twice daily for two or four weeks in subjects with ocular hypertension or primary open-angle glaucoma.[1] The drug was well-tolerated, producing no meaningful ocular or systemic side effects. It produced a statistically significant reduction in IOP that increased with greater dosage, and the reduction was significantly greater at day 28 than day 14 (p=0.0163), indicating increasing effect over time. The IOP reduction was also found to be consistent across different patient populations. Evidence from animal studies also suggests that the drug has a neuroprotective effect on retinal cells, but no studies have yet looked for that effect in human eyes.

"I don't think trabodenoson will outperform a prostaglandin," says Cadmus Rich, MD, vice president of clinical development at Inotek Pharmaceuticals. "We're not looking at necessarily being a first-line agent for most patients. However, we have a very good safety profile and clinically significant IOP lowering which I think makes us a good alternative if patients don't respond to or tolerate a prostaglandin. Our recent Phase II study that was published last month showed a median 4.1-mmHg IOP lowering from baseline, and that was at a lower dose than we're testing in our current Phase III study. The safety profile in Phase II was very good; we found minimal to no hyperemia and no systemic side effects.

"Trabodenoson produces a clear dose response when you look at the diurnal IOP lowering, and we have not reached an efficacy plateau," he continues. "For that reason we're using higher doses in our Phase III study, one that's twice as high as the dose in Phase II and one that's three times as high. We feel confident that we may get more pressure reduction than 4.1 mmHg; we just don't know how much higher."

Dr. Rich says they are currently testing a fixed combination with latanoprost. "We're hoping this will provide greater IOP lowering with minimal side effects," he says. "Unlike the prostaglandins, trabodenoson works at the trabecular meshwork through the conventional outflow pathway, so the mechanism is complementary. We conducted an unfixed combination study; patients on the combination showed very good lowering, and the additional lowering [caused by the

addition of trabodenoson] was similar to the amount of lowering seen in trabodenoson monotherapy." Noting that the Rho kinase drugs offer this potential advantage as well, Dr. Rich points out that trabodenoson has produced minimal hyperemia in studies—less than that seen with Rho kinase drugs. "Hyperemia is already a concern with prostaglandins," he notes. "Not adding more side effects to the prostaglandin would put us in a different category."

Another promising drug under investigation is latanoprostene bunod, a novel nitric oxide-donating prostanoid FP receptor agonist. Once inside the eye it's metabolized into latanoprost acid and butanediol mononitrate, which in turn releases nitric oxide. The nitric oxide causes relaxation of the trabecular meshwork and Schlemm's canal, resulting in increased outflow.

A Phase III, randomized, controlled, double-masked, parallel-group clinical study, involving 387 subjects 18 years of age or older with a diagnosis of ocular hypertension or open-angle glaucoma in one or both eyes, compared the diurnal IOP-lowering effect of latanoprostene bunod once every evening to timolol b.i.d. LBN reduced IOP significantly more than timolol throughout the day over three months of treatment; adverse events were similar in both groups.[2] Previous studies, including the Phase II VOYAGER study, compared the efficacy of LBN and latanoprost. VOYAGER involved 396 patients with open-angle glaucoma and OH; it showed that reduction in mean diurnal IOP from baseline was significantly greater with LBN than with latanoprost, suggesting the value of the added nitric oxide-donating component.[3]

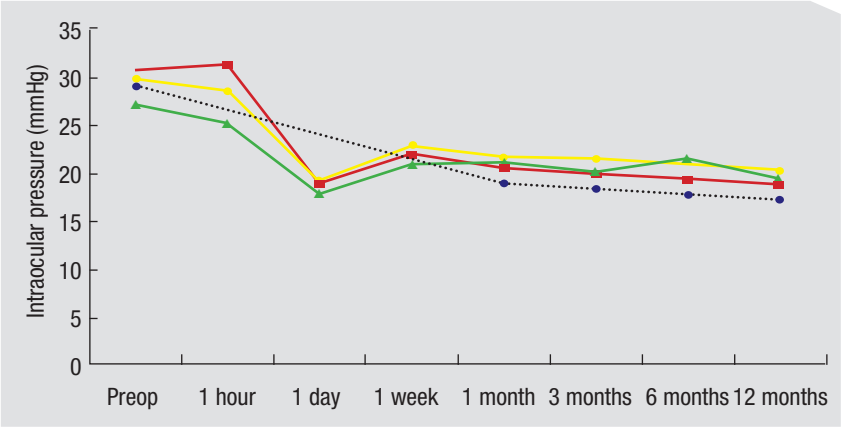
New Combination Drops

Adding one or more drops to a first-line prostaglandin is a common way to try to reduce IOP further when the prostaglandin alone isn't bringing the pressure down to a safe enough level. The drawback, of course, is that this tends to exacerbate the problems associated with adherence. Combining multiple drugs in a single formula minimizes that concern, but so far, no combination drug has come close to deposing prostaglandins from the first-line spot. With new drugs in the pipeline, however, that could change.

Dr. Realini points out that the choice to prescribe a fixed-combination drop as a first-line therapy has become more popular in the past two or three years, but it doesn't look like this option will replace prostaglandins as the first-line mainstay any time soon. "I do have a few patients who are on fixed combinations as primary therapy, but in most of those cases we started with a PGA and didn't get a great response," he says. "What we need is a drug that adds really well to a PGA. None of our current single drugs adds more than 2 to 4 mmHg of pressure reduction when combined with a PGA."

Dr. Realini notes that fixed-combination drops are doing better as adjuncts to first-line prostaglandins. "Now that generic fixed combinations have started to become available, fixed combinations are becoming much more commonly used as an adjunct to PGAs—they can give you 5 to 8 mmHg of additional IOP reduction," he says. "But this still means the patient is dealing with two bottles and dosing at least twice a day. The ROCK inhibitors may change that. Preliminary data suggest additivity to PGAs, and a fixed combination [Roclatan] is in clinical trials now. If that works out, the patient could use one drop per day and get a better IOP reduction than with PGA monotherapy. Once a drug lowers pressure 3 or 5 points better than a PGA with once-daily dosing, it's going to be many people's first-line choice."

Latanoprost vs. SLT (90, 180 and 360 Degrees)



Selective laser trabeculoplasty is about as effective as a prostaglandin when used as first-line therapy instead of as an adjunct, as demonstrated in this 2005 study.[6] (Black line–latanoprost; green–SLT 90 degrees; yellow–SLT 180 degrees; red–SLT 360 degrees.)

Dr. Teymoorian agrees. "Naturally, we will run across patients in whom a prostaglandin isn't sufficient to control pressure," he says. "In that situation our alternatives would be either to add a second medication or find a better first-line medication. Adding a drug that uses multiple different pathways would be a reasonable option, and if you end up using Rhopressa as a secondary agent and the patient does well, the patient could then be switched to a Roclatan type of product. That would take the patient from two medications once a day back to a single medication once a day, and it would be quadruple-mechanism therapy without any major systemic side effects."

SLT as First-line Therapy

Another candidate for first-line treatment is selective laser trabeculoplasty. Dr. Realini has done extensive work with SLT; he believes its relatively limited use as first-line therapy is the result of some inaccurate popular beliefs. "SLT is at least as safe—and probably safer—than a prostaglandin," he says. "Plus, it has convenient once-every-year-or-two dosing, as opposed to once-daily dosing. And despite what many people believe, SLT is comparable in efficacy to a prostaglandin when used as a first-line option. Studies in the literature that have compared SLT to a prostaglandin have found them comparable.[4-6]

"The idea that SLT is less efficacious is perpetuated partly because most surgeons use SLT as their second, third or fourth intervention and find that it doesn't work as well as a first-line prostaglandin," he continues. "That's not a reasonable comparison, because no drug works as well third-line as it does first-line. Consider what happened when latanoprost came on the market. At first, no one knew what to do with it. It had all these weird side effects. So, for the first year after Xalatan launched, it was being used third- or fourth-line. Not surprisingly, people's perception was that it didn't work nearly as well as it seemed to work in the studies, where it lowered pressure 7 to 9 points. The reason it worked better in the studies was that it was dosed as first-line monotherapy, not third- or fourth-line therapy. Clinicians were using it in eyes that had already proven themselves difficult to treat because they needed three or four medications.

"That's exactly where we are now with SLT," he says. "We just need to get more people trying it first-line. I encourage most of my newly diagnosed patients to consider SLT over prostaglandins as their first therapy."

Dr. Realini notes that surgeons' intellectual understanding of the benefits of SLT hasn't yet translated to a paradigm shift in the clinic. "I've been at meetings in a room with hundreds of glaucoma specialists," he says, "and I've asked, 'How many of you encourage newly diagnosed glaucoma patients to do first-line laser therapy?' On average, 5 to 8 percent of hands will go up. Then I ask, 'How many of you, if you developed glaucoma tomorrow, would want SLT first-line?' Virtually every hand in the room goes up. Why would you take care of your patients differently than you would take care of yourself?

"I think there are several reasons the shift to first-line SLT hasn't happened yet," he continues. "If you haven't thought about how to talk to patients about SLT it becomes awkward. It's much easier to write a prescription and say, 'Here, take this,' than it is to have a conversation about a procedure." He also notes that the doctor's perception of SLT's efficacy will have a huge impact on whether a patient is willing to try it. "You have to believe that it works or you won't be able to sell it," he says.

"Many surgeons who offer SLT at the outset say something like, 'There's this laser we could try,' " he continues. "A patient is not going to find that inviting. On the other hand, you could say something like this: 'We could try a once-a-day eye drop, but there's also a laser treatment that's available. Personally, if I developed glaucoma tomorrow, I'd have the laser tomorrow afternoon. I don't want to have to remember to put drops in my eye every day and deal with potential side effects, and have to remember to go to the pharmacy every month to get the drops.' If you present the SLT option that way, most of your patients will say

'OK, I want the laser, too.'

"Another obstacle is a feeling some doctors have that offering SLT as a first-line treatment isn't standard," he says. "If you believe that, then you have to have a longer discussion with the patient and justify what you're doing. That will never be time-efficient, and you're not likely to get the patient to agree to have the procedure. You have to believe in your heart that laser is a better first-line option and say so."

Dr. Realini points out that trying SLT doesn't reduce the viability of any other options (such as drops) down the road. "Even if SLT only worked as a first-line treatment in half of your patients," he says, "wouldn't it be worth trying on everyone so that half of your patients are living a drop-free lifestyle, with no preservatives, no ongoing costs, no adherence issues and no tolerability concerns?"

Extended-release Options

Given that a major drawback of prostaglandin drops is adherence, it seems reasonable that an extended-release modality—whether delivering a prostaglandin or some other drug—might eventually replace prostaglandin drops. However, this type of delivery system is turning out to be difficult to achieve, and it might not be ideal as a first-line choice for most patients even if it works.

According to Gary D. Novack, PhD, professor of pharmacology and ophthalmology at the School of Medicine at the University of California, Davis, and president of PharmaLogic Development of San Rafael, Calif., which provides development expertise to pharmaceutical and medical device companies, there are at least seven prostaglandin drug delivery systems in clinical development. "Some of these systems apply the drug to the front of the eye via a punctal plug or a scleral ring," he says. "Some require subconjunctival injection, and some require intracameral injection. The ones on the front of the eye are noninvasive, which is a plus. However, each of those has its own issues. For example, punctal plug delivery systems have to remain in place in order to work, which is hard to guarantee, and the patient has to be able to tell if the plug has fallen out.

"There was a sustained-delivery product back in the 1970s called Ocusert, a pilocarpine delivery system that was developed by Alza," he recalls. "That was a good delivery system for pilocarpine, which is very short-acting and effective at lowering IOP. The pilocarpine was cast as a film with alginic acid and then surrounded by an ethylene/vinyl acetate copolymer; it was placed in the lower cul-de-sac where it slowly released the drug, making it last a week. The product was approved and worked especially well for younger patients with accommodation because the pulsatile nature of pilocarpine delivered as a drop resulted in irregular accommodation over the course of the day. That effect had been bothersome to many patients, and this system stabilized that. The downside was that the device could unexpectedly slide across the cornea and obscure visibility. That could be a big problem if the patient happened to be driving at the time, and there were some case reports of that happening. These are the kinds of issues you run into with an external drug source.

"Injected drug delivery options have different issues," he continues. "We're more comfortable with intraocular injections these days, but any time you go into the eye there are a number of risks. Also, these systems are not injecting drugs in solution; a solution would dissipate. These involve delivery units that take up space. That means there is the potential for the injected material to occlude part of the angle. Subconjunctival injections might be a happy medium, in terms of the injection risks, because they don't

Sustained-delivery options under investigation include Envisia's ENV515 (left) designed to deliver travoprost and reduce pressure for more than six months; and Allergan's Bimatoprost SR (right) shown with its prefilled, single-use applicator for intracameral administration.

go inside the eye."

Dr. Teymoorian is skeptical that patients will accept long-term delivery options that are invasive. "My concern is, if I offer to give the patient an injection, I think people will still opt for eye drops," he says. "Obviously, we want to eliminate the problem of noncompliance, and an injection would accomplish that. But there are risks you take with an injection that you don't with an eye drop. If an eye drop doesn't work, you simply stop using it. If the injection doesn't work, you have something inside the eye."

Dr. Novack notes another problem with sustained delivery systems: Not every glaucoma drug will work if delivery is steady rather than pulsatile. "A so-called zero-order delivery system that provides a steady output of a drug might work well for pulsatile drugs like timolol or pilocarpine," he says. "It's not clear how well that type of delivery will work with prostaglandins, which are somewhat unique. We know that placing a drop of a prostaglandin twice a day is less effective than doing so once a day. That raises the question as to whether steady-state delivery is the way to go, or whether these drugs need some pulsatility in order to work. We don't know what the consequences of constant delivery might be. Even with drugs like timolol or brimonidine, steady delivery could conceivably raise the risk of systemic side effects."

Dr. Realini says he doesn't see devices that provide sustained drug delivery as a holy grail for glaucoma drug therapy. "First of all, it appears that they are slightly less effective than their eye-drop counterparts," he says. "It turns out that if you constantly flood the eye with drug molecules, the receptors appear to downregulate over time; they become a little desensitized. In contrast, in daily therapy you put a drop in the eye and it binds to the receptor; then the receptor goes for hours without seeing any more drug, so there's no reason for it to become sensitized. It has a downtime recovery period between doses. Admittedly, the difference in effect is very small, probably on the order of a millimeter of mercury or so, and the long-term benefits of a sustained-release option—such as reduction in exposure to preservatives, assurance that the patient isn't missing doses and better overall circadian coverage—probably outweigh that.

"However, another question is, when would these devices be used?" he continues. "Suppose Mrs. Johnson has been taking a prostaglandin every day for the past 20 years and she's doing really well. Why would you switch to something invasive and more expensive? And why would her insurance company pay for that? That's the situation most of our patients are in. And if you have a patient who is not doing well and is getting worse, the only way in which sustained delivery could possibly improve that situation is if you are absolutely convinced that adherence is the reason the patient is getting worse. And how are you going to prove that?

"So I don't know where those things will fit in," he says. "Everyone says, 'Look at macular degeneration. The patients tolerate monthly injections and the insurance companies pay for it.' But would they pay for it if there was a topical anti-VEGF drop that patients could take every day? It's not an apples-to-apples comparison."

Dr. Novack says he doesn't believe we have enough data yet to say too much about the efficacy and safety of these devices. "So far, we've only seen Phase II data on a few of these products, and of those, only three have shown ocular hypotensive efficacy similar to what you might expect from a daily drop of prostaglandin," he says. "To date, no delivery system has produced greater IOP lowering that you would achieve with a drop, and some have been less effective. So, given the data we have right now, it appears that these options will be primarily for patients with financial or capability limitations."

Dr. Novack also wonders whether the American health-care system will be able to cover the cost of these devices. "We're talking about paying the cost of compensating for poor patient adherence and performance," he says. "Along with the problem of patients not always wanting or remembering to take their drugs at the right time—and continuing to do that for the rest of

their lives—we also know that people have difficulty getting the drops onto their eyes. I coauthored a paper with Alan Robin, MD, showing that only one-third of experienced glaucoma patients could put in a drop correctly.[7] If we can solve this using a new delivery system that's priced at a premium, will the health-care system pay for it? We don't know."

Nevertheless, Dr. Novack believes a sustained-delivery system could become a first-line option for certain patients. "There are some patients for whom eye drops don't work," he says. "Some patients clearly can't adhere to a treatment protocol or get the drops onto their eye. It's possible that a drug delivery system could be a first-line treatment for that kind of patient. And whether or not they become a first-line treatment option, they will serve a crucial purpose. Years ago I worked in the contraceptive field. We used to argue that abstinence is 100-percent effective; the problem is, its 'real-use' effectiveness isn't that great. You may have the greatest drug in the world, but if the patient doesn't take it won't be very effective. So you could argue that some of these delivery systems will offer patients real effectiveness. That's not a small thing." REVIEW

Dr. Realini is a consultant to Alcon, B+L, Valeant and Inotek; he receives research support from Alcon, Topcon and OptoVue and is on the speaker's bureau for Lumenis. Dr. Novack has worked with more than 300 companies, including Aerie Pharmaceuticals and B+L, to develop products. Dr. Teymoorian is a researcher and consultant for Aerie.

1. Myers JS, Sall KN, DuBiner H, Slomowitz N, McVicar W, Rich CC, Baumgartner RA. A dose-escalation study to evaluate the safety, tolerability, pharmacokinetics, and efficacy of 2 and 4 weeks of twice-daily ocular trabodenoson in adults with ocular hypertension or primary open-angle glaucoma. J Ocul Pharmacol Ther 2016 Mar 22. [Epub ahead of print]

2. Robert N. Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: The APOLLO study. Ophthalmol 2016:123;5;965-73.

3. Weinreb RN, Ong T, Scassellati Sforzolini B, et al. A randomised, controlled comparison of latanoprostene bunod and latanoprost 0.005% in the treatment of ocular hypertension and open angle glaucoma: The VOYAGER study. Br J Ophthalmol 2015;99:738–745.

4. McIlraith I, Strasfeld M, Colev G, Hutnik CM. Selective laser trabeculoplasty as initial and adjunctive treatment for open-angle glaucoma. J Glaucoma 2006;15:2:124-30.

5. Katz LJ, Steinmann WC, Kabir A, Molineaux J, Wizov SS, Marcellino G; SLT/Med Study Group. Selective laser trabeculoplasty versus medical therapy as initial treatment of glaucoma: A prospective, randomized trial. J Glaucoma 2012;21:7:460-8.

6. Nagar M, Ogunyomade A, O'Brart DPS, Howes F, Marshall J. A randomised, prospective study comparing selective laser trabeculoplasty with latanoprost for the control of intraocular pressure in ocular hypertension and open angle glaucoma. Br J Ophthalmol 2005;89:11:1413–1417.

