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REVIEW® of Ophthalmology

October 2015

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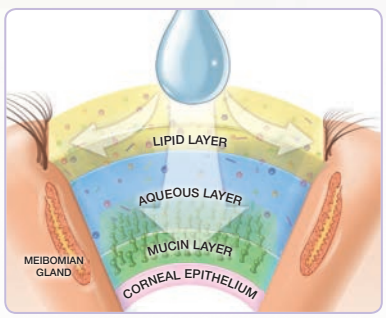

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References: 1. Akpek EK, Smith RA. Overview of age-related ocular conditions. *Am J Manag Care.* 2013;19 (5 suppl):S67-S75. **2.** Korb DR, Blackie CA, Meadows DL, Christensen M, Tudor M. Evaluation of extended tear stability by two emulsion based artificial tears. Poster presented at: 6th International Conference on the Tear Film and Ocular Surface: Basic Science and Clinical Relevance; September 22-25, 2010; Florence, Italy.

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REVIEW NEWS
Volume XXII • No. 10 • October 2015

BPEI/FIE Collaboration May Offer Next-Generation OCT

A collaborative biomedical engineering team from Bascom Palmer Eye Institute and Florida International University has developed what it calls a breakthrough retinal imaging technology that could help clinicians diagnose and assess the extent of vision loss in patients with a wide range of conditions.

After three years of work, the Bascom Palmer and FIU researchers successfully tested the first visible-light optical coherence tomography (VIS-OCT) technology for imaging rhodopsin, the light-sensing molecule contained in the retinal photoreceptors that convert light signals to neuronal signals sent to the brain.

Shuliang Jiao, PhD, an associate professor in the department of biomedical engineering at FIU and a Bascom Palmer alumnus, led the project. He designed and built the first VIS-OCT capable of imaging rhodopsin, and is the senior author of an article describing the novel VIS-OCT technology, "Depth-resolved rhodopsin molecular contrast imaging for functional assessment of photoreceptors," published recently in *Scientific Reports*. The research was supported by grants from the National Institutes of Health.

Tan Liu, PhD, a postdoctoral associate in the FIU biomedical engineering program, was first author of the paper. Co-authors were Bascom Palmer professors of ophthalmology Rong Wen, MD, PhD, and Byron L. Lam, MD, the Robert Z. and Nancy J. Greene Chair in Ophthalmology; and Carmen A. Puliafito, MD, MBA, dean of the Keck School of Medicine of the University of Southern California. Dr. Puliafito was one of the pioneers in the development of OCT.

"OCT has been used extensively in ophthalmology clinics," said Dr. Jiao. "Our work shows the new technology can be used to construct an accurate map showing the distribution of rhodopsin—a functional biomarker of the rod photoreceptors in the retina. We now are working on making this imaging equipment more patient-friendly to move it into the clinical setting."

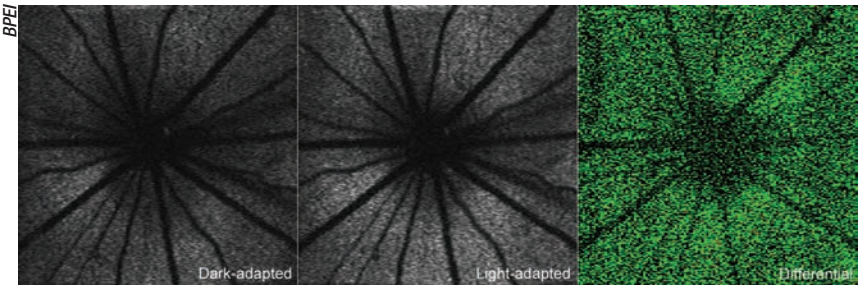
Dr. Jiao added that the VIS-OCT-created map could help determine the effectiveness of treatments in retinal disorders that affect the photoreceptors. For example, the progressive loss of photoreceptors in patients with hereditary retinal degeneration can be objectively measured and documented for clinical care and evaluation of treatments.