7. Stone JL, Robin AL, Novack GD, Covert DW, Cagle GD. An objective evaluation of eyedrop instillation in patients with glaucoma. Arch Ophthalmol 2009;127:6:732-6.

8. Lewis RA, Levy B, Ramirez N, C Kopczynski C, Usner DW, Novack GD; PG324-CS201 Study Group. Fixed-dose combination of AR-13324 and latanoprost: A double-masked, 28-day, randomised, controlled study in patients with open-angle glaucoma or ocular hypertension. Br J Ophthalmol 2016;100:3:339-44. doi: 10.1136/bjophthalmol-2015-306778. Epub 2015 Jul 24.

Flatten the iStent Learning Curve

Walter Bethke, Managing Editor

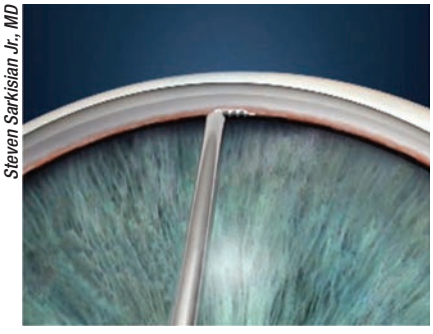
The pearls to employ, and pitfalls to avoid, when using the device.

Assimilating a new surgical technique into your practice can be a slow, sometimes painful process in which you battle with unforeseen results and complications until you eventually feel competent. If you're currently starting out with the iStent, or maybe have a few cases under your belt but are hungry for more tips, surgeons say there are steps you can take before, during and after the surgery to avoid problems and get better outcomes. To benefit from these surgeons' experiences, read on.

The Procedure Explained

For surgeons who are unfamiliar with the iStent procedure, which occurs in the setting of cataract surgery, here's a brief summary of the main implantation steps:

- Under viscoelastic, the surgeon puts the iStent inserter through the cataract wound;
- The surgeon uses a gonio prism to view the angle; and
- The inserter engages the trabecular meshwork and the iStent is advanced into Schlemm's canal, into which it's released and secured.



Steven Sarkisian Jr., MD

After engaging the trabecular meshwork with the tip of the iStent, the surgeon flattens it out and implants it in the canal.

Practice Makes Perfect

Surgeons say you can do your own version of a wet lab in your OR by practicing some of the maneuvers required during iStent implantation during some of your routine cataract procedures.

"I definitely recommend that, before you start to do the iStent officially, you do some practice," avers Steven Sarkisian Jr., MD, director of the glaucoma fellowship at the Dean McGee Eye Institute at the University of Oklahoma. "On a routine day when you're doing a lot of surgery, actually practice turning the patient's head 30 degrees away from you and turning the microscope as well. Also practice using the gonio prism. You can do this after you put the lens in but before you remove the viscoelastic; just put a little viscoelastic on the cornea, turn the head and use the gonio prism to visualize the

trabecular meshwork. See if you can identify the meshwork, the scleral spur and the ciliary body. Become familiar with how the process feels. I wouldn't necessarily go in with any instrumentation while you're doing this, though some have advocated putting a Sinskey hook or similar instrument through the cataract wound to see what it feels like to have it in your dominant hand with the gonio prism in the other. However, be careful, because if the patient moves, there could be an added risk since the head isn't taped at that moment of the surgery. If you get familiar with the necessary head position and what's required to adequately visualize the angle and angle structures, that would mean fewer variables for you to deal with on the day you start your first iStent surgery."

Timing the Implantation

The first decision the surgeon will be faced with is to implant the stent before or after phaco. Experts say there are pros and cons to each approach.

Nathan Radcliffe, MD, director of the glaucoma service and clinical assistant professor at New York University's Langone Medical Center, prefers to implant the iStent after the cataract surgery has been completed. "I was trained to do it this way and have never had any problems," he says. "The potential disadvantage of this approach is, if you have corneal edema after the cataract surgery, you may have trouble visualizing the trabecular meshwork. I have found that even with corneal edema, however, the view is usually good enough."

Dr. Sarkisian also performs the implantation after phaco. "I don't advocate placing it before phaco, especially when you're learning, because when you put an iStent in a phakic eye, the angle structures look different. When the eye is slightly hypotonous after phaco, especially if the patient has a lightly pigmented trabecular meshwork, you want to see that blood reflux in the canal, which you're not going to experience as much when the eye is phakic. Plus, if there should be any bleeding during the iStent implantation, it can distort your view when you make your capsulorhexis."

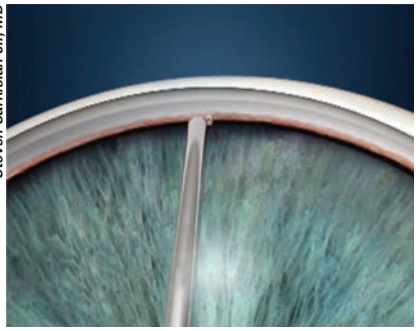
York, Pa., ophthalmologist Denise Visco, who has been learning quickly as she's begun implanting the iStent, offers another reason why some surgeons prefer to implant the device after their cataract surgery. "I like implanting it at the end of the procedure," she says, "because if there are issues or problems with the iStent, I don't want them disrupting the cataract surgery. I want to perform a perfect cataract procedure and have that completed before I attempt the iStent insertion. However, there will be more blood reflux from Schlemm's when you implant it after the cataract surgery, which can be a hindrance in some cases."

Modifying Your Technique

Since implanting the iStent introduces a new wrinkle into your cataract surgery, surgeons say minor modifications to your cataract technique can be helpful.

"While I know that most physicians will be making temporal incisions, those who currently make superior incisions have some decisions to make," explains Dr. Radcliffe. "It's certainly possible to place a stent in the inferior angle through the superior incision, but I don't think it's easy. To begin with, you'll be dependent on torqueing the eye inferiorly, rather than simply tilting the head position as temporal surgeons can do. The Vold Gonio lens, available from Transcend Medical, and a gonio lens clip available from Glaukos may facilitate moving the globe without changing head position.

"One tip that I think is important for surgeons, wherever they make their wounds, is to be sure not to involve any limbal vessels in your wound construction if you're planning on placing a stent," continues Dr. Radcliffe. "Even the smallest bleeding vessels around the region of the wound can cause blood to be mixed in with the Goniosol on the surface of the eye, hampering the view and making things quite frustrating."



Steven Sarkisian Jr., MD

Just because the tip is in doesn't mean the job's done; tapping the snorkel ensures that the iStent is fully implanted.

Dr. Visco says a temporal wound is key for her. "I like to make my cataract wound temporally so I can come straight through the incision instead of coming at an angle," she says. "This is because when you hold the gonio lens with one hand and you're coming straight with the other, you don't want to have your hand at an angle; you want your incision right in front of you. I'll make the incision at 180 degrees or zero degrees, depending on which eye I'm operating on.

"And if you're performing femtosecond AK incisions with your cataract surgery, wait to open the incisions until after the iStent is in place," Dr. Visco adds. "That way, you won't risk having issues with visualization. If you open an AK incision and the patient happens to have a little bit of epithelium that erodes off of there or has a little abrasion near the AK incision, that could potentially have a negative effect on your image with the gonio lens when you're looking at the angle."

Dr. Visco keeps the same topical anesthesia regimen as in her normal cataract cases. "Though iStent implantation is easier for you if you use retro-

bulbar, giving you more control over the eye, I didn't want to have to say to my patients, 'You're getting a retrobulbar injection because you're getting the iStent.' However, if you're really struggling, retrobulbar is one thing you could do to help make it easier."

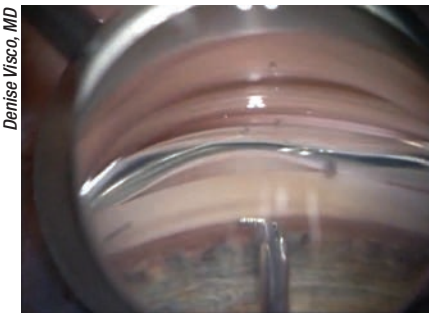
The Insertion Phase

Once the surgeon has set the stage with the proper cataract wound creation and has practiced with the gonio lens preoperatively, he's ready to tackle the iStent implantation itself. It's at this stage, surgeons say, that there are several tips and techniques that can add up to improved outcomes.

• ***Proper positioning.*** Getting the patient's head, the gonio lens and the surgical microscope into perfect alignment makes the procedure a lot easier, experts say.

"Generally speaking, we tilt the patient's head 30 degrees away from us," says Dr. Radcliffe. "However, each physician may develop a personalized angle. If the patient has a neck problem or is unable to tilt the head, it's possible to get the appropriate angle entirely with scope positioning. Additionally, for patients under topical anesthesia, the patient may remain in the supine position and just direct her eyes away from the surgeon. An issue in that case is that if the patient decides to move her eyes back to primary position while an instrument is in the angle, a cyclodialysis cleft could develop. The other issue is that patients aren't always able to titrate their degree of eye movement, and it may vary from moment to moment, so this introduces some additional variability into the procedure."

"You may have to move the head around a bit," says Dr. Sarkisian. "Even after having done hundreds of cases of angle surgery, I will still have to move it sometimes. In some cases, I note that I've not turned the head enough or I've turned it too far. People's heads are simply different. There's no one fixed place it has to be. Just put it in a place where you see the best. Sometimes the patient will help you with the head positioning, and sometimes he won't help and will instead look toward you."



Denise Visco, MD

Some surgeons may find it easier to manipulate the iStent inside the eye using a micrograsper forceps.

Dr. Visco says if you're having an issue with visualization, you can also manipulate the microscope angle. "If you've turned the patient's head the recommended number of degrees but are still having issues with visualization, you can turn your microscope more toward yourself," she says. "Because if you turn the patient more, then you'll just be reaching at an unnatural angle to try to put in the stent. To help prepare patients, I'll instruct them in the office and in the preop area to remember to keep their eyes looking straight ahead even when I turn their head and not to shift their gaze back toward me."

Your approach to gonioscopy will have an effect on the ease of the procedure as well, and there are even specially made stabilizers for gonio lenses to assist the iStent surgeon. "When using the gonio lens, you don't want to press too firmly on the cornea, which can create striae and obstruct your view," explains Dr. Sarkisian. "The kind of gonio prism you use will help when you're starting out with the iStent. There's a new device from B+L/Storz that can be placed onto your gonio prism to help stabilize the globe, the Berdahl Gonio Prism Stabilizer. I've done a trial of it and I was impressed with the way it stabilizes the globe in a way that's more friendly to the conjunctiva than, say, a Thornton ring might be, since it's more comfortable for the patient. It's also a lot easier to use even if the interpalpebral fissure is very narrow; you can still stabilize the lens nicely."

The amount of viscoelastic you use can also play a role in visualization. "Don't over- or underinflate the anterior chamber with viscoelastic," advises Dr. Sarkisian. "If you overinflate, you'll tamponade the blood in Schlemm's canal and possibly distort the angle architecture. If you underinflate, the iris will get in the way. You need to get the right level of inflation."

• ***Finding the best implant site.*** Surgeons say there are signs you can look for in order to find the right place to implant the iStent, but add that, if you're starting out with the device, it might be best to not get too hung up on finding the perfect spot. "Though Dr. Ike Ahmed has discussed targeting specific regions in the trabecular meshwork to enhance efficacy, my advice for most surgeons is to simply put the stent in the location where you have the greatest chance of getting it in correctly," says Dr. Radcliffe. "For most people, this is going to be directly nasal to the temporal corneal incision, or perhaps offset by less than one clock hour. For example, if I'm doing a right eye and I have a temporal incision, then I may put the left-handed stent in at the 2 o'clock position, because the natural curvature of the eye will provide a 15-degree angle, which is ideal for stent insertion."

If you want to hunt for the ideal spot, Dr. Sarkisian says there are landmarks to watch for. "After phaco, the patient is in a relatively hypotonous state, so you can see blood in Schlemm's canal," he says. "Seeing pockets of blood there clues you in on where the outflow is going to be best, and where there's probably a collector channel. That's really where you want to put in the iStent, and you'll find your results significantly

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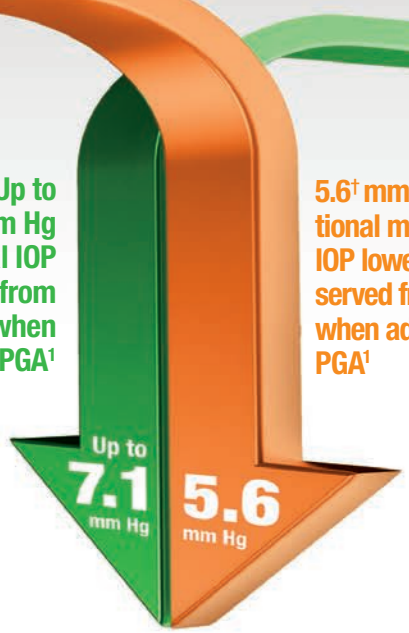
Up to 7.1 mm Hg additional IOP reduction from baseline when added to a PGA[1]

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



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

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

		Mean Diurnal IOP (mm Hg)[1‖]
Treatment Arm		
PGA + SIMBRINZA® Suspension (N=83)	Baseline¶	22.7
	Week 6	17.1
PGA + Vehicle (N=92)	Baseline¶	22.4
	Week 6	20.5

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

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

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

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

BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

Contamination of Topical Ophthalmic Products After Use - There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products. These containers have been inadvertently contaminated by patients who, in most cases, had a concurrent corneal disease or a disruption of the ocular epithelial surface *[see Patient Counseling Information]*.

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

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

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

Tricyclic Antidepressants - Tricyclic antidepressants have been reported to blunt the hypotensive effect of systemic clonidine. It is not known whether the concurrent use of these agents with SIMBRINZA® Suspension in humans can lead to resulting interference with the IOP lowering effect. Caution is advised in patients taking tricyclic antidepressants which can affect the metabolism and uptake of circulating amines.

Monoamine Oxidase Inhibitors - Monoamine oxidase (MAO) inhibitors may theoretically interfere with the metabolism of brimonidine tartrate and potentially result in an increased systemic side-effect such as hypotension. Caution is advised in patients taking MAO inhibitors which can affect the metabolism and uptake of circulating amines.

USE IN SPECIFIC POPULATIONS

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

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

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

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

It is not known whether brinzolamide and brimonidine tartrate are excreted in human milk following topical ocular administration. Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from SIMBRINZA® (brinzolamide/brimonidine tartrate ophthalmic suspension) 1%/0.2%, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use - The individual component, brinzolamide, has been studied in pediatric glaucoma patients 4 weeks to 5 years of age. The individual component, brimonidine tartrate, has been studied in pediatric patients 2 to 7 years old. Somnolence (50-83%) and decreased alertness was seen in patients 2 to 6 years old. SIMBRINZA® Suspension is contraindicated in children under the age of 2 years *[see Contraindications]*.

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

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

U.S. Patent No:
6,316,441

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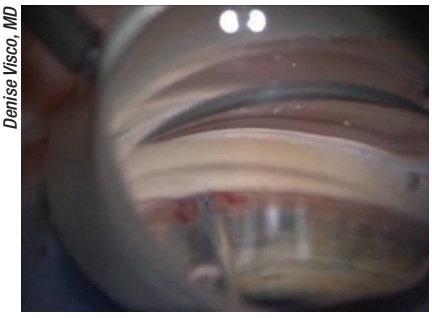
improved if you do that. Another tip is to look for collections of pigment in the angle because, again, what the draining action looks like will reveal where the higher levels of outflow are. It's kind of like finding the drain in the bottom of a bathtub: Look for where the hair is collecting and that's where the drain is. In the eye, where the pigment is collecting is likely where the outflow is the fastest.

"Sometimes," Dr. Sarkisian adds, "if there's a lot of bleeding at the insertion site—especially early on in your experience with the stent when the procedure might take longer—you may need to take your I/A, remove the viscoelastic, and then place more of it. This is because, though more viscoelastic can help clear some blood, in some cases you'll get a blood clot in the angle. Taking out the viscoelastic and putting more in can clear the clot and restore your view."

• ***Maneuvering tips.*** Like many implantation techniques, placing an iStent involves some finesse as well as technical skill, say surgeons. "When you're placing the iStent in the trabecular meshwork, make sure you don't take too steep of an angle of approach," warns Dr. Sarkisian. "For beginning iStent surgeons, the training instructs them to go at a 15-degree angle into the meshwork and then flatten out. But I think whatever angle you need to pierce the trabecular meshwork is fine. However, as you place the iStent, remember that the eye is curved. You almost want the feel of using a fine paintbrush as you implant it, like painting eyelashes on the Mona Lisa. You go in, then kind of come toward yourself a little as you're implanting it so you don't hit the back wall of the canal. If you hit the back wall, the entire eye will move in the direction of your motion and you won't be able to implant it. You have to have a light touch. Once the iStent is in, tap the heel to make sure it's set firmly. Think about it like putting on a shoe. For a lot of surgeons, when they first implant the iStent, it's easy for them to get their toe in the shoe—to get the tip of the iStent implanted—but unless the heel of the stent is also planted firmly in, it's not going to work effectively. Just piercing the wall of the trabecular meshwork doesn't mean it's going to be effective. If you implant the iStent and find the heel is in somewhat but not in completely, I suggest re-grabbing the snorkel and pushing it in just a little bit more so that it's set firmly. Also, don't use a Healon cannula to tap it in. Use the inserter. This is because the lumen of the cannula is bigger than the snorkel of the iStent, so you can inadvertently explant the iStent with a Healon cannula."



Denise Visco, MD

When the iStent pierces the trabecular meshwork, the resulting blood can sometimes make visualization challenging.

• ***Consider using forceps.*** Dr. Visco says it may be easier for some surgeons to eschew the iStent inserter for the actual implantation and instead use a micrograsper forceps. "I'll release the iStent from the iStent inserter in the area of the angle, remove the inserter, and then go back in with a micrograsper," she says. "I'll use the forceps to pick up the iStent and then insert it. I find this gives me more control over the iStent, because I can open and close the forceps as needed. Specifically, it's easier to engage Schlemm's at the 15-degree angle and then flatten it and thread it into the canal with the forceps, because you can tap it down flat, and then re-grab it immediately and continue to advance it. *(See image, p.42)* There's less manipulation and wrist movement necessary than with the injector. With the inserter, once you hit that 15-degree angle, you have to rotate your wrist in a way that doesn't necessarily come easily or feel natural. And, if you put too much pressure on the stent before you release it, you cause a problem in which the stent is ejected that messes up the insertion. With the forceps, you can easily change the angle of approach by continually releasing and re-grasping the iStent. Also, with the inserter, you have to make large moves with your wrist to make small adjustments inside the eye which can cause corneal distortions at the entry wound that can interfere with your view. With the forceps, you don't have to move your hand as much to maneuver the iStent in the eye."

Adverse Event Management

In the Food and Drug Administration trial of the iStent, Glaukos reported the most common adverse events were early postoperative corneal edema (8 percent); loss of a line of best-corrected vision at or after three months postop (7 percent); posterior capsular opacification (6 percent); stent obstruction (4 percent); early postoperative anterior chamber cells (3 percent); and early postoperative corneal abrasion (3 percent). Surgeons say their experience with the device has taught them some things about managing adverse events, as well.

"Corneal abrasions or erosions can occur with the lightest touch," says Dr. Visco. "Certain patients with anterior basement membrane dystrophy or even just dry eye can have these issues. I had one patient with very dry eyes who, by the time we got to the OR, had such a dry eye from the preop dilation drops that I had difficulty seeing when performing her cataract surgery. I didn't even attempt the iStent because she had such a keratopathy from just the dilation drops."

Dr. Sarkisian says to watch your postop medication regimen. "Frankly, the number-one complication with the iStent is the use of too strong a steroid or too high a steroid dosage postop," he avers. "You can get a steroid response from either of these factors. The party line is not to change your postop phaco medication regimen, which is fair, since you don't want to overhaul your normal postop management. However, I personally use loteprednol, a milder steroid, afterward rather than prednisolone acetate, due to the many steroid responses I've seen. Also, you won't know what the patient's final IOP will be for two to three months. So, if the patient isn't quite at your target IOP right away, be patient. Remember that even low-dose loteprednol can have a steroid response.

"The other postop complication," Dr. Sarkisian adds, "is, in rare cases, if patients aren't compliant at all with their steroids, or if the angle was slightly narrow before surgery, you can have peripheral anterior synechiae focally of the iris to the iStent. Interestingly, using very low energy, you can YAG the tip of the iStent and get rid of the PAS. I've only seen that twice in hundreds of iStent cases, however." Surgeons say there can be transient hyphema in a few patients postop, as well.

Denise Visco, MD

Some surgeons say using forceps allows them to release and re-grasp the stent without large, unnatural wrist movements.

Dr. Sarkisian says if things aren't spectacular from the outset, stick with it. "Surgeons who start using the iStent may be discouraged in their first couple of cases if they don't feel that it went very well or it wasn't as effective as they'd hoped," he says. "You have to stick with it, because once you get comfortable implanting the iStent—and that takes between five and 20 cases depending on the surgeon—you'll get better at predicting where to implant the device so it will be more effective." REVIEW

Drs. Sarkisian and Radcliffe are consultants for Glaukos. Dr. Visco has no financial interest in the products discussed.

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

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

Indications and Usage

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

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

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

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

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

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

Preservative-Free

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

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

Istalol®
(timolol maleate ophthalmic solution) 0.5%

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

BODY AS A WHOLE: Headache, asthenia/fatigue, and chest pain.

CARDIOVASCULAR: Bradycardia, arrhythmia, hypotension, hypertension, syncope, heart block, cerebral vascular accident, cerebral ischemia, cardiac failure, worsening of angina pectoris, palpitation, cardiac arrest, pulmonary edema, edema, claudication, Raynaud's phenomenon, and cold hands and feet.

DIGESTIVE: Nausea, diarrhea, dyspepsia, anorexia, and dry mouth.

IMMUNOLOGIC: Systemic lupus erythematosus.

NERVOUS SYSTEM/PSYCHIATRIC: Dizziness, increase in signs and symptoms of myasthenia gravis, paresthesia, somnolence, insomnia, nightmares, behavioral changes and psychic disturbances including depression, confusion, hallucinations, anxiety, disorientation, nervousness, and memory loss.

SKIN: Alopecia and psoriasiform rash or exacerbation of psoriasis.

HYPERSENSITIVITY: Signs and symptoms of systemic allergic reactions including anaphylaxis, angioedema, urticaria, and localized and generalized rash.

RESPIRATORY: Bronchospasm (predominantly in patients with pre-existing bronchospastic disease), respiratory failure, dyspnea, nasal congestion, cough and upper respiratory infections.

ENDOCRINE: Masked symptoms of hypoglycemia in diabetic patients (see WARNINGS).

SPECIAL SENSES: Signs and symptoms of ocular irritation including conjunctivitis, blepharitis, keratitis, ocular pain, discharge (e.g., crusting), foreign body sensation, itching and tearing, and dry eyes; ptosis; decreased corneal sensitivity; cystoid macular edema; visual disturbances including refractive changes and diplopia; pseudopemphigoid; choroidal detachment following filtration surgery (see PRECAUTIONS, *General*); and tinnitus.

UROGENITAL: Retroperitoneal fibrosis, decreased libido, impotence, and Peyronie's disease.

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

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Istalol® (timolol maleate ophthalmic solution) 0.5%

Initial U.S. Approval: 1978

STERILE

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

6.2 Postmarketing Experience

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

DRUG INTERACTIONS

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

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

PATIENT COUNSELING INFORMATION

Patients with bronchial asthma, a history of bronchial asthma, severe chronic obstructive pulmonary disease, sinus bradycardia, second or third degree atrioventricular block, or cardiac failure should be advised not to take this product. (see **CONTRAINDICATIONS, 4.1, 4.2**) Patients should also be instructed that ocular solutions, if handled improperly or if the tip of the dispensing container contacts the eye or surrounding structures, can become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated solutions. (see **WARNINGS AND PRECAUTIONS 5.8**) Patients should also be advised that if they have ocular surgery or develop an intercurrent ocular condition (e.g., trauma or infection), they should immediately seek their physician's advice concerning the continued use of the present multidose container. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five minutes apart. Patients should be advised that Istalol® contains benzalkonium chloride which may be absorbed by soft contact lenses. Contact lenses should be removed prior to administration of the solution. Lenses may be reinserted 15 minutes following Istalol® administration.

Rx Only

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Micro-invasive Devices: One in Play, More Ahead

Michelle Stephenson, Contributing Editor

Micro-invasive glaucoma surgery devices are currently under investigation, with others not far behind.

Micro-invasive glaucoma surgery is intended to lower intraocular pressure with less tissue disruption than traditional glaucoma surgeries. Currently, the iStent from Glaukos is the only Food and Drug Administration-approved MIGS implant; however, several more are at various stages of the FDA approval process.

"All of these devices have a small footprint on the eye, are very focused on the tissue being treated, and don't cause significant collateral damage. Many of them are also coupled with cataract surgery," says Malik Kahook, MD, who is a professor of ophthalmology at the University of Colorado School of Medicine.

According to Leonard Seibold, MD, when compared to filtering surgeries, MIGS may not be quite as effective at achieving very low IOP goals. "However, they are very effective for treating mild to moderate glaucoma that doesn't require such low target pressures in a much safer manner. Additionally, the surgery itself is more efficient, there is less risk for complications, and vision recovery is faster," adds Dr. Seibold, an assistant professor of ophthalmology at the University of Colorado School of Medicine.

Because of their safety, MIGS are typically used earlier in the disease process than other glaucoma procedures. "Our traditional glaucoma surgeries have been fraught with the potential for multiple, vision-threatening complications. Historically, we have waited until end-stage disease in many cases to do glaucoma surgery because the risk/benefit analysis was skewed due to the possibility of vision-threatening complications. Now, with MIGS, we can intervene surgically a lot sooner in a safer manner, and patients can be less reliant on medications, with better quality of life," Dr. Seibold explains.

iStent

The iStent trabecular micro-bypass implant (Glaukos) is the only FDA-approved device for the treatment of mild to moderate open-angle glaucoma. It is the first MIGS implant to improve the eye's natural fluid outflow by creating a permanent opening in the trabecular meshwork to lower IOP. It can be safely implanted in the eye during cataract surgery, and it spares important eye tissue that is often damaged by traditional surgeries. Interestingly, it is the smallest medical device ever approved by the FDA, and it can be implanted through a 1.5-mm corneal incision.

A recent German study found that

This article has no commercial sponsorship.

implantation of the iStent during cataract surgery was safe and effective as measured by sustained IOP reduction and reduced medication use.[1] Additionally, it demonstrated an excellent safety profile through three years postoperatively. In this prospective, open-label, non-randomized study, a single iStent was implanted through the same temporal, limbal incisions used for cataract surgery in 62 eyes of 43 consecutive patients. A total of 41 eyes have been followed for three years postoperatively. Mean preoperative IOP was 24.1 ±6.9 mmHg on a mean of 1.8 ±0.9 medications. Eyes with no secondary surgical intervention demonstrated a mean IOP reduction to 14.8 ±4.2 mmHg at 12 months postoperatively, 14.5 ±2.2 mmHg at 24 months, and 14.9 ±2.3 mmHg at 36 months. At 36 months postoperatively, medications were eliminated in 74 percent of eyes. There were no intraoperative or postoperative complications.

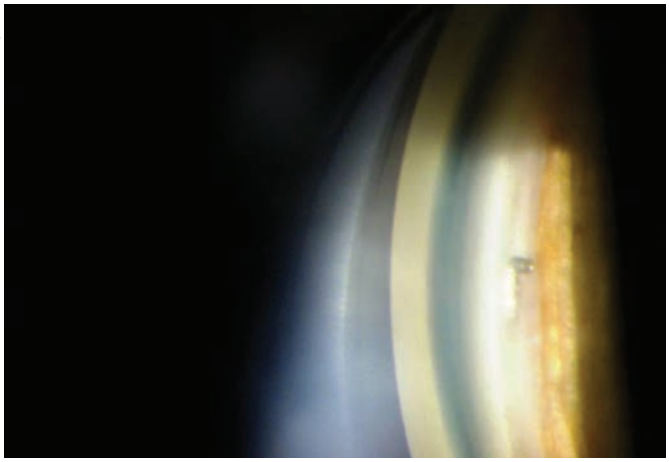

Leonard Seibold, MD

Figure 1. iStent implanted in the eye.

Xen45

The Xen stent (Allergan) is made of a soft, collagen-derived gelatin. It is 6 mm long and is approximately the width of a human hair. The stent is injected through a small self-sealing corneal incision using a simple, preloaded IOL-like injector. After being implanted in the eye, it creates a gentle outflow of aqueous from the anterior chamber into the subconjunctival space. It has CE Mark internationally, but is not FDA-approved for use in the United States.

A study conducted in Spain found that cataract surgery combined with Xen45 implant surgery effectively reduces IOP and the number of IOP-lowering medications in eyes with mild to moderate open-angle glaucoma.[2] This prospective study included 30 eyes that required cataract surgery and at least two medications to control IOP. Surgery was performed through two temporal incisions, separated by 90°, using the inferior to implant the Xen45 into the superior nasal region. Best-corrected visual acuity was 0.37 ±0.2 before surgery and 0.72 ±0.15 12 months after surgery. Additionally, preoperative IOP was 21.2 ±3.4 mmHg with 3.07 medications. IOP decreased by 61.65 percent at one day, 37.26 percent at one month, 35.05 percent at three months, 31 percent at six months, 30.6 percent at nine months, and 29.34 percent at 12 months. And, the number of medications decreased by 94.57 percent.

"This device was originally developed by AqueSys, and the company was just picked up by Allergan," Dr. Kahook says. "I believe it is the closest to FDA approval. This is a full-thickness *ab interno* device, and it may or may not be coupled with cataract surgery. Basically, this device is introduced with a small needle across the anterior chamber, through the sclera, into the sub-Tenon space. When the needle is retracted, the device is left behind so that it connects the sub-Tenon space to the anterior chamber. Available data show that it might lower pressure more than the iStent and some of the other MIGS devices, but the safety profile is currently not clear."

E. Randy Craven, MD, who has a joint appointment at Johns Hopkins and at the King Khaled Eye Specialist Hospital in Riyadh, agrees. "This device produces a Xen bleb and a pressure reduction similar to what can be achieved with trabeculectomies. But, it has a different bleb appearance than a trabeculectomy bleb," he says.

CyPass Micro-Stent

The CyPass Micro-Stent was developed by Transcend Medical, which was purchased in February by Alcon Laboratories. This micro-stent is a supraciliary device designed to create a controlled outflow pathway to the suprachoroidal space. The device is a 6.35-mm-long tube made of a polyimide material with an outer diameter of 0.51 mm. It can be placed through a 1.5-mm corneal incision and is inserted on a small guidewire with a special tip that separates the iris from the scleral spur. The CyPass Micro-Stent is inserted into the cleft that's created, and the openings along the length of the tube allow aqueous to flow out. This device has CE Mark approval, but is not yet FDA-approved in the United States. Dr. Kahook believes that it could potentially be approved sometime in the next year or two.

"This is a suprachoroidal device, which is a separate category of MIGS devices, and it should be the first to market for this unique category," Dr. Kahook says. "It is being explored as a tandem device with cataract surgery, which would be performed either before or after implantation of this device. It is implanted *ab interno* under

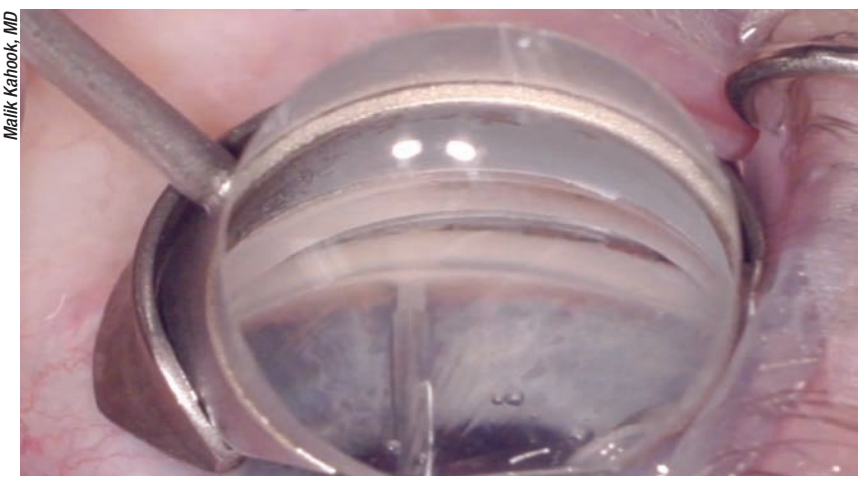
Malik Kahook, MD

Figure 2. The Kahook dual blade.

gonioscopic view. The device goes in across the anterior chamber and is then inserted in the suprachoroidal space. I have not implanted this particular device, but I have implanted suprachoroidal devices in the past and found them to be relatively straightforward to position."

In a recent study, CyPass Micro-Stent implantation combined with cataract surgery resulted in minimal complications and reduced IOP and IOP-lowering medication use at 12 months after surgery.[3] In this study, 167 eyes with open-angle glaucoma and cataract underwent phacoemulsification and IOL implantation combined with micro-stent implantation into the supraciliary space. IOP-lowering medications were discontinued or tapered at the time of surgery. Eyes were divided into two groups: those with IOPs of 21 mmHg or higher (65 eyes) and those with IOPs of less than 21 mmHg. Patients were followed for a mean of 294 days, and no major intraoperative or postoperative complications occurred. Mean preoperative IOP was 20.2 ±6.0 mmHg, and the mean number of IOP-lowering medications was 2.0 ±1.1. In the eyes with higher preoperative IOPs, there was a 35-percent decrease in mean IOP and a 49-percent reduction in mean IOP-lowering medication usage. The eyes with lower preoperative IOPs experienced a 75-percent reduction in mean medication usage while maintaining a mean IOP of less than 21 mmHg. For all eyes in this study, mean IOP at 12 months postoperatively was 15.9 ±3.1 mmHg (a 14-percent reduction from baseline).

"All of the data that have been published so far show that it results in a 30 percent reduction in IOP. It seems to have a really good safety profile, and it looks very encouraging. I am personally encouraged about it because I went to Africa to the Sinskey Eye Institute, and we taught some of the African surgeons how to implant the device. They had no trouble adopting it. It looks promising for the global treatment of glaucoma. It offers a route of pressure reduction that doesn't rely on the outflow system of the trabecular meshwork, Schlemm's canal, or the subconjunctival space," Dr. Craven explains.



Malik Kahook, MD

Figure 3. The Kahook dual blade removing trabecular meshwork under gonioscopic view.

iStent Inject

This is the newest iteration of the iStent. It is similar in some ways to the current iStent, but the insertion is different. "It is made to be inserted by essentially projecting it directly into Schlemm's canal in a procedure that should be easier to perform than the current iStent that's on the market. Data are just now coming out on this device, and it is showing similar efficacy to the current iStent," Dr. Kahook says.

A recent study has found that the iStent Inject is at least as effective as two medications at lowering IOP in open-angle glaucoma patients, and it has a highly favorable safety profile.[4] The study was conducted to compare the outcomes of patients with open-angle glaucoma that was not controlled on one medication who either underwent implantation of two iStent Inject trabecular micro-bypass devices or received a fixed combination of latanoprost/timolol. Of the 192 patients enrolled in the study, 94 were randomized to surgery, and 98 were randomized to receive medical therapy. At 12 months postoperatively, 89 of the 94 eyes that underwent surgery (94.7 percent) reported an unmedicated IOP reduction of 20 percent or more, and 88 of the 98 eyes that received medical therapy (91.8 percent) reported an IOP reduction of 20 percent or more compared with baseline unmedicated IOP. Additionally, a 17.5 percent between-group difference in favor of the iStent Inject was statistically significant at lowering IOP 50 percent or more. An IOP of

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18 mmHg or less was reported in 92.6 percent of eyes in the iStent Inject group and in 89.8 percent of eyes in the medical therapy group. Mean IOP decreases of 8.1 mmHg in the iStent group and 7.3 mmHg in the medical therapy group were reported, and a high safety profile was observed in both groups.

"I believe that they have closed out all of their data collection, and the FDA is considering a more rapid review, so it is probably not too far away from being approved," Dr. Craven says. 'The two stents over one standard iStent seem to hold some promise and hope for better pressure reduction."

Additionally, Glaukos has developed a suprachoroidal device called iStent Supra, which is similar to the CyPass. "We don't have a lot of public clinical information on that device, but the thought process is that it would be similar to what we are seeing with the CyPass implant," Dr. Kahook says. "This is currently going through the FDA approval process, but is still likely years away from the U.S. market."

Hydrus

The Hydrus device (Ivantis) is an intracanalicular scaffold that is about the size of an eyelash. It is made from nitinol, a highly elastic, biocompatible alloy used in many implantable medical devices. The device is placed inside Schlemm's canal during cataract surgery, and it increases outflow by allowing aqueous to bypass the trabecular meshwork.