"This technology can be used to monitor disease progression for retinitis pigmentosa, age-related macular degeneration and other retinal diseases," said Dr. Lam, a physician-scientist who specializes in photoreceptor degeneration. "It can also be used to objectively measure the outcomes for treatments and clinical trials of new therapies," he added. Dr. Wen, a photoreceptor cell biologist, believes VIS-OCT technology will also be useful to study future photoreceptor regeneration, including transplant stem cell-derived photoreceptors, gene therapies, neuroprotection therapies using neurotrophic factors and other neuroprotective agents.

"The rapid development in regenerative medicine to restore vision has raised a hope that regeneration of photoreceptors and restoration of photoreceptor function will become reality in the near future," he said. "When the time comes, this technology will be used to see whether the new photoreceptors are functional."

This work started three years ago when Drs. Jiao, Wen and Lam were seeking an objective way to measure the function of photoreceptors in patients. The prototype rhodopsin VIS-OCT is an important step toward clinical application of the new technology.

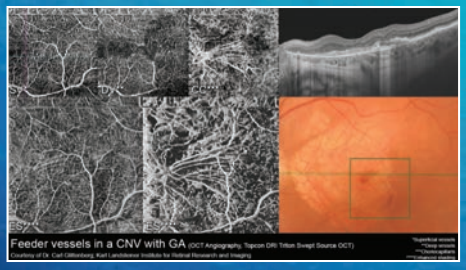
BPEI

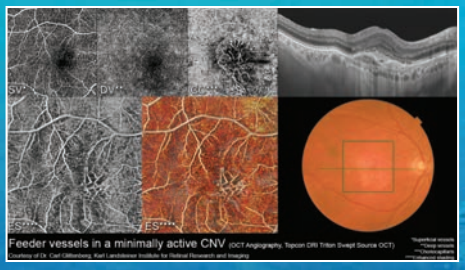


Rhodopsin distribution (en face OCT image, right) was obtained by calculating the difference in fundus reflection of OCT light (λ=520 nm) between dark-adapted (left) and light-adapted retina (middle).

SAVE THE DATE!

Clinical Advantages of Swept-Source OCT and OCT Angiography*





Feeder vessels in a CNV with GA and a minimally active CNV
(Courtesy of Dr. Carl Glittenberg, Karl Landsteiner Institute for Retinal Research and Imaging)

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6:00 pm Presentation

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Room Margaux 1

Speaker	Affiliation	Presentation Title
Robert Weinreb, MD	University of California San Diego	*"Swept-Source OCT in the Management of Glaucoma"*
Richard Spaide, MD	Vitreous-Retina-Macula Consultants of New York	*"Swept-Source OCT and OCT Angiography for Evaluation of the Retina"*
Luis Arias, MD	Bellvitge University Hospital	*"En Face SS-OCT and OCT Angiography Contributions in Macular Degeneration"*

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REVIEW News

Outdoor Activity Combats Myopia In Young Children

The addition of a daily outdoor activity class at school for three years for children in Guangzhou, China, resulted in a reduction in the rate of myopia, according to a study in the September 15 issue of *JAMA*.

Myopia has reached epidemic levels in young adults in some urban areas of East and Southeast Asia. In these areas, 80 to 90 percent of high school graduates now have myopia. Myopia also appears to be increasing, more slowly, in populations of European and Middle Eastern origin. Currently, there is no effective intervention for preventing onset. Recent studies have suggested that time spent outdoors may prevent the development of myopia, according to background information in the article.

Mingguang He, MD, PhD, of Sun Yat-sen University, Guangzhou, and colleagues conducted a study in which children in grade one from 12 primary schools in Guangzhou (six intervention schools [n=952 students]; six control schools [n=951 students]), were assigned to one additional 40-minute class of outdoor activities, added to each school day, and parents were encouraged to engage their children in outdoor activities after school hours, especially during weekends and holidays (intervention schools); or children and parents continued their usual pattern of activity (control schools). The average age of the children was 6.6 years.