A recent study assessed the safety and efficacy of the Hydrus Microstent implantation combined with cataract surgery for reducing IOP in patients with open-angle glaucoma.[5] The study included 100 eyes with open-angle glaucoma in 100 patients with IOPs of 24 mmHg or less with four or fewer hypotensive medications and a washed-out diurnal IOP of 21 to 36 mmHg. Patients were randomized to

Figure 4. Alcon's CyPass Micro-Stent.

receive either cataract surgery with the micro-stent or cataract surgery alone. At 24 months postoperatively, the proportion of patients with a 20-percent reduction in washed-out diurnal IOP was significantly higher in the Hydrus patients than in the patients who only underwent cataract surgery (80 percent compared with 46 percent), and the mean diurnal IOP was significantly lower in the Hydrus group than in the group that underwent cataract surgery alone (16.9 ±3.3 mmHg compared with 19.2 ±4.7 mmHg). Additionally, the number of patients using no hypotensive medications was significantly higher in the Hydrus group at 24 months (73 percent compared with 38 percent in the cataract surgery alone group).

According to Dr. Craven, the company is still gathering two-year data and is closing out the FDA trial. "All of the data I have seen have been very favorable, but approval is still probably over a year away," he adds.

Dr. Kahook notes, "I believe the Hydrus holds great promise to lower IOP significantly by reaching three clock hours of collector channels with a single implant. I also found this device to be extremely comfortable to implant in several patients I operated on recently."

When to Use a MIGS Device?

According to Dr. Kahook, patients are still undergoing trabeculectomy or glaucoma drainage device implantation if they have advanced glaucoma or require significant IOP lowering. MIGS devices play a more significant role when modest IOP lowering is sufficient and particularly where the main goal is to decrease dependence on topical medications. "I also believe there is a role for MIGS devices in more advanced disease if the patient and treating physician are very motivated to avoid filtration surgery," says Dr. Kahook. "I have been surprised at times by how much IOP lowering can be achieved in a small subset of patients with more advanced disease after MIGS procedures." He is increasingly relying on the Kahook Dual Blade (New World Medical, Rancho Cucamonga, Calif.), which he developed. "This has become our go-to surgery for lowering IOP in both pseudophakic and phakic patients. I have been impressed with the results we and others have been getting since the device was introduced in November of last year," he adds. REVIEW

Dr. Kahook has a financial interest in as the inventor of the Kahook Dual Blade. He is an unpaid consultant to Ivantis. Dr. Kahook has received intellectual property payments from Glaukos.

Dr. Craven is a consultant to Allergan, Alcon, Ivantis and Transcend.

Dr. Seibold has served as a consultant for New World Medical and Allergan and has received research support from Alcon and Glaukos.

1. Neuhann TH. Trabecular micro-bypass stent implantation during small-incision cataract surgery for open-angle glaucoma or ocular hypertension: Long-term results. J Cataract Refract Surg 2015;41:2664-2671.
2. Perez-Torregrosa VT, Olate-Perez A, Cerda-Ibanez M, et al. Combined phacoemulsification and XEN45 surgery from a temporal approach and 2 incisions. Arch Soc Esp Oftalmol 2016; E-pub ahead of print.
3. Hoeh H, Vold SD, Ahmed IK, et al. Initial clinical experience with the CyPass Micro-Stent: Safety and surgical outcomes of a novel supraciliary microstent. J Glaucoma 2016;25:106-112.
4. Fea AM, Belda JI, Rekas M, et al. Prospective unmasked randomized evaluation of the iStent inject versus two ocular hypotensive agents in patients with primary open-angle glaucoma. Clin Ophthalmol 2014;8:875-882.
5. Pfeiffer N, Garcia-Feijoo J, Martinez-de-la-Casa JM, et al. A randomized trial of a Schlemm's canal microstent with phacoemulsification for reducing intraocular pressure in open-angle glaucoma. Ophthalmology 2015;122:1283-1293.

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Combination Therapies: Recipes for Success

Putting two drugs together in one formulation can sometimes achieve better results than either agent can by itself.

Mark B Abelson, MD, CM, FRCSC, FARVO, Andrea Leonard-Segal, MD, FACR, James McLaughlin, PhD, and David Hollander, MD, Andover, Mass.

What is the formula for a therapeutic success? Start with a chemical or a compound with properties that allow it to positively impact the signs and symptoms of a target disease. Next, concoct a suitable vehicle: solid; liquid; or something in-between. Whatever the mixture, the ingredients should pave the way for efficient delivery of active drug substance to the site of action. But why stop there? If one active ingredient is good, why not add several? Of course it's not that simple, and issues such as formulation and drug interactions—especially those involving drug metabolism—often limit the utility of combination therapies.

For ocular therapies that are most often delivered topically, combination therapy development is much more nuanced than a simple mix and match. The critical issue is establishing that the combination of drugs is a demonstrably better therapy than any of the individual active ingredients. Drug regulators believe firmly in an economic version of Occam's Razor: The most parsimonious solution, or in this case therapy, is best. Those wishing to use combinations have a high bar to clear. Yet, we all know that there are many examples of drug mixtures that are excellent medicines. This month we'll delve into the why and how of combination drugs, focusing primarily on therapies for ocular surface conditions.

Pharmaco-matchmaking

A need for combination therapies typically stems from some limitation of existing agents. Issues such as suboptimal efficacy, short duration of action or tachyphylaxis can spawn the need for a combination approach when no single agent is available that provides a sufficient degree of therapeutic relief. Combining two or more active ingredients is about balance and synergy. When pharmacokinetic or pharmacodynamic profiles complement each other, a mixture can yield a treatment that's superior to existing monotherapies.

In practice, combination formulations are often an attempt to address specific limitations of existing treatments. A classic example of combination therapy directed at altering drug kinetics is the insulin mixture. In these mixtures, short-acting insulin is combined with a longer-acting variant to reduce the number of injections patients need.[1] The components act independently to provide a bolus of insulin followed by a prolonged duration of glucose control. In practice, many combinations have some aspect of both pharmacokinetic- and pharmacodynamic-based effects. The combinations used for ocular hypertension provide one of the best examples of this type of formulation.

Prior to the advent of prostaglandin analogs, three classes of compounds were used to lower intraocular pressure: β-adrenergic antagonists (such as timolol); α-adrenergic agonists (brimonidine); and carbonic anhydrase inhibitors such as dorzolamide.[2] Each of these agents came with a set of limitations, such as application discomfort, hyperemia, cardiac effects, visual effects and tachyphylaxis. All three drug classes act by decreasing the amount of aqueous humor, yet each has a unique mechanism for achieving that outcome. β-blockers lower aqueous humor formation pharmacologically, while CA inhibitors do so enzymatically. The α-agonists are thought

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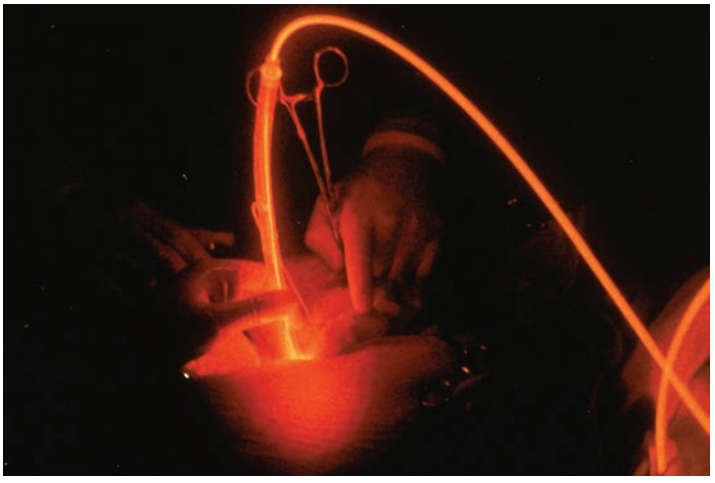
to act by a combination of decreased AH formation and increased uveoscleral outflow. These differences in PD allow for additive effects on IOP when used in combination. In addition, combinations can use decreased doses of each component, providing relief from some of the adverse effects of each class of compounds. For example, the combination of timolol and brimonidine had fewer adverse events than either single-agent therapy.[3] The gold standard is head-to-head comparisons of efficacy: In one head-to-head study, the combination of β-blockers and α-agonists proved superior to either single agent for lowering IOP in controlled clinical trials.[3] Currently, all three possible combinations of β-blockers, α-agonists and CA inhibitors are available as Food and Drug Administration-approved therapies for treatment of ocular hypertension.



Photodynamic therapy is a unique type of therapy where laser light and a photosensitizing agent are combined to target specific tissues.

The benefit of improved efficacy isn't the only reason for combination therapies, and treatment of patients with glaucoma provides a good example of another important benefit: improved patient compliance. The single largest hurdle in compliance for these drugs is often the difficulty patients have administering drops,[2,4] so combining two agents into a single drop provides a clear benefit regardless of whether the drop is for IOP, allergy or dry eye. Combination treatments are also often more comfortable than higher concentration monotherapies, further improving patients' inclination to properly medicate.[4]

Secret Ingredients to Success

Sometimes, combination therapies involve a single active agent combined with a second, inactive compound that can impact the overall efficacy. A classic example of this is clavulanic acid, a compound without any antibiotic activity that acts as an inhibitor of bacterial β-lactamases, enzymes that can significantly reduce the effectiveness of sensitive β-lactam antibiotics.[5] This compound prevents breakdown of drugs such as ampicillin, and in doing so enhances both potency and spectrum of the drug's action. This rationale of one active agent and one "facilitator" may become more common as we gain a better understanding of the mechanisms and limitations of existing therapeutics.

Another important class of this type of combination therapy is represented by the benzoporphyrin photosensitizers, including verteporfin (Visudyne; Valeant), compounds that are used in treatment of a number of diverse diseases. By selectively targeting tissue absorption of specific wavelengths of light, these compounds have been used to apply selective laser ablation to treat skin diseases, some cancers and choroidal neovascularization. Here, the idea of a combination therapy is extended to include a combination of interventions, but again the same standard applies: The combination must be superior to either of the individual component interventions. Photodynamic therapy is an important therapeutic option in treating neovascular disease, and its value derives from the underlying combination.[6,7]

Combination therapies also have some significant limitations deriving from the fixed-dose formulations. Some patients may benefit from a titration of one of the actives, and for these individuals a fixed-combination product is suboptimal. In addition, fixed-dose formulation can be an issue when the pharmacokinetics of components is significantly different, especially if each active drug component is indicated to treat a different symptom. In that situation, the component with the shorter pharmacokinetic profile may tend to drive more frequent patient use, leading to accumulation of the longer-acting component and increased adverse events. In the nonprescription drug setting, there is always the concern that patients may inadvertently choose to use a combination product for symptomatic relief when they don't need all drug components of the product. For example, consumers with conjunctivitis and nasal congestion but no pain or fever may mistakenly choose to use a product containing an antihistamine, a nasal decongestant and an analgesic/antipyretic, thus exposing themselves to acetaminophen or a nonsteroidal anti-inflammatory drug unnecessarily.

Therapies for Unmet Needs

Dry eye and chronic ocular allergy are two areas in which there's a need for new therapies, possibly including the use of combination therapies.

Both conditions are primarily treated with topical agents, and both are subject to a significant placebo effect, since artificial tears (vehicle) can provide significant, if transient, relief from the signs and symptoms of both dry eye and allergic conjunctivitis. Combinations must surmount this hurdle in addition to demonstrating superiority to each active ingredient. Combination therapies have been used for allergy relief for many years, and while there are no currently available combination treatments for dry eye, there are some indications that this may soon be changing as well.

The two predominant symptoms and signs experienced by allergic conjunctivitis patients are ocular itching and redness. Alpha adrenergic agonists were among the first compounds used topically to treat AC, and they provided modest relief of itching combined with complete or nearly complete reduction in redness.[8] Topical antihistamines exhibited a reciprocal pattern, with a nearly complete relief of ocular itching combined with a modest reduction in redness.[9] The combination of active ingredients from each of the two drug classes should provide almost complete relief from both itching and redness.

Combination products currently available to treat ocular allergy include two actives: an antihistamine and a vasoconstrictor. These products are all marketed as over-the-counter formulations. All contain the first-generation antihistamine pheniramine and the vasoconstrictor naphazoline.[10] These products are short-acting, designed for use up to four times per day, with a duration of relief of four hours or less.[8] In contrast, newer antihistamines (including both OTC and prescription drugs) have a duration of eight hours or more.[9] Similarly, alternative vasoconstrictors with substantially longer durations of action than naphazoline are available.[11] Even in the OTC marketplace, where patients are making many of their own treatment decisions, a number of available potential components have a long history of safety and efficacy. Combining a well-matched, extended-dose antihistamine and a longer-duration vasoconstrictor could provide a longer-acting formulation for ocular allergy. Development of longer-acting, higher-efficacy combination therapies for allergic conjunctivitis seems like an idea whose time has come.

Chronic allergic conditions are often treated with short courses of corticosteroids, and it's possible that the combination of an antihistamine and a corticosteroid may provide relief to those with perennial ocular allergy. There have been reports of some limited success using this approach to treat chronic rhinitis.[12]

How might combination therapies be used to treat dry eye? As with ocular allergy, dry-eye treatments are aimed at relief of both signs (such as corneal staining or tear production) and symptoms (discomfort, burning) of dry eye. Many treatments tested as potential dry-eye therapies have shown efficacy for one of these, but not both. When the variability of patients is factored in—some patients have signs but no symptoms and vice versa—the task of getting regulatory approval seems exceedingly daunting. Despite this, one recent study tested the combination of diquafosol, a secretagogue, and hyaluronic acid, a naturally occurring lubricant.[13] After three months of q.i.d. dosing, the combination was statistically superior to either component for both fluorescein staining and for symptom scores measured with the Ocular Surface Disease Index score. This result suggests that combination therapies may be an important avenue for future dry-eye treatment.

As with all drug development, the design, formulation and testing of combination therapies is rife with both pitfalls and promises. Finding the right components, designing the appropriate trials and targeting a suitable patient population all play a role in the process. Despite the difficulties, we believe that devising formulas for new combinations of therapeutics is an approach that can and will yield valuable treatment progress in the coming years. REVIEW

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1. Heise T, Nosek L, Klein O, et al. Insulin degludec/insulin aspart produces a dose-proportional glucose-lowering effect in subjects with type 1 diabetes. Diabetes Obes Metab 2015;17:7:659.
2. Medical Letter Treatment Guidelines, "Some drugs to treat eye disorders" M Abramowitz, ed. 2012;10:123:79-86.
3. Craven ER, Walters TR, Williams R, et al. Brimonidine and timolol fixed-combination therapy versus monotherapy: A 3-month randomized trial in patients with glaucoma or ocular hypertension. J. Ocul Pharmacol Ther 2005;21:4:337-48.
4. Higginbotham EJ. Considerations in glaucoma therapy: Fixed combinations versus their component medications. Clin Ophthal 2010;4:1-9.
5. Georgopapadakou NH. Beta-lactamase inhibitors: Evolving compounds for evolving resistance targets. Expert Opin Investig Drugs 2004;13:10:1307-18.
6. Lu HQ, Wang EQ, Zhang T, Chen YX. Photodynamic therapy and anti-vascular endothelial growth factor for acute central serous chorioretinopathy: A systematic review and meta-analysis. Eye (Lond) 2016;30:1:15-22.
7. Arevalo JF, Espinoza JV. Single-session combined photodynamic therapy with verteporfin and intravitreal anti-vascular endothelial growth factor therapy for chronic central serous chorio-retinopathy: A pilot study at 12-month follow-up. Graefes Arch Clin Exp Ophthalmol 2011;249:8:1159-66.
8. Abelson MB, Allansmith MH, Friedlander MR. Effects of topically applied ocular decongestant and antihistamine. Amer J Ophthal 1980;90:254-257.
9. Abelson MB, McLaughlin JT, Gomes PJ. Antihistamines in ocular allergy: Are they all created equal? Curr Allergy Asthma Rep 2011;11:205–211.
10. Dockhorn RJ, Duckett TG. Comparison of Naphcon-A and its components (naphazoline and pheniramine) in a provocative model of allergic conjunctivitis. Curr Eye Res 1994;13:319-324.
11. Duzman E, Warman A, Warman R. Efficacy and safety of topical oxymetazoline in treating allergic and environmental conjunctivitis. Ann Ophthalmol 1986;18:28-31.
12. Wolthers OD. New patents of fixed combinations of nasal antihistamines and corticosteroids in allergic rhinitis. Recent Pat Inflamm Allergy Drug Discov 2013;7:3:223-8.
13. Hwang HS, Sung YM, Lee WS, Kim EC. Additive Effect of preservative-free sodium hyaluronate 0.1% in treatment of dry eye syndrome with diquafosol 3% eye drops. Cornea 2014;33:9:935-41.

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Seeing Glaucoma from The Patient's Perspective

One surgeon shares what he has learned from being both a glaucoma patient and doctor.

Ralph M. Sanchez, MD, MPH, Slingerlands, N.Y.

Sometimes it's the challenges we face in life that really make us who we are. I've been treating glaucoma for several decades, but my road to this point in life involved many unexpected turns—most notably, receiving a diagnosis of glaucoma when I was in my 20s. It may sound kind of crazy, but getting that diagnosis led me to change my career and make a serious life commitment that I hadn't been motivated to make until then. So although I wouldn't wish glaucoma on anybody, in some ways that diagnosis was a blessing in disguise.

In my early high school years I was very interested in science and medicine. I thought I'd pursue a career in medicine, and I was able to get into Johns Hopkins. However, the pre-med experience wasn't what I was expecting. I was put off by how competitive it was; the students were very grade-conscious and driven without seeming to appreciate what they were getting into. So within a year I switched my major to philosophy and then earned my degree. Along the way I started doing social work and helped run an inner city tutoring program for kids in Baltimore. When I graduated, I got a full-time position at the university running that program, which I did for a number of years.

Then, in my mid 20s, I was driving down the New Jersey turnpike when I noticed my vision getting blurry off and on. I went to see an eye doctor and found out that my eye pressure was in the low 30s. At the time, I knew nothing about glaucoma, but the doctor seemed rather alarmed. Knowing that I'd gone to Johns Hopkins as an undergrad, he offered to connect me with some of the people at Hopkins and Wilmer Eye Institute to get a second opinion and a higher level of care than he felt he could offer me.

Sure enough, my diagnosis was confirmed, and I started on drops and treatment. This experience sparked my curiosity about glaucoma, so I tried to learn as much as I could, at least partly as a way to head off my own fears about the disease. Eventually I asked about working in glaucoma research, and I became a lab tech in a glaucoma research group at Wilmer. Needless to say, over the course of the next three years I learned an enormous amount about glaucoma. Ultimately, that reignited my interest in going to medical school—but this time I was several years older and I had a pretty clear idea about what it was I wanted to learn and pursue. That made it much easier to do.

The Other Side of the Slit Lamp

Having been a glaucoma patient myself, I can tell you that the experience is difficult to appreciate if you haven't been there. Today, when I work with glaucoma patients —especially at the outset of treatment—I am acutely aware of what they're experiencing. It puts me in a unique position to address those fears that the patient may be afraid to express—fears that the physician may not be aware of.

Here, I'd like to share a few of the things I've learned as a result of being both a glaucoma doctor and patient.

• ***Be aware that a diagnosis of glaucoma can be a very frightening experience.*** Essentially, you're being told that you could lose your sight, which is many people's greatest fear. The initial diagnosis is very unsettling

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and can be profoundly life-changing. I've had patients cry upon hearing the news, and I totally understand that reaction. After I first found out that I had a potentially blinding disease, there were times when I was distraught. I remember asking "Why me?" and thinking how unfair this was.

The impact was even greater when I was first told I would need surgery. I remember the doctor saying that the best thing to do was a trabeculectomy. After this announcement, my ophthalmologist continued to talk for 20 minutes, explaining what this meant. For the life of me, I have no recollection of anything he said after he told me I needed surgery. I was in a state of shock. I remember walking out of the exam room into the hallway and seeing a large print of a Van Gogh painting. I looked at it in a way I had never looked at a painting before. The realization that my vision could be gone just really hit me. It was a very scary moment.

Because of these experiences, I'm very sensitive to how patients may be feeling when they learn they have glaucoma or find out they need surgery. A patient's feelings are not always obvious, because for the most part patients keep it together. It's rare to have a patient break down and reveal what he or she is feeling. But if you want to serve your patients well—not to mention making sure they hear what you're saying to them—you need to realize the state your patient may be in after hearing the news.

Fears that glaucoma patients often have include:

— fear of going blind;

— fear of asking you questions;

— fear that vision loss will cost them their job;

— fear of not being able to pay for the drugs you prescribe;

— fear of pain during or after surgery;

— fear that a surgical procedure—or even an eye drop—will change the appearance of their eyes.

Fortunately, these fears decrease significantly over time as patients learn to live with their disease and experience successful treatment. The fear never goes away completely, but the initial shock does gradually dissipate.

• ***Make sure to clarify that glaucoma is unlikely to lead to blindness when treated appropriately.*** Given that patients are almost certain to feel some fear, one of the most important things you can do is reassure the patient during the first few visits, especially when the disease is first diagnosed. Make sure the patient understands that glaucoma is very treatable, something that can be controlled, and that very few patients go blind from it. *(For example, see the table above.)*

At the same time, you need to emphasize that this is conditional. The condition is that the patient takes his medications, follows your instructions and follows up with appointments. This could mean using drops and/or having surgical procedures periodically for the rest of the patient's life, but if he's willing to stay with the program, the disease is very likely to remain under control, preserving the vision that the patient currently has. That understanding should go a long way toward allaying the patient's fears.

• ***Keep in mind that field loss may be invisible to the patient.*** One of the surprising things I've learned from having glaucoma is that you can lose a significant amount of visual field without being aware of it. I have significant field loss in both eyes, including a very large nasal step and arcuate scotoma in one eye. Remarkably, I never notice any defect in my vision in that eye at all. My other eye has a paracentral defect pretty close to fixation, and again, I'm oblivious to it unless I cover the other eye and deliberately search for it using an Amsler grid.

Ironically, medical books about glaucoma that describe visual field loss show big black spots on pictures, as if

Lifetime Visual Prognosis for Patients with POAG or NTG

Time point	Reason for poor vision	No. of POAG/LTG patients eligible for partial-sight or blind certification	
		Partial sight	Blind
At presentation	Glaucoma damage alone	1 (0.8 percent)	0
	Glaucoma plus other pathology	7 (5.8 percent)	0
	Total	8 (6.6 percent)	0
At final clinic visit	Glaucoma damage alone	8 (6.6 percent)	0
	Glaucoma plus other pathology	9 (7.4 percent)	4 (3.3 percent)
	Total	17 (14 percent)	4 (3.3 percent)

A 2004 retrospective study of 121 case histories of Caucasians with primary open-angle glaucoma (n=113) or normal-tension glaucoma (n=8) found that the diagnosis did not lead to blindness for 96.7 percent of the patients. Those reaching blindness all had other ocular pathologies in addition to glaucoma. Only 14 percent qualified for partial sight certification at their final visit before death, and of those only 6.6 percent were due to glaucoma alone.[1]

Corneal Hysteresis is more associated with visual field progression than CCT or IOP.[1-3]

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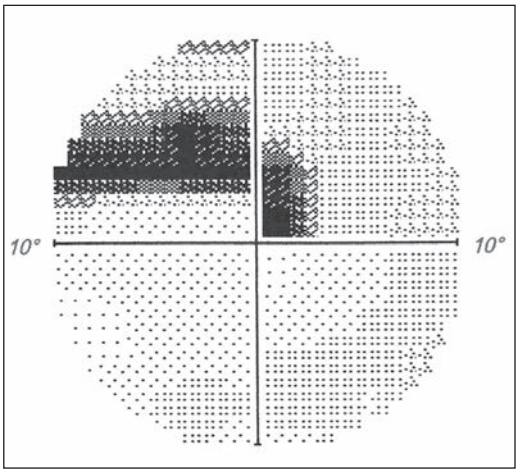
References: 1. Medeiros FA, Meira-Freitas D, Lisboa R, Kuang TM, Zangwill LM, Weinreb RN. Corneal hysteresis as a risk factor for glaucoma progression: a prospective longitudinal study. Ophthalmology. 2013 Aug;120(8):1533-40. **2.** De Moraes CV, Hill V, Tello C, Liebmann JM, Ritch R. Lower corneal hysteresis is associated with more rapid glaucomatous visual fi eld progression. J Glaucoma. 2012 Apr-May;21(4):209-13. **3.** Aashish Anand, MD, Carlos Gustavo De Moraes, MD, Christopher C Teng, MD, Celso Tello, MD, Jeffrey M Liebmann, MD Robert Ritch, MD. Lower Corneal Hysteresis Predicts Laterality in Asymmetric Open Angle Glaucoma, IOVS Papers in Press. Published on June 23, 2010 as Manuscript iovs.10-5580.

a patient looks out into the world and sees big black splotches. You don't; your mind is unaware of what you're not seeing. That's why so many patients lose vision for years without noticing. (Needless to say, that's one reason vision screening is so important.) For that reason, when you do find vision loss it's important to go over the visual field results with the patient and explain what the printout is showing, as well as explain why she may not be aware of the problem. Compliance may depend on the patient understanding that she really is losing vision, despite not being aware of it.



Doctors need to be aware that patients can lose a significant amount of visual field without being aware of it. This 10-2 field of the author's left eye reveals a dense paracentral defect, but he is rarely aware of the deficit unless he specifically looks for it.

• ***Know your patient's background and level of understanding.*** Getting patients to understand what we're saying is a key to compliance. They have to understand the disease; believe that it's treatable; and understand what our treatments are doing, so they're motivated to follow our instructions. In reality, patients have tremendously different backgrounds and levels of understanding, but we tend to give the same explanations to everybody.

I'm a firm believer that even patients with little formal education will understand you if you express what's going on in the proper language and use the proper analogies. At the other extreme, ophthalmologists are notorious for abbreviating everything. We have a language of our own, and if you use that language when speaking to patients, they may not have a clue what you're talking about.

• ***Ask about your patient's daily routine and eye-drop schedule.*** Most of us work 9 to 5, and we tend assume that our patients do too. In fact, plenty of patients work the night shift; if they do, they have to stay awake a couple of extra hours to see you in the office. You check their eye pressure and it's nice and low, and you think everything's great. The reality is, you're checking the pressure sitting up during their normal sleeping hours. At 3 a.m. when they're working their shift, their IOP could be twice as high. If you know what kind of a schedule your patients have, you can not only evaluate the pressure reading with that in mind, you'll have a better idea of when they should be taking their eye drops and medications.

• ***Ask about the patient's ability to use the medication at work.*** Putting in drops at work may be difficult or impossible for some patients. Someone may work on an assembly line, for example, where he literally can't step away to put in eye drops at the appropriate time, or carrying drops with him might not be permitted. You need to ask about limitations your patient may have in terms of being able to use drops during working hours.

• ***Inquire about the patient's support system.*** I've seen elderly patients with poorly controlled pressures who are by and large on their own when it comes to taking their medications. Eventually they go into a nursing home, and suddenly the medications are working perfectly. Without assistance, the patient was either forgetting to take the drops or missing the eye.

In fact, it's hard to be perfect about using drops even if you're totally competent. My memory is pretty much intact and I take my drops on a schedule, but there are days when my schedule gets interrupted and I can't remember whether or not I used the drops. Naturally, sticking to a schedule can be even harder if you're dealing with memory limitations and you're on your own. An elderly patient may come in one day with a pressure 8 mmHg higher than normal; if you ask him if he took his drops, he'll most likely say yes, but I'm not always convinced. So I may bring the patient back in a couple of days or a week and recheck him. If the pressure is back down, if may be worth inquiring about the patient's support system. (If the pressure is still elevated, then you may have a different problem on your hands.)

• ***Ask if the patient can manage and afford the drops you're prescribing.*** Compliance can be undermined by a number of factors besides forgetfulness and difficulty getting drops in. Cost is a big factor for many patients. Some patients will flat out tell you, "I can't afford these medications." Others won't tell you that; they simply won't use them. I think it's incumbent on us, with the economics of treating being what they are, to inquire about whether the patient can afford the medical treatment.

As you know, compliance can also be undermined by a complex regimen. Sometimes you can save everyone time and money by asking your patients up front if they can manage multiple drops at different times of day. I'll say, "This is a really tough schedule, will you be able to keep up with this?" Some will say, "Sure, no problem, it's my eyesight, it's worth it to me so I'll do it." Others will

Getting the patient to understand the disease and reasons for using the medications you prescribe is essential to achieving compliance. Doctors should avoid using one-size-fits-all language or "doctor-speak"; instead, tailor your explanations to the patient's background. (Quelling a patient's fears before proceeding will also help ensure comprehension.)

say, "Not likely." (Of course, in order for this conversation to be meaningful you need to have a combination of good communication and trust so the patient is willing to be honest.)

When you know compliance is going to be difficult for your patient, it's worth considering surgery. There may be a higher risk up front, but in the long run, getting the pressure under control is what's going to preserve vision.

Physician, Know Thyself

To truly help patients who have glaucoma, you also need to be aware of your own limitations and biases.

• ***Remember that we're here to counsel the patient and provide support and motivation, not just be technicians.*** There are several reasons we as physicians can lose focus and end up just "doing the job" of getting to the next patient. Not having firsthand experience being a glaucoma patient is, of course, part of the problem for many doctors. But another factor is that the state of medicine and economics today has largely dehumanized the process of medicine, pushing us in the direction of being technicians. In the rush to keep our business afloat we can easily minimize our patient counseling and support. In addition, managing the technical side of medicine is relatively easy in comparison to counseling the patient. However, that doesn't change the fact that counseling and support are exactly what many of our patients need.

Staying motivated, in particular, can be a challenge for glaucoma patients. They're tired. Many of them have had this disease for years or decades and they've done countless visual fields and taken gallons of eye drops over their lifetime. Some of them are OK with this, but others have a hard time. If you want them to succeed in holding off the disease, you have to remember that their motivation may be waning; you need to encourage them to keep going and stick with the protocol.

Part of that is providing positive feedback: "You did a good job on the visual field," or "I can tell you're doing a great job with the drops because your optic nerve looks good and your pressure is stable. Keep up the good work!" The reality is, your patients are the ones taking care of their disease. They live with it every day and do the work of following your protocol, while you only see them a couple of minutes out of the year. You need to let them know that you recognize their efforts and that they're doing a good job.

Educating the patient is another important aspect of providing proper care, and while this can be time-consuming, it's mostly only necessary at the outset or when you run into problems. Once patients understand and are compliant with treatment, visits become shorter and easier because patients understand the reason they're in your office. In the long run it pays off if you spend time educating your patients up front.

• ***Be aware of your own limitations.*** All of us come to the office with different levels of experience, knowledge and comfort when it comes to managing different types of eye disease. For the general ophthalmologist, managing glaucoma can be pretty overwhelming given the number of medications and side effects and surgical options; even glaucoma specialists find this challenging and can make mistakes. The point is that there's no shame in getting advice or passing a patient on to a specialist. I've seen doctors hold onto a glaucoma patient until the patient had end-stage disease and then finally send him to a specialist when what could be saved was too little and too late. At the other ex-

treme, I've seen patients who were being grossly overtreated, placed on multiple eye drops with minimal, if any, disease.

Another problem is using unrealistic methods to try to achieve results. For example, I've seen patients with pressures in the 40s where the ophthalmologist chose to do selective laser trabeculoplasty. The doctor didn't realize that an SLT laser is not going to drop a pressure that high down into a safe zone and is only delaying a more definitive treatment. I'm not suggesting that a general ophthalmologist should hesitate to treat glaucoma; but on the other hand, limited experience with these drugs and surgeries can lead to trouble, unnecessary expense and poor outcomes for your patients.

There are also issues of time and equipment. Do your really have the time necessary to counsel patients who have glaucoma? Do you have the proper equipment to help diagnose the disease? Just checking pressure and taking a look at the optic nerve isn't really adequate in this day and age, given that we have the ability to do optical coherence tomography and quantitative measurements of the nerve fiber layer, corneal pachymetry or hysteresis and sophisticated progression analysis. Unless you're truly equipped to manage glaucoma, you should be asking for a specialist's help.

That's why it's important to be aware of your level of experience and err on the side of using the specialist as a resource. Take the time to make a phone call and ask a question. Then, determine whether the patient needs to be seen by a specialist. Don't wait until you can't think of anything else to do and then pass the patient on.

• ***Beware of bias that glaucoma will inevitably lead to vision loss.*** Not every doctor is optimistic about glaucoma outcomes in the long run. The problem is, if you believe that eventually everybody goes blind from glaucoma you'll be willing to accept your patient's visual field loss getting worse over time, instead of realizing that you need to change your strategy, seek the assistance of a specialist or consider an alternative therapy or surgery. Unfortunately, I've seen a lot of this.

Operating more as a partner with the patient will produce better results.

I think we can do better. We need to have a high standard for outcomes and a low threshold for changing our approach. If we see a patient getting worse, our conclusion should be that we're not doing enough. We're missing something. Maybe the patient is not taking her drops—but it's up to us to figure that out and do something about it. I believe that if we hold ourselves to a higher standard, we'll deliver more successful treatments.

• ***Avoid the authoritarian, paternalistic model of doctoring.*** In the past, many doctors in all areas of medicine followed a top-down, authoritarian model of how patients should be treated. Ophthalmologists were no exception: "Take this drop and come back in a month, we'll see what your pressure is." In this model, little attention is paid to explaining the reasons for treatment, assuaging patient fears or motivating the patient. That's a recipe for poor outcomes, because a patient who doesn't have any symptoms or awareness that he's losing vision is not likely to take a drop that stings, has a lot of side effects or discolors his skin, especially if he doesn't grasp the reason.

Over the past several decades we've seen much improvement in terms of moving our doctor-patient model to a more consensus-based approach. However, ophthalmology is still one of the most conservative areas in medicine in this respect; many of us continue to use a paternalistic, authoritarian approach to treatment. Making a conscious decision to operate more as a partner with the patient will produce better results (and happier patients).

• ***Respect the patient's values and wishes.*** I've heard of doctors using the possibility of losing vision as a threat, as if blindness were a punishment for not following the doctor's directions. Treatment is supposed to be about education, establishing a trust-based relationship and empowering the patient to take responsibility to treat the condition.

The reality is, patients don't always agree with our recommendations. For example, I've encountered patients whose disease has progressed to the point at which they have only hand motion or light perception. I may recommend a procedure, but sometimes the patient wants to just let nature take its course. (The reason might be as simple as the patient not wanting to come to your office every couple of weeks to have something monitored and/or treated.) I think as long as patients understand the consequences of not taking our recommendation, we have to respect their autonomy and values and leave the decision in their hands. The truth is, we're here in an advisory capacity; our job is to improve quality of life as the patient sees it, not as we see it. People are individuals with different goals and priorities.

Of course, I understand the fear of legal liability when a patient doesn't want to follow our advice. If the patient says, "No, I don't want to do that," you should make extensive comments in the chart about the conversation and

(continued on page 66)

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Tips for Taking on Borderline Cases

If you feel a patient with a pre-existing issue is worth the risk, here's how to increase your chances for a good outcome.

Walter Bethke, Managing Editor

Once in a while, a patient with an unusual medical history and an interest in refractive surgery will present at your office. The person's history can include a disease, such as herpes simplex virus keratitis, or a history of a corneal surgery that might pose a potential risk to a good LASIK outcome. Here, refractive surgeons share their approaches to three risky candidates: the person with a history of HSV keratitis; the post-RK patient; and the individual with a history of rheumatoid arthritis.

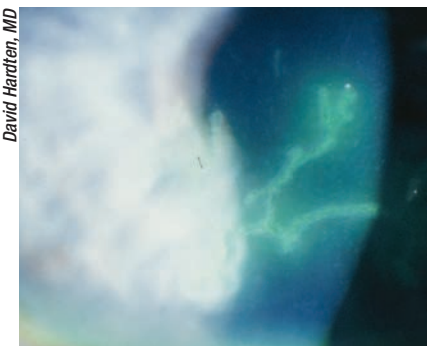
Hedging Against Herpes

Surgeons say a history of HSV keratitis is a relative contraindication for laser refractive surgery. Some feel, however, that with the proper evaluation and preparation patients with a history of HSV can have a good outcome.

The main risk surgeons are concerned about is reactivating the herpes, since case reports and animal studies have found that excimer laser procedures might be able to reactivate the HSV. The other risk, surgeons say, comes from trying to laser through any corneal scars left over from previous HSV episodes.

In one report, an elderly woman underwent phototherapeutic keratectomy for band-shaped keratopathy. Researchers took tear samples preop and postop, and then performed polymerase chain reaction assays to quantify the HSV DNA in her tears. They found that the PTK appeared to have triggered viral shedding, as the HSV DNA only appeared in the postop samples.[1]

In another paper, researchers infected the ocular surface of 23 rabbits with HSV, then waited for it to resolve. The investigators then split the rabbits into two groups: de-epithelialization alone; and de-epithelialization plus PRK. Sixty-seven percent of the PRK group experienced HSV reactivation, compared to none of the former group.[2]



David Hardten, MD

A history of herpes simplex keratitis poses the risk of recurrence post-LASIK or PRK.