The three-year cumulative incidence rate of myopia was 30.4 percent (259 cases among 853 eligible participants) in the intervention group and 39.5 percent (287 cases among 726 eligible participants) in the control group. Cumulative change in spherical equivalent refraction (myopic shift) after three years was significantly less

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in the intervention group than in the control group.

"Our study achieved an absolute difference of 9.1 percent in the incidence rate of myopia, representing a 23 percent relative reduction in incident myopia after three years, which was less than the anticipated reduction," the authors write. "However, this is clinically important because small children who develop myopia early are most likely to progress to high myopia, which increases the risk of pathological myopia. Thus a delay in the onset of myopia in young children, who tend to have a higher rate of progression, could provide disproportionate long-term eye health benefits. Further studies are needed to assess long-term follow-up of these children and the generalizability of these findings."

DR Screenings For Kids May Be Delayed

A new study has found that the occurrence of advanced forms of a diabetic eye disease remains low among children living with diabetes, regardless of how long they have had the disease or their ability to keep blood sugar levels controlled. Researchers are therefore recommending that most children with type 1 diabetes delay annual diabetic retinopathy screenings until age 15, or five years after their diabetes diagnosis, whichever occurs later. Their findings were published online in *Ophthalmology*.

It is well-established that early detection and timely treatment of diabetic retinopathy reduces vision loss in adults, and some physician organizations recommend screening children for diabetic retinopathy annually starting at an early age—after age 9, or from three to five years after diagnosis. However, the value of screening children has not been clearly documented and the prevalence of severe diabetic retinopathy among the young has been unclear.

Researchers based at the Children's Hospital of Philadelphia and the Scheie Eye Institute, Perelman School of Medicine at the University of Pennsylvania began to question current diabetic retinopathy screening guidelines for children. They were concerned that these annual exams may create an excessive financial and logistical burden for families and the health care system.

The researchers conducted a retrospective study of 370 children under age 18 with type 1 and type 2 diabetes. Some of the study participants had blood sugar levels three times that of a person without diabetes. All had received at least one diabetic eye disease screening exam between 2009 and 2013, but none were found to have diabetic retinopathy.

The researchers then examined the data that led to the current screening guidelines. They discovered that previous studies reported a diabetic retinopathy prevalence rate between 0 and 28 percent among children studied, but the majority of the cases were very mild and thus would not qualify for treatment. They also found that the youngest person reported to have severe diabetic retinopathy was between 15 and 19 years old, and five to six years was the shortest reported duration of having diabetes before developing severe diabetic retinopathy.

In light of the available evidence, the researchers recommend that screenings for children with type 1 diabetes could begin at a later age than previously recommended.

"Many of our young patients with diabetes diligently come in every year for screenings that consistently show no sign of the disease," said Gil Binenbaum, MD, MSCE, co-author of the study and attending surgeon in the ophthalmology division at Children's

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Hospital. "Of course, that's good news for them, and it is very important to have annual eye exams once the risk of vision loss develops. But, is it worth the burden on the family and the health-care system if evidence shows that diabetic retinopathy doesn't reach a treatable stage until years later?"

Researchers say exceptions should be made for children with type 2 diabetes and those identified by their endocrinologists as having high risk for diabetic complications. They should start diabetic retinopathy screenings upon diagnosis, similar to adults with type 2 diabetes, since many type 2 diabetes patients live with the disease uncontrolled before they are diagnosed. Because there is limited published researched on children with type 2 diabetes and diabetic retinopathy, researchers noted that a retinopathy screening examination upon diagnosis is their recommendation for those patients until additional data showing otherwise is available.

The American Academy of Ophthalmology currently recommends that people with type 1 diabetes have annual screenings for diabetic retinopathy beginning five years after the onset of their disease, and that those with type 2 diabetes should have an examination at the time of diagnosis and at least once a year thereafter.