Because of this risk, surgeons are wary of such cases, but will perform refractive surgery under certain conditions. "Though such a case is a relative contraindication, I think a lot of surgeons have loosened their criteria a bit and will operate on this type of patient," says Richard Davidson, MD, medical director for the faculty practice at the University of Colorado Hospital Eye Center. "If this patient's history of herpes consisted of just one episode, with not much scarring, and the eye has been quiet for a while, I think surgeons would be willing to operate," he says. "I'd plan on doing a PRK rather than a LASIK in such a patient; I'd rather not cut through corneal nerves in eyes that already have some damage to their corneal nerves. I'd start a patient with HSV history on antivirals a week preoperatively, and then probably keep him on them for two to three weeks postoperatively as things heal, in order to make sure he doesn't get a reactivation. The key is making sure he's been quiet for a decent period

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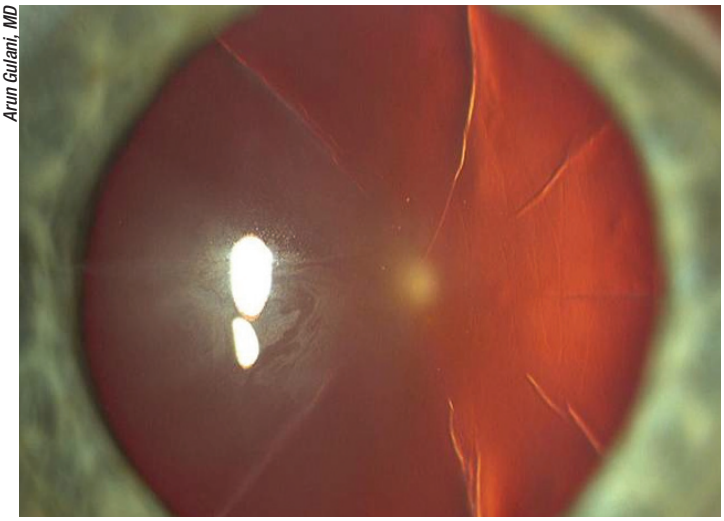
of time beforehand, and making sure you're not treating a cornea that has significant scarring."

Norfolk, Va., surgeon Elizabeth Yeu says she takes a very conservative approach to such patients. "Unfortunately, we corneal specialists end up seeing many corneal complications from disease such as HSV, and bad outcomes leave a lasting impression," she says. "In personal correspondence with [LSU corneal specialist] Herb Kaufman, he has stated that, with proper antiviral prophylaxis, he's seen great outcomes after performing LASIK in such patients, and doesn't see a distant history of HSV keratitis as a hard contraindication."

Los Altos, Calif., surgeon Bryan Lee says ophthalmologists shouldn't feel the need to operate on such a patient, however, and that it's all right to be more conservative. "For me, personally, if someone has a history of ocular HSV, I wouldn't perform LASIK on him," he says. "This is because many of these patients have corneal scars, so they won't be able to have a femtosecond laser flap. If someone can't have a femtosecond flap, I don't do LASIK on him. Beyond that, there are reports of post-LASIK reactivation of the HSV. This reactivation might be related to the LASIK, or it might not be, since it also happens fairly frequently to patients who don't have LASIK." Dr. Lee also has a law degree, which he says makes him acutely aware of the legal ramifications of operating on such a patient. "For any type of situation in which you're doing a refractive procedure on a patient that has a relative contraindication, having a very thorough informed consent conversation is critical," he advises. "The patient should know all the risks and be able to make the most informed decision possible."



Arun Gulani, MD

The two main risks post-RK patients need to be aware of are the cornea's possible unpredictable reaction to subsequent refractive surgery and the possibility of problems with the incisions during LASIK or PRK.

The Post-RK Patient

The fluctuations in vision experienced by RK patients, as well as the presence of the incisions, make subsequent laser refractive surgery a dicey proposition. Given the right circumstances, though, surgeons say it can be done.

Dr. Davidson again prefers PRK over LASIK in such a patient. "I think it's better to remove the epithelium than to cut a flap in some of these corneas," he says. "If you talk to 10 different surgeons, though, you'd probably get 10 different answers. However, I feel strongly about PRK in this type of situation.

"You don't have to modify your PRK technique so much as watch the RK incisions carefully," Dr. Davidson continues. "Don't put a lot of pressure on the globe, because even a moderate amount of pressure could potentially open up the incisions again. The key is being gentle." The risk posed by the incisions was elucidated in a 2007 paper in *Cornea*. In it, a 39-year old LASIK patient who had a history of RK experienced a separation of his old incisions during the lifting of the femtosecond flap, with one of the incisions extending into the center of the cornea due to the force from the blunt spatula.[3] "The incisions are unlikely to open with PRK, but it could possibly occur as you remove the epithelium and the epithelium turns out to be plugging some of the incisions," Dr. Davidson says. "Obviously, you need to inform the patient ahead of time that the incisions opening is a possibility. If a surgeon were to perform LASIK over RK, he should be careful during the docking of the femtosecond laser. He has to understand that these RK incisions are made to the full depth of the cornea—there's no way to avoid cutting through them."

Personally, Dr. Lee wouldn't do LASIK on a patient who has had RK. He acknowledges, though, that surgeons might consider PRK in such a patient, but advises the use of mitomycin-C. "The use of mitomycin-C is perfectly safe in the setting of PRK, but make sure you discuss mitomycin's risks as experienced with its use in glaucoma surgery with the patient," he says. "Also, discuss the fact that the RK cornea never stops changing. It fluctuates throughout the day and, over time, we know such patients become more hyperopic. The cornea becomes less predictable in terms of its reaction to future treatments. This discussion is important."

Rheumatoid Arthritis

A patient with RA carries the risk of immunologic corneal melting po-

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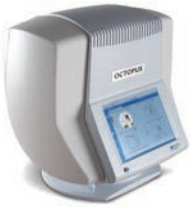

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stop, as well as a strong possibility of ocular surface issues that can impede a good result.

Dr. Yeu says that, similar to the HSV patient, it's critical that the eye be as quiet as possible. "Autoimmune connective tissue diseases such as lupus and rheumatoid arthritis can pose unique challenges," she says. "The disease severity and clinical presentation can vary greatly from patient to patient, and the overall picture really helps me decide whether or not they're LASIK candidates. I want to ensure that their serologic levels are under control, and the patient is under the care of a rheumatologist for systemic control."

Dr. Lee says the preop discussion is important, just as in the other conditions. "I'd let the patient know that there is at least a case report of someone having a post-LASIK corneal melt," he says.[4] "That's why this is considered a relative contraindication. But, explain that it is relative; if he's highly motivated and has really well-controlled disease—which has been under very good control for a year or longer without systemic problems—it's all right to perform the surgery if he's otherwise a candidate."

Along with the systemic problems, however, RA also poses the risk of ocular surface issues, which can disrupt a LASIK outcome even in a non-RA patient. "I'd get the ocular surface under control for anyone, but for someone with RA, I'd definitely pretreat him," Dr. Lee says. "I'd consider having the patient on pulsed oral steroids around the time of surgery, pretreat with warm compresses, artificial tears, omega-3 supplements and Restasis. Restasis takes three months before it really starts to kick in, but in terms of pretreatment for LASIK I'd want to do it for at least one or two months. I'd start all the other elements of the pretreatment regimen after I first saw the patient in clinic, and have them continue them for a month or two before the procedure. Postoperatively, taper the patient off the oral prednisone over a couple of weeks. You then have to be aggressive in treating the dry eye with plugs and the like. You want to stay on top of the ocular surface with those patients." REVIEW

Drs. Lee and Yeu have consulted for Allergan. Dr. Davidson has no financial interest in the products discussed.

1. Deai T, Fukuda M, Tomoda Y, Higaki S, Hayashi K, Shimomura Y. Excimer laser photokeratectomy reactivates latent herpes simplex virus. Jpn J Ophthalmol 2004;48:6:570-2.
2. Epstein SP, Fisher EM, Sternberg GJ, et al. Recurrent ocular herpes simplex keratitis following excimer laser photorefractive keratectomy in a rabbit model. CLAO J 2001;27:2:94-9.
3. Perente I, Utine CA, Cakir H, Yilmaz OF. Complicated flap creation with femtosecond laser after radial keratotomy. Cornea 2007;26:9:1138-40.
4. Lahners WJ, Hardten DR, Lindstrom RL. Peripheral keratitis following LASIK. J Refract Surg 2003;19:6:671-5.

(continued from page 61)

the explanation you provided. If you have a good relationship with your patient and her choice leads to a loss of vision, she's unlikely to blame you.

Medicine at Its Best

Developing glaucoma at an early age gave me a much deeper sense of purpose and direction. It motivated me to push myself in ways I otherwise might not have. It's given me the chance to study and learn; to travel and teach; and it's given me a dif-ferent perspective about life and the obstacles we all face. It has helped me define who I am and what I'm capable of.

I turned 60 this year. Early on, when I decided to pursue this and go to med school, one of my biggest fears was that I wouldn't be able to continue to be a doctor because of vision loss. That turned out not to be the case, as is often true with the things we fear. Our glaucoma patients share similar fears, but the reality is that most of them will retain their vision as long as they live. As physicians, we should be reassuring them that they have an excellent chance of maintaining their vision with the treatments we can offer (and we'll undoubtedly have even more effective treatments in the future). It might even be worth noting that obstacles in life, no matter how frightening, sometimes lead us to accomplish great things.

When it comes to empathizing with patients, I have an advantage because I know what it feels like to be on the other side of the slit lamp. But we've all faced illness at one time or another (and we prob-ably will again as we get older). Remembering what that feels like can help us not just provide medical advice, but also give our patients the support they need, whether that means assuaging their fears, giving them positive reinforcement for their efforts, helping them work around practical obstacles in their lives or just reassuring them that we'll be there as long as they need our help.

That's what medicine is supposed to be about. REVIEW

Dr. Sanchez practices at Glaucoma Consultants of the Capital Region. He has traveled extensively, teaching glaucoma treatment and surgical techniques to ophthalmologists in developing countries around the world.

1. Ang GS, Eke T. Lifetime visual prognosis for patients with primary open-angle glaucoma. Eye (Lond) 2007;21:5:604-8.

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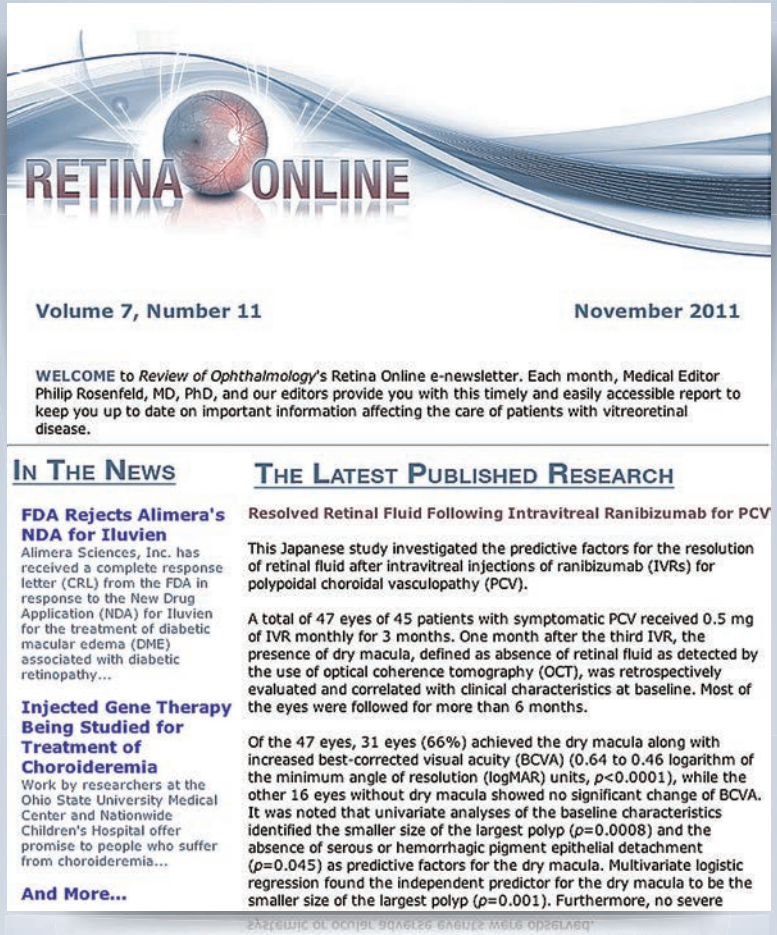

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A total of 47 eyes of 45 patients with symptomatic PCV received 0.5 mg of IVR monthly for 3 months. One month after the third IVR, the presence of dry macula, defined as absence of retinal fluid as detected by the use of optical coherence tomography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

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

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Complement Inhibition For the Treatment of GA

Large-scale studies support the role of aberrant activation of the alternative complement pathway in AMD pathophysiology.

David S. Ehmann, MD, and Carl D. Regillo, MD, FACS, Philadelphia

Geographic atrophy is an advanced form of age-related macular degeneration characterized by loss of the retinal pigment epithelium and photoreceptors in the macula.[1] Irreversible visual acuity loss occurs once GA involves the central fovea.[1] Patients with earlier stages of GA typically experience visual function deficits even before visual acuity is affected.[1,2] Approximately 0.5 percent of people aged 40 years and older in the United States have GA,[3] and once diagnosed it has been reported to progress at a growth rate of 2 mm^2 per year with a median time to foveal involvement of 2.5 years.[4]

The underlying pathophysiology of geographic atrophy is not completely understood; however, complement hyperactivity leading to over-activation of the immune system and chronic inflammation in the macula is thought to be a contributing factor.[1,5] At present, there are no approved treatments for geographic atrophy, and multiple investigational approaches targeting a range of therapeutic mechanisms are being explored.[1,5-8] This review will focus on complement inhibition as a potential therapy for GA growth inhibition and prevention of visual loss.

The Complement System

The complement system consists of more than 30 proteins and is a key driver of the innate immune system.[8,9] Complement proteins exist as either soluble blood proteins or membrane-associated protein complexes. Activation of the complement system may be initiated by one of three biochemical pathways: the classical; lectin; and alternative pathways.[5,8,9] The classical pathway is driven primarily by the formation of antibody-antigen complexes, while the lectin pathway is activated by polysaccharides on microbial surfaces.[9] Unlike the classical and lectin pathways, the alternative pathway is triggered by surface pathogens and does not rely on the formation of an immune complex.[9,10] Each pathway converges on the cleavage of complement component C3 (the most abundant complement protein in the blood) resulting in the formation of the activation products C3a, C3b, C5a and the membrane attack complex (MAC=C5b-9).[10]

Complement activation through the alternative pathway is initiated through the continuous hydrolysis of C3 to C3b.[5,10] Complement factor B (CFB) binds to C3b to form the C3bB complex. Complement factor D (CFD), a rate-limiting enzyme in the alternative complement pathway, in turn cleaves the C3bB complex to form active C3 and C5 convertases.[10] C3 convertase can then cleave additional C3 into C3a and C3b forming an amplification loop. Complement factor H (CFH) and complement factor I (CFI) are negative regulators of the alternative complement pathway that work together to deactivate C3b and halt the cascade that triggers pro-inflammatory responses and ultimate cell death.[1]

The Complement System in AMD

Dysregulation of the complement system is thought to play an important role in the development and progression of AMD.[9,11,12] Several potential triggers of the complement system in AMD have been described, including photo-oxidized A2E,[13] amyloid beta[14,15] and oxidative stress.[16,17] A number of complement activation

This article has no commercial sponsorship.

products have been identified in drusen, including C3a, C5a, C5b-9 (i.e., the MAC) and CFH.[9,18,19] Furthermore, vitreous samples, Bruch's membrane and choroid from patients with advanced AMD have shown elevated levels of complement proteins compared with controls.[12,20,21]

Along with these findings, complement inhibitors have been found to be lacking in eyes with GA.[22] For example, CD59 is a membrane-bound inhibitor of MAC formation and has been found at reduced levels in GA patients.[22] Similarly, MCP is a membrane-bound complement regulator that has cofactor activity for CFI, which serves to inactivate C3b and C4b and has been reported at reduced levels in GA.[23]

Although largely produced by the liver, complement synthesis has been found to occur extrahepatically in the neural retina, RPE and choroid.[12,16,24] In addition, systemic plasma complement levels have been shown to be significantly elevated in patients with AMD.[16] Whether elevations in local or systemic complement proteins play the leading role in GA pathogenesis is yet to be determined.[16]

A strong genetic correlation has been established between the risk of AMD and variations in genes encoding complement pathway proteins.[5,9] CFH was the first complement gene shown to be associated with AMD risk.[25-27] Additional genetic analyses, including a recent AMD gene consortium meta-analysis comprising more than 17,100 patients with advanced AMD and more than 60,000 controls identified genetic polymorphisms in complement pathway loci associated with advanced AMD risk, including complement component 2 (C2), C3, CFB, CFH and CFI.[28] Rare variants in CFI have recently been shown to contribute to the pathogenesis of AMD through dysregulation of alternative complement activation.[29] However, conflicting evidence regarding CFI and GA growth rates has been reported.[30]

Geographic atrophy remains a significant unmet medical need with no approved or effective treatments.

Not all complement activity in the eye is detrimental. In fact, complement activity has been shown to have both important developmental and protective effects in the retina.[31,32,33] Ruslan Medzhitov, PhD, established the concept of para-inflammation: a beneficial, well-controlled, intermediate, inflammatory response to tissue stress or malfunction with the primary role of maintaining tissue homeostasis.[34] This concept has been applied and studied in the aging retina.[35] Although the process is certainly multifactorial, what remains to be fully determined is why, when and how this para-inflammatory mechanism changes from being protective to destructive.

Investigational Agents

Currently, several complement inhibitors targeting various points along the complement pathway are being investigated for the treatment of GA, but none are yet approved or proven to be effective.[1,6-8] C5 inhibitors include eculizumab/SOLIRIS (Alexion), LFG-316 (Novartis/MorphoSys) and ARC-1905 (Ophthotech).[1,6-8] Inhibition of the complement cascade at the level of C5 prevents the formation of C5a and the membrane attack complex (MAC=C5b-9).

Eculizumab was evaluated in the Phase II COMPLETE Study (NCT00935883).[30] Eculizumab is a humanized monoclonal antibody derived from the murine anti-human C5 antibody. The COMPLETE study enrolled 30 patients aged 50 years and older, with a total GA area of 1.25 to 18 mm^2, and visual acuity of 20/63 or better (ETDRS).[30] Despite decreasing systemic C5 levels to less than 1 percent of normal by week two, the researchers found that intravenous administration of eculizumab did not significantly slow GA growth rates in patients with GA at the six-month endpoint or after an additional six months of follow-up.[30] Furthermore, they did not detect an association between GA progression and at-risk alleles.[30] Possible explanations for eculizumab's failed effect include inhibition of the wrong complement component, or wrong delivery mechanism. Reports have shown Bruch's membrane to become less permeable to serum proteins with age and involution of the choriocapillaris under areas of GA.[36,37] These previous findings may result in subtherapeutic doses when given systemically.

LFG-316 (Novartis/MorphoSys) is a fully human, full-length monoclonal anti-C5 antibody. The drug was well-tolerated in Phase I testing by intravitreal administration.[1,6] In a Phase II study, 150 patients with GA received monthly intravitreal injections of LFG-316 with the primary outcome measure being growth of GA at month 12. At the completion of the trial, LFG-316 was found to have an acceptable safety profile, but it was not efficacious in reducing GA lesion growth rate or improving visual acuity (NCT01527500).

ARC-1905 (Ophthotech) is an anti-C5 pegylated aptamer targeting C5 that has completed Phase I testing as an intravitreal injection for patients with GA (NCT00950638). Plans for initiating a Phase II/III trial of ARC-1905 are reported to be under way (ophthotech.com).

POT-4 (AL-78898A; Alcon) is a cy-

clic peptide comprising 13 amino acids derived from compstatin, which binds reversibly to C3 and prevents its proteolytic activation to C3a and C3b. A Phase I study looking at POT-4 for neovascular AMD has been completed (NCT00473928). A Phase II dry AMD study designed to demonstrate superiority of POT-4 intravitreal injections to sham injections by assessing GA lesion growth at month 12 was terminated due to slow recruitment (NCT01603043).

A complement inhibitor in advanced stages of clinical development is lampalizumab (FCFD45142), a humanized, monoclonal, antigen-binding fragment that specifically inhibits the alternative complement pathway by targeting CFD (Genentech/Roche).[1,6] CFD is a chymotrypsin-like serine protease specific for factor B (fB). It is the rate-limiting factor in the ACP and has the lowest serum concentration of all the complement proteins.[38] When associated with C3, fB is a substrate for fD. Cleavage of C3-fB to its active form fBb yields the ACP C3 convertase.[38]

The safety, tolerability and evidence of activity of lampalizumab in patients with GA were assessed in the MAHALO Phase II trial (NCT01229215) *(Regillo C. Late Breaker Paper presentation, American Academy of Ophthalmology Retina Sub-day Meeting 2013)*. MAHALO was a prospective, multicenter, randomized, single-masked, sham-injection-controlled study in which 129 patients aged 60 to 89 years with GA secondary to AMD were randomized 2:1:2:1 to lampalizumab 10 mg monthly, sham monthly, lampalizumab 10 mg every other month, or sham every other month. The sham arms were pooled for the analyses. The primary endpoint was change in GA area from baseline to month 18, as assessed by fundus autofluorescence imaging. The relationship between specific genetic polymorphisms associated with GA

Not all complement activity in the eye is detrimental. In fact, complement activity has been shown to have both important developmental and protective effects in the retina.

characteristics and lampalizumab treatment response was also explored.

In total, 123 patients received ≥one sham or lampalizumab treatment and had at least one post-baseline primary efficacy measurement (sham pooled, n=40; lampalizumab monthly, n=42; lampalizumab every other month, n=41), which satisfied pre-specified criteria for evaluation. A 20-percent reduction in GA area progression was reported in the all-comer lampalizumab monthly arm relative to the pooled sham arm. This positive treatment effect was observed at month six through month 18. An even greater reduction in GA area progression relative to the sham control was observed in a CFI genetic biomarker-defined subpopulation treated monthly with lampalizumab and more than one-half of the tested study population was positive for this biomarker. Lampalizumab demonstrated an acceptable safety profile in the Phase II study; there were no ocular or systemic serious adverse events suspected to be study drug-related.

Currently Roche has two ongoing Phase III trials: CHROMA (NCT02247479) and SPECTRI (NCT02247531) investigating GA treatment with lampalizumab. CHROMA and SPECTRI are identical, double-masked, randomized studies comparing a 10-mg dose of lampalizumab administered every four or six weeks by intravitreal injection to sham injections. Approximately 936 patients will be enrolled in each study (188 biomarker-positive patients and 124 biomarker-negative patients each for the sham, lampalizumab q4wk, and lampalizumab q6wk treatment groups, in each study). Inclusion criteria are similar to the phase II MAHALO study. The primary endpoint will be progression of GA at one year as measured by fundus autofluorescence. The secondary endpoint will be the impact of lampalizumab on visual function at two years (roche.com).

Geographic atrophy remains a significant unmet medical need with no approved or effective treatments. Results from large-scale genetics studies support the role of aberrant activation of the alternative complement pathway in AMD pathophysiology. The lampalizumab Phase II clinical trial was the first study to show a positive treatment effect in reducing GA progression through complement inhibition. Additional Phase II and III trials investigating complement inhibition as a potential treatment for geographic atrophy are currently under way. REVIEW

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1. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: Clinical features and potential therapeutic approaches. Ophthalmology 2014;121:1079-1091.
2. Sunness JS, Rubin GS, Applegate CA, et al. Visual function abnormalities and prognosis in eyes with age-related geographic atrophy of the macula and good visual acuity. Ophthalmology 1997;104:1677-1691.
3. Klein R, Chou C-F, Klein BEK, Zhang X, Meuer SM, Saaddine JB. Prevalence of age-related macular degeneration in the US population. Arch Ophthalmol 2011;129:75-80.
4. Lindblad AS, Lloyd PC, Clemons TE, et al. Change in area of

geographic atrophy in the Age-Related Eye Disease Study: AREDS report number 26. Arch Ophthalmol 2009;127:1168-1174.
5. van Lookeren Campagne M, LeCouter J, Yaspan BL, Ye W. Mechanisms of age-related macular degeneration and therapeutic opportunities. J Pathol 2014;232(2):151-164.
6. Holz FG, Schmitz-Valckenberg S, Fleckenstein M. Recent developments in the treatment of age-related macular degeneration. J Clin Invest 2014;124(4):1430-1438.
7. Leung E, Landa G. Update on current and future novel therapies for dry age-related macular degeneration. Expert Rev Clin Pharmacol 2013;6(5):565-579.
8. Weber BHF, Charbel Issa P, Pauly D, Herrmann P, Grassmann F, Holz FG. The role of the complement system in age-related macular degeneration. Dtsch Arztebl Int 2014;111(8):133-138.
9. Khandhadia S, Cipriani V, Yates JRW, Lotery AJ. Age-related macular degeneration and the complement system. Immunobiology 2012;217(2):127-146.
10. Sarma JV, Ward PA. The complement system. Cell Tissue Res. 2011;343(1):227-235.
11. Fritsche LG, Fariss RN, Stambolian D, Abecasis GR, Curcio CA, Swaroop A. Age-related macular degeneration: Genetics and biology coming together. Annu Rev Genomics Hum Genet 2014;15:151-171.
12. Anderson DH, Radeke MJ, Gallo NB, et al. The pivotal role of the complement system in aging and age-related macular degeneration: hypothesis re-visited. Prog Retin Eye Res 2010;29(2):95-112.
13. Zhou J, Jang YP, Kim SR, Sparrow JR. Complement activation by photooxidation products of A2E, a lipofuscin constituent of the retinal pigment epithelium. Proc Natl Acad Sci U.S.A. 2006;103(44):16182-16187.
14. Isas JM, Luibl V, Johnson LV, et al. Soluble and mature amyloid fibrils in drusen deposits. Invest Ophthalmol Vis Sci 2010;51(3):1304-1310.
15. Wang J, Ohno-Matsui K, Yoshida T, et al. Altered function of factor I caused by amyloid beta: implication for pathogenesis of age-related macular degeneration from Drusen. J Immunol 2008;181(1):712-720.
16. Warwick A, Khandhadia S, Ennis S, Lotery A. Age-Related Macular Degeneration: A Disease of Systemic or Local Complement Dysregulation? J Clin Med 2014;3(4):1234-1257.
17. Wang AL, Lukas TJ, Yuan M, Du N, Handa JT, Neufeld AH. Changes in retinal pigment epithelium related to cigarette smoke: possible relevance to smoking as a risk factor for age-related macular degeneration. PLoS ONE 2009;4(4):e5304.
18. Gehrs KM, Jackson JR, Brown EN, Allikmets R, Hageman GS. Complement, age-related macular degeneration and a vision of the future. Arch Ophthalmol 2010;128:349-358.
19. Troutbeck R, Al-Qureshi S, Guymer RH. Therapeutic targeting of the complement system in age-related macular degeneration: a review. Clin Experiment Ophthalmol 2012;40(1):18-26.
20. Loyet KM, Deforge LE, Katschke KJ, et al. Activation of the alternative complement pathway in vitreous is controlled by genetics in age-related macular degeneration. Invest Ophthalmol Vis Sci 2012;53(10):6628-6637.
21. Yuan X, Gu X, Crabb JS, et al. Quantitative proteomics: Comparison of the macular Bruch membrane/choroid complex from age-related macular degeneration and normal eyes. Mol Cell Proteomics 2010;9(6):1031-1046.
22. Ebrahimi KB, Fijalkowski N, Cano M, Handa JT. Decreased membrane complement regulators in the retinal pigmented epithelium contributes to age-related macular degeneration. J Pathol 2013;229(5):729-742.
23. Vogt SD, Curcio CA, Wang L, et al. Retinal pigment epithelial expression of complement regulator CD46 is altered early in the course of geographic atrophy. Exp Eye Res 2011;93(4):413-423.
24. Luo C, Chen M, Xu H. Complement gene expression and regulation in mouse retina and retinal pigment epithelium/choroid. Mol. Vis. 2011;17:1588-1597.
25. Edwards AO, Ritter R, Abel KJ, Manning A, Panhuysen C, Farrer LA. Complement factor H polymorphism and age-related macular degeneration. Science 2005;308(5720):421-424.
26. Haines JL, Hauser MA, Schmidt S, et al. Complement factor H variant increases the risk of age-related macular degeneration. Science 2005;308(5720):419-421.
27. Hageman GS, Anderson DH, Johnson LV, et al. A common haplotype in the complement regulatory gene factor H (HF1/CFH) predisposes individuals to age-related macular degeneration. Proc Natl Acad Sci U.S.A. 2005;102(20):7227-7232.
28. Fritsche LG, Chen W, Schu M, et al. Seven new loci associated with age-related macular degeneration. Nat Genet 2013;45(4):433-439, 439e1-2.
29. Seddon JM, Yu Y, Miller EC, et al. Rare variants in CFI, C3 and C9 are associated with high risk of advanced age-related macular degeneration. Nat Genet 2013;45(11):1366-1370.
30. Yehoshua Z, de Amorim Garcia Filho CA, Nunes RP, et al. Systemic complement inhibition with eculizumab for geographic atrophy in age-related macular degeneration: The COMPLETE study. Ophthalmology 2014;121:693-701.
31. Hoh Kam J, Lenassi E, Malik TH, Pickering MC, Jeffery G. Complement component C3 plays a critical role in protecting the aging retina in a murine model of age-related macular degeneration. Am J Pathol 2013;183(2):480-492.
32. Kawa MP, Machalinska A, Roginska D, Machalinski B. Complement system in pathogenesis of AMD: Dual player in degeneration and protection of retinal tissue. J Immunol Res 2014;2014:483960.
33. Yu M, Zou W, Peachey NS, McIntyre TM, Liu J. A novel role of complement in retinal degeneration. Invest Ophthalmol Vis Sci 2012;53(12):7684-7692.
34. Medzhitov R. Origin and physiological roles of inflammation. Nature 2008;454(7203):428-435.
35. Xu H, Chen M, Forrester JV. Para-inflammation in the aging retina. Prog Retin Eye Res 2009;28(5):348-368.
36. Moore DJ, Clover GM. The effect of age on the macromolecular permeability of human Bruch's membrane. Invest Ophthalmol Vis Sci 2001;42(12):2970-2975.
37. McLeod DS, Grebe R, Bhutto I, Merges C, Baba T, Lutty GA. Relationship between RPE and choriocapillaris in age-related macular degeneration. Invest Ophthalmol Vis Sci 2009;50(10):4982-4991.
38. Katschke KJ, Wu P, Ganesan R, et al. Inhibiting alternative pathway complement activation by targeting the factor D exosite. J Biol Chem 2012;287(16):12886-12892.

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Imprimis Expands, Debuts New Sedation Technique

Imprimis Pharmaceuticals announced plans to launch its IV Free MKO Melt conscious sedation formulations and a new triple-combination eye drop that includes nepafenac.

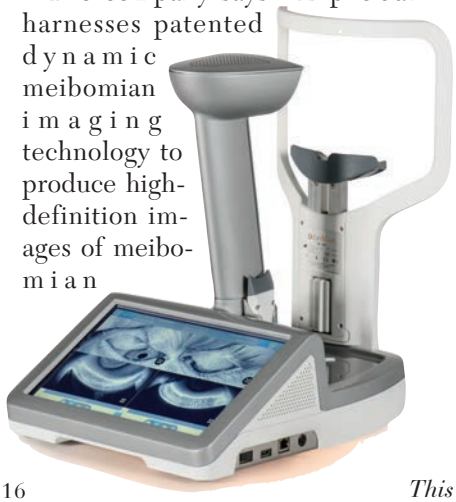
The company's patent-pending IV Free MKO Melt (midazolam, ketamine and ondansetron) compounded, conscious-sedation formulation is an alternative option to IV anesthetic that is administered sublingually to sedate patients undergoing ocular and other surgical procedures. The MKO Melt, in troche format, provides consistent and predictable dosing and allows for quick and easy administration, resulting in increased positive experiences for patients and staff. Traditionally, sedation medications for ocular surgery have been administered intravenously, which requires IV medications and supplies, and additional staff to assist in preparation, administration and monitoring related to this process; all of these factors often cause delays and disruptions in the operating room. The formulations or variations thereof have been used in more than 1,000 LASIK and cataract surgeries to date as part of the investigators' evaluation process, and a growing number of physicians have made the switch to IV Free conscious sedation, which is now available for $25.00 per two-troche pack. For more information visit IVFree.com.

The company also introduced its new Pred-Moxi-Nepafenac (prednisolone acetate, moxifloxacin hydrocholoride and nepafenac) combination topical eye drop formulation. Imprimis now offers four unique proprietary antibiotic, steroid and nonsteroidal combination LessDrops topical formulations: Pred-Moxi; Pred-Ketor; Pred-Moxi-Ketor; and the new Pred-Moxi-Nepafenac for use following cataract, LASIK, photorefractive keratectomy and other ocular surgeries. For information, visit godropless.com or lessdrops.com.

TearScience LipiScan Debuts

TearScience, manufacturer of LipiView II and LipiFlow for the treatment of meibomian gland dysfunction, announced the release of LipiScan, the only dedicated high-definition gland imager that allows eye care professionals to efficiently evaluate meibomian glands in busy practices.

The company says LipiScan harnesses patented dynamic meibomian imaging technology to produce high-definition images of meibomian glands. LipiScan allows physicians to assess meibomian gland structure during routine workups in any practice setting.



In the past year, TearScience says it has significantly adjusted prices of LipiView II and LipiFlow equipment and treatment activators (disposables). The introduction of LipiScan will allow busy practices to efficiently integrate assessment of meibomian glands and do so at an affordable price. For information, visit tearscience.com.

BVI Offers FLACS Cannula to Manage Femto Incisions

Beaver Visitec International announced the global launch of a new, multi-functional cannula, designed to improve surgical efficiency and optimize clinical outcomes during femto laser-assisted cataract surgery. The primary function of the Visitec FLACS Cannula is to ensure all types of femto incisions (sideport, main and arcuate) are opened smoothly, easily and cleanly. The cannula's leading edge is blunt to safeguard against stretching, distortion or creation of a second tunnel. It is also very thin, allowing it to glide through and open femto incisions with minimal effort, BVI says.

In addition, the cannula can be used to inject viscoelastic and/or other solutions into the eye, thereby reducing the number of instrument

This article has no commercial sponsorship.

passes into the eye and hand-offs between surgeon and scrub nurse. As a multifunctional tool, use of the Visitec FLACS Cannula may decrease procedure time, potentially leading to increased room turn over and more efficient patient flow.

Because it is a single-use device supplied in a manufacturer-sealed sterile package, the cannula removes the risk of cross-contamination associated with reusable instruments and eliminates the need for costly and time-consuming sterilization protocols.

The Visitec FLACS Cannula complements other single-use product offerings from BVI that can be used during FLACS, including the 27G Visitec Hydrodissection cannulae and blunt Capsulorhexis Forceps. For information, visit beaver-visitec.com.

iCare Tonometer: IOP Precision

Icare USA has released the Icare ic100 tonometer. The Icare ic100 uses the same rebound technology as its predecessor, the Icare TA01i, with added ergonomic features and a user interface that takes intraocular pressure measuring to a new level, the company says.

The Icare EasyNav interface and the unit's large color screen make this device exceptionally easy to use. It requires no calibration and is suitable for use on all patient types in virtually any setting. And, like its predecessor, the Icare ic100 requires no drops, air or specialized skills for use.

A built-in intelligent position assistant, called the Icare EasyPos, makes the Icare ic100 easier to use than ever before. Red and green lights help operators guide the tonometer into the correct position for testing. Examiners simply load, align and measure.

The unit features Icare AMS, an automated measuring sequence that takes a series of six measurements with a single touch of a button. For information, visit icare-usa.com.

ArcScan Precision Ultrasound For AC Measurement

ArcScan announced Food and Drug Administration 510(k) clearance for its ArcScan Insight 100 precision ultrasound device for imaging and biometry of the eye. Indicated for refractive surgical planning and evaluation of anterior segment pathology, the Insight 100 images and measures anterior chamber depth, angle-to-angle width, individual corneal layers, sulcus-to-sulcus width and more—with micron-level precision.

Unlike hand-held ultrasound, the Insight 100 allows users to easily obtain reproducible images with stunningly high resolution, the company reports. The ArcScan Insight 100 delivers visualization of the anterior segment's true anatomy, including areas such as behind the iris in ways that optical technologies can not. Epithelial thickness mapping, one of its many applications, enables surgeons to confidently perform LASIK on patients they might have otherwise rejected because of suspect topography, and exclude candidates with early keratoconus who have normal-looking topography on less-advanced imaging technology.

To learn more about the ArcScan Insight 100 or to schedule a demonstration, visit arcscan.com; email info@arcscan.com, or call 1 (877) 363-7226. REVIEW

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Study Finds In-Office Surgery Safe, Effective

In what its authors call the largest U.S. study to investigate the safety and effectiveness of office-based cataract surgery performed in minor procedure rooms, office-based efficacy outcomes were consistently excellent, with a safety profile expected of minimally invasive cataract procedures performed in ambulatory surgical centers and hospital outpatient departments.