Shiley Group: New Target to Prevent & Treat Glaucoma

Scientists at the University of California, San Diego, School of Medicine have elucidated a genetic interaction that may prove key to the development and progression of glaucoma.

The findings, published online in *Molecular Cell*, suggest a new therapeutic target for treating the disease.

Primary open-angle glaucoma affects more than 3 million Americans,

primarily after the age of 50, with intraocular pressure and age being the leading risk factors. Genetics also plays a role. Recent genome-wide association studies have identified two genes—SIX1-SIX6 and p16INK4a—as strongly associated with POAG. SIX6 is required for proper eye development. p16INK4a irreversibly arrests cell growth, or senescence.

Principal investigator Kang Zhang, MD, PhD, professor of ophthalmology and chief of ophthalmic genetics at Shiley Eye Institute at UC San Diego Health, and colleagues report that some variants of SIX6 boost expression of p16INK4a, which in turn accelerates senescence and death of retinal ganglion cells. "We also show that high IOP in glaucoma increases expression of p16INK4a, making it a key integrator of inherent genetic and environmental risk factors that can result in glaucoma," said Dr. Zhang.

The findings suggest that inhibiting p16INK4a could offer a new therapeutic approach for glaucoma, currently treated by IOP-lowering drugs. "Although lowering IOP can slow worsening of the disease, it does not stop it and prevent further cell death or possible blindness," said co-author Robert N. Weinreb, MD, distinguished professor of ophthalmology and director of Shiley Eye Institute.

The authors note that earlier studies in mouse models have shown that selective elimination of p16INK4a-positive senescent cells can prevent or delay age-related tissue deterioration.

According to the UC San Diego team, the next step is to conduct preclinical studies to assess the efficacy and safety of antisense oligonucleotides—strands of synthesized DNA or RNA that can prevent transfer of genetic information—which might inhibit p16INK4a expression and prevent worsening of glaucoma. "If they are effective, we may contemplate a human clinical trial in the future," Dr. Zhang said. REVIEW

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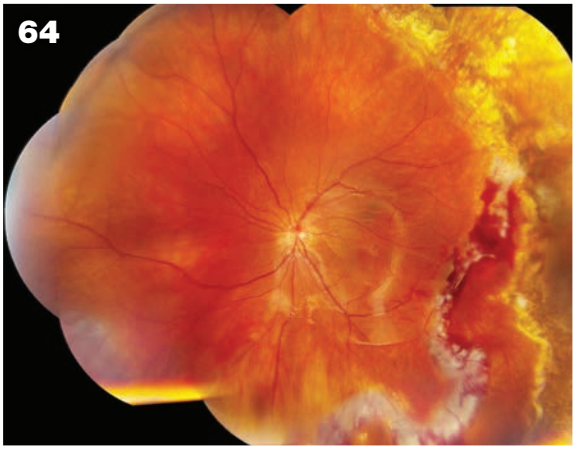

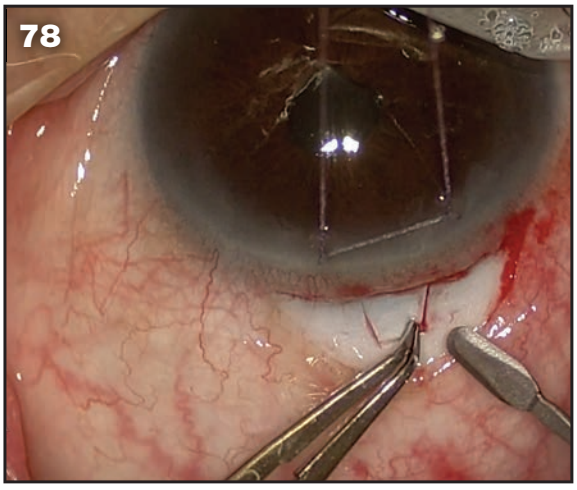