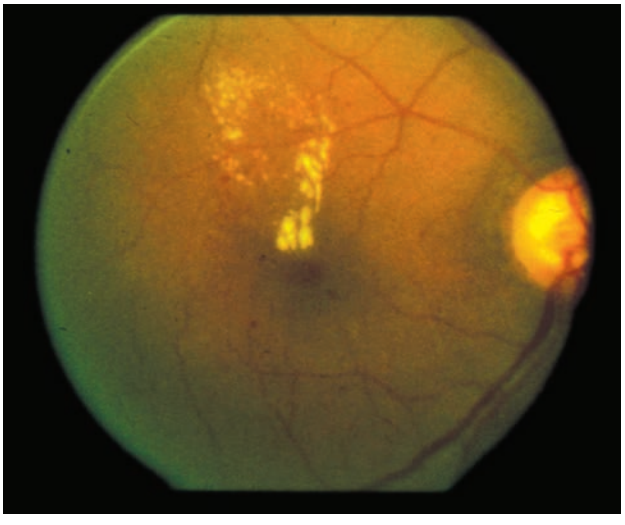
The large-scale, retrospective, consecutive case series included more than 13,500 patients undergoing elective office-based cataract surgery performed in minor procedure rooms (MPRs) of Kaiser Permanente health-care centers in Colorado.

Office-based cataract surgery was completed in 21,501 eyes (13,507 patients, age 72.6 ±9.6 years). Phacoemulsification was performed in 99.9 percent of cases, and manual extracapsular extraction was performed in 0.1 percent of cases. Systemic comorbidities included hypertension (53.5 percent), diabetes (22.3 percent) and chronic obstructive pulmonary disease (9.4 percent). Postoperative mean best-corrected visual acuity measured 0.14 ±0.26 logarithm of the minimum angle of resolution units. Intraoperative ocular AEs included 119 (0.55 percent) cases of capsular tear and 73 (0.34 percent) cases of vitreous loss. Postoperative AEs included iritis (n=330, 1.53 percent), corneal edema (n=110, 0.53 percent) and retinal tear or detachment (n=30, 0.14 percent). No endophthalmitis was reported. Second surgeries were performed in 0.70 percent of treated eyes within six months. There were no life- or vision-threatening intraoperative or perioperative AEs.

Ophthalmology 2016;123:723-8.
Ianchulev T, Litoff D, Ellinger D, Stiverson K, Packer M.

Five-Year Results of Four DME Treatment Options Compared

Researchers from the Wilmer Eye Institute, Baltimore, and several southeastern U.S. health centers compared long-term vision and anatomic effects of ranibizumab with prompt or deferred laser versus laser or triamcinolone + laser with very deferred ranibizumab in diabetic macular edema.



In their trial, 828 eyes with visual acuity 20/32 to 20/320 and DME involving the central macula were randomly assigned to intravitreous ranibizumab (0.5 mg) with either 1) prompt or 2) deferred laser; 3) sham injection + prompt laser; or 4) intravitreous triamcinolone (4 mg) + prompt laser. The latter two groups could initiate ranibizumab as early as 74 weeks from baseline, for persistent DME with vision impairment. The main outcome measures were visual acuity, optical coherence central subfield thickness, and number of injections through five years; 558 (67 percent) completed the five-year visit.

At five years mean (± standard deviation) change in Early Treatment Diabetic Retinopathy Study visual acuity letter scores from baseline were: 10 ±13 letters in the ranibizumab + deferred laser group (n=111); 8 ±13 in the ranibizumab + prompt laser group (n=124); 5 ±14 in the laser/very deferred ranibizumab group (n=198); and 5 ±14 in the

(continued on page 81)

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OPHTHALMOLOGY

Bassett Healthcare Network
Bassett Medical Center

Bassett Healthcare Network, a progressive health care network in central New York and major teaching affiliate of Columbia University is seeking a **General Ophthalmologist** to join a busy ophthalmology department based in the lovely village of Cooperstown. Glaucoma experience a plus!

Bassett Healthcare Network is an integrated health care system that provides care and services to people living in an eight county region covering 5,600 square miles in upstate New York. The organization includes six corporately affiliated hospitals, as well as skilled nursing facilities, community and school-based health centers, and health partners in related fields.

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- Comprehensive benefit package, including but not limited to medical, dental, CME, relocation assistance and paid malpractice insurance

Bassett Medical Center is located in Cooperstown, New York, a beautiful resort village on Otsego Lake. Home to the National Baseball Hall of Fame and Museum, the Glimmerglass Opera Company, and the Fenimore Art Museum, the area also boasts many cultural and four season recreational advantages including theater, music, museums, golf, sailing, hiking, and skiing.

EEO Employer

For confidential consideration, please contact:
Debra Ferrari, Manager, Medical Staff Recruitment,
Bassett Medical Center, One Atwell Road, Cooperstown, NY, 13326
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or visit our web-site at www.bassettopportunities.org

Chronic sinusitis along with a recent, two-week history of left-sided facial pain and swelling prompt an ER visit by a middle-aged man.

Ayan Chatterjee, MD, MSEd

Presentation

A 45-year-old Caucasian male with past medical history significant for chronic sinusitis presented to the Wills Eye emergency room with a two-week history of left-sided facial pain and swelling, presumed to be due to an acute exacerbation of sinusitis. The patient first noted left ear pain as well as left upper and lower eyelid swelling and redness about two weeks earlier. He recalled having a moderate, transient left-sided headache at the time of symptom onset, which had not recurred. There was no history of trauma. A full course of oral azithromycin with a rapid oral steroid taper provided no relief. He was also prescribed tobramycin/dexamethasone (0.3%/0.1%) ophthalmic suspension three times daily to the left eye for one week, with no relief. He reported no blurry vision, eye pain or double vision.

Medical History

The patient was healthy except for a history of multiple previous sinus infections spanning several years, which had all been successfully treated with oral antibiotics. There was no history of tobacco use, diabetes, hypertension or malignancy. He had no history of intravenous drug use and drank only socially.

Examination

The patient's vital signs on arrival were significant for a regular pulse of 72 and a blood pressure of 166/112. He was afebrile. A brief systemic physical exam was unremarkable.

Ophthalmologic examination revealed a visual acuity of 20/40 in the right eye (OD) and 20/25+2 in the left eye (OS). Both pupils were round and reactive, with no relative afferent pupillary defect. In ambient lighting, the patient's pupils measured 3 mm OD and 2 mm OS; in the dark, the patient's pupils were 5 mm OD and 2.5 mm OS. Extraocular movements and confrontation visual fields were grossly full in both eyes. External examination revealed an upper eyelid margin to corneal reflex distance of 3.0 mm OD and 1.5 mm OS. The lower eyelid positions were symmetric. There was no evidence of eyelid edema, erythema or tenderness. There was no palpable lymphadenopathy. On slit-lamp exam, the anterior segment exam was unremarkable. Intraocular pressure was 18 mmHg in both eyes. Dilated funduscopic examination was deferred until further testing was completed.

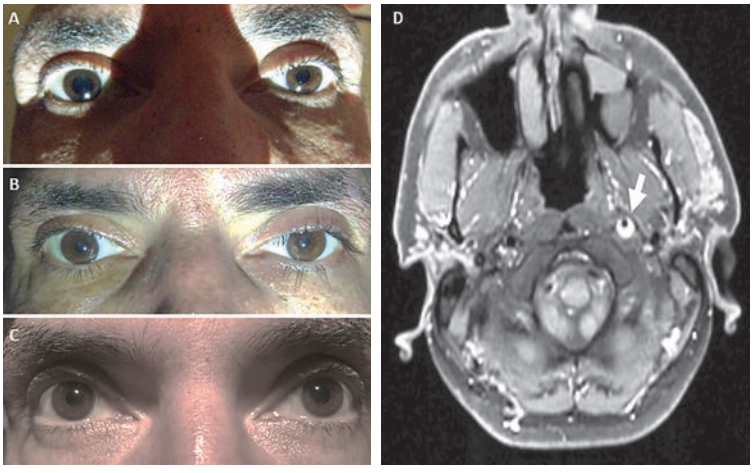

Figure 1. View of the patient's eyes (A) immediately after ambient light was decreased and (B) after ambient light was increased once again. (C) Is post apraclonidine testing OU. An axial T1 MR image (D) revealed a hyperintense, crescent-shaped thrombus (arrow) in the distal cervical segment of the left internal carotid artery (ICA) consistent with an ICA dissection.

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

Diagnosis, Workup and Treatment

Assessment of the patient's anisocoria both in light and dark conditions revealed a worsening anisocoria in the dark *(See Figure 1A & B)*. Instillation of one drop of 0.5% apraclonidine into both eyes resulted in reversal of the anisocoria *(See Figure 1C)*, consistent with a left Horner syndrome. Urgent MRI/MRA of the head and neck revealed a left internal carotid artery dissection at the skull base *(See Figure 1D)*. Dilated funduscopic examination of both eyes was unremarkable.

The patient was admitted to the Neurology service for inpatient anticoagulation. He was continued on aspirin and ramipril on discharge, with close follow-up for long-term monitoring.

Discussion

Acute Horner syndrome, which results from disruption of sympathetic innervation, can be recognized by the triad of ptosis, miosis and anhydrosis, but all three features are rarely present together.[1] Of note, ptosis can be extremely subtle, and it is reportedly absent in 12 percent of HS cases. Because sympathetically innervated muscle is also found in the lower lid (the inferior tarsal muscle), the lower lid may be elevated in HS, producing a so-called "reverse ptosis."[2] Anisocoria due to sympathetic paresis is more pronounced in the dark because the affected pupil exhibits a dilation lag; in physiologic anisocoria, the difference in pupillary sizes would remain constant in ambient light and in the dark.

The causative pathology of the HS is generally apparent in more than 80 percent of patients at the time of the first neuro-ophthalmologic consultation based on history or clinical localization of the lesion.[3] A "painful HS" is the most common sign of internal carotid artery (ICA) dissection, with an estimated sensitivity of 58 percent.[4,5] Any patient presenting with ptosis and ipsilateral miosis associated with acute ipsilateral eye, face or neck pain should be considered to harbor an ICA dissection until proven otherwise; of note, the pain can be subtle, often described as a dull ache, and is often revealed only after specific questioning by the clinician.[6] In the case presented, the patient had a history of sinus disease with a constellation of incidental symptoms and findings that led to delayed recognition of his underlying condition until his presentation to the emergency room.

The differential diagnosis of acute HS is broad and traditionally divided anatomically into first-order causes (central; which can include pituitary tumor, stroke, demyelination, neck trauma, etc.), second-order causes (intermediate; which can include brachial plexus injury, Pancoast tumor, mesothelioma, aortic aneurysm or dissection, etc.), and third-order causes (post ganglionic; which can include ICA dissection or aneurysm, skull base tumors, herpes zoster, etc.).[1]

When HS is suspected, one of several confirmatory pharmacologic tests may be employed. Generally these tests cannot reliably localize the lesion to a particular site and thus cannot guide imaging choice. Traditionally, cocaine has been highly effective at separating HS patients from controls, with an average post-cocaine anisocoria of reportedly greater than 0.8 mm.[7] Cocaine's biggest advantage over other agents is its ability to pharmacologically diagnose HS immediately after onset. Therefore, a negative cocaine test effectively rules out HS at any stage, including the acute phase. Unfortunately, cocaine drops have a short shelf life and are not readily available in clinical practice. Similarly, apraclonidine can confirm the diagnosis of HS within approximately 36 to 72 hours of symptom onset; however, a negative test prior to this time frame does not rule out HS.[8] With an overall sensitivity of approximately 87 percent,[9] the apraclonidine test remains a viable alternative to the cocaine test. Apraclonidine testing in HS has not yet been validated in a large sample, and several reports of false negative tests have been published.[10,11] Diluted phenylephrine and hydroxyamphetamine are cumbersome tests that have no practical use in the diagnosis and management of HS.[12]

In one large series of 146 consecutive patients with extracranial carotid artery dissection, a nonreversible ocular or hemispheric stroke occurred in 27 patients, within a mean of 6.2 days among the 76 (52 percent) patients that had ophthalmologic symptoms or signs as the presenting findings of dissection. About 67 percent of these occurred within the first week of symptom onset, 89 percent occurred within the first two weeks, and none occurred after 31 days.[6] This reinforces the importance of early diagnosis and initiation of treatment before a devastating stroke ever occurs.

Imaging can be targeted or nontargeted, based on the clinical presentation. One retrospective cohort study of 52 patients with HS who were being examined for the first time by a neuro-ophthalmologist revealed that the etiology was already known in most patients (62 percent) and that the most common etiology was surgical trauma to the head, neck or chest.[3] Targeted imaging revealed the cause in 21 percent of patients (most commonly carotid dissection

or cavernous sinus mass), and non-targeted imagining was required in the remaining 17 percent of cases. This has led Jonathan Trobe, MD, and colleagues to propose a relatively straightforward algorithm for evaluation of HS: (1) confirm that there is indeed HS using either topical cocaine or aproclonidine; (2) determine whether there has been previous accidental or surgical trauma that would explain the HS; (3) perform urgent targeted imaging guided by the presenting complaints (CT/CTA or MRI/MRA of the head and neck), especially if the HS has been present for less than than two weeks; (4) imaging of the lung apex, while important in uncovering rarer causes of HS such as lung tumors, can be performed as an outpatient.[13]

In conclusion, early recognition of acute HS is extremely important. Ipsilateral pain in HS represents ICA dissection until proven otherwise and calls for urgent soft tissue and vascular imaging of the appropriate anatomy (neck and skull base) if identified within the first two weeks from symptom onset, when risk for stroke is greatest. Pharmacologic tests (cocaine or apraclonidine) should be employed to confirm HS, but do not aid in localizing the underlying pathology along the sympathetic chain. Acute ICA dissection requires urgent neurosurgical or vascular evaluation and treatment. REVIEW

1. Davagnanam I, Fraser CL, Miszkiel K, Daniel CS, Plant GT. Adult Horner's syndrome: A combined clinical, pharmacological, and imaging algorithm. Eye (Lond) 27, 291-298, doi:10.1038/eye.2012.281 (2013).
2. Maloney WF, Younge BR, Moyer NJ. Evaluation of the causes and accuracy of pharmacologic localization in Horner's syndrome. Am J Ophthalmol 1980;90:394-402.
3. Almog Y, Gepstein R, Kesler A. Diagnostic value of imaging in horner syndrome in adults. J Neuroophthalmol 2010;30:7-11. doi:10.1097/WNO.0b013e3181ce1a12.
4. Mokri B. Traumatic and spontaneous extracranial internal carotid artery dissections. J Neuroophthalmol 1990;237:356-361.
5. Guillon B, Levy C, Bousser MG. Internal carotid artery dissection: An update. J Neurol Sci 153;1998;146-158.
6. Biousse V, Touboul P, D'Anglejan-Chatillon J, Lévy C. Ophthalmologic manifestations of internal carotid artery dissection. Am J Ophthalmol 1998;126:565-577.
7. Kardon RH, Denison CE, Brown CK, Thompson HS. Critical evaluation of the cocaine test in the diagnosis of Horner's syndrome. Arch Ophthalmol 1998;108:384-387.
8. Lebas M, Seror J, Debroucker T. Positive apraclonidine test 36 hours after acute onset of horner syndrome in dorsolateral pontomedullary stroke. J Neuroophthalmol 2010;30:12-17, doi:10.1097/WNO.0b013e3181b1b41f.
9. Koc F, Kavuncu S, Kansu T, Acaroglu G, Firat E. The sensitivity and specificity of 0.5% apraclonidine in the diagnosis of oculosympathetic paresis. Br J Ophthalmol 2005;89:1442-1444, doi:10.1136/bjo.2005.074492.
10. Kawasaki A, Borruat FX. False negative apraclonidine test in two patients with Horner syndrome. Klin Monbl Augenheilkd 2008;225:520-522, doi:10.1055/s-2008-1027349.
11. Dewan MA, Harrison AR, Lee MS. False-negative apraclonidine testing in acute Horner syndrome. Can J Ophthalmol 2009;44:109-110, doi:10.3129/i08-162.
12. Moster ML, Galiani D, Garfinkle W. False negative hydroxyamphetamine test in horner syndrome caused by acute internal carotid artery dissection. J Neuroophthalmol 2003;23:22-23.
13. Trobe, J. D. The evaluation of horner syndrome. J Neuroophthalmol 2010;30:1-2.

(continued from page 76)

triamcinolone + laser/very deferred ranibizumab group (n=125). The difference (95 percent confidence interval) in mean change between ranibizumab + deferred laser and laser/very deferred ranibizumab and triamcinolone + laser/very deferred ranibizumab was 4.4 (1.2 to 7.6, p=.001) and 2.8 (-0.9 to 6.5, p=.067), respectively, at five years.

The authors recognize the limitations of follow-up available at five years, but conclude that eyes receiving initial ranibizumab therapy for center-involving DME likely have better long-term vision improvements than eyes managed with laser or triamcinolone + laser followed by very deferred ranibizumab for persistent thickening and vision impairment.

Am J Ophthalmol 2016 Apr;164:57-68.

Bressler SB, Glassman AR, Almukhtar T, Bressler NM, Ferris FL, Googe JM Jr, Gupta SK, Jampol LM, Melia M, Wells JA 3rd; Diabetic Retinopathy Clinical Research Network (DRCR.net).

More Data on Sunlight, AMD

Researchers in Cologne, Germany, and Nijmegan, the Netherlands evaluated the effects of current and past sunlight exposure and iris color on early and late age-related macular degeneration. Previous studies, they note, suggested a connection between sunlight exposure and light iris color and greater risk for AMD, but with inconsistent results.

They reviewed 3,701 cases from the EUGENDA database; 752 (20.3 percent) showed early AMD; 1,179 (31.9 percent) late AMD; and 1,770 (47.8 percent) were controls. Information about current and past sunlight exposure, former occupation type, subdivided to indoor working and outdoor working, and iris color were obtained by standardized interviewer-assisted questionnaires. Associations between environmental factors adjusted for age, gender and smoking and early and late AMD were performed by multivariate regression analysis.

Current sunlight exposure showed no association with early AMD or late AMD, but past sunlight exposure (≥eight hours outside daily) was significantly associated with early AMD (odds ratio: 5.54, 95 percent confidence interval 1.25 to 24.58, p=0.02) and late AMD (odds ratio: 2.77, 95 percent CI 1.25 to 6.16, p= 0.01). Outside working was found to be associated with late AMD (odds ratio: 2.57, 95 percent confidence interval 1.89 to 3.48, p=1.58 × 10). No association was observed between iris color and early or late AMD.

Sunlight exposure during working life is an important risk factor for AMD, they conclude, whereas sunlight exposure after retirement seems to have less influence on the disease development. Therefore, preventive measures such as wearing sunglasses to minimize sunlight exposure should start early to prevent development of AMD later in life.

Retina 2016;36:787-90.

Schick T, Ersoy L, Lechanteur YT, Saksens NT, Hoyng CB, den Hollander AI, Kirchhof B, Fauser S.

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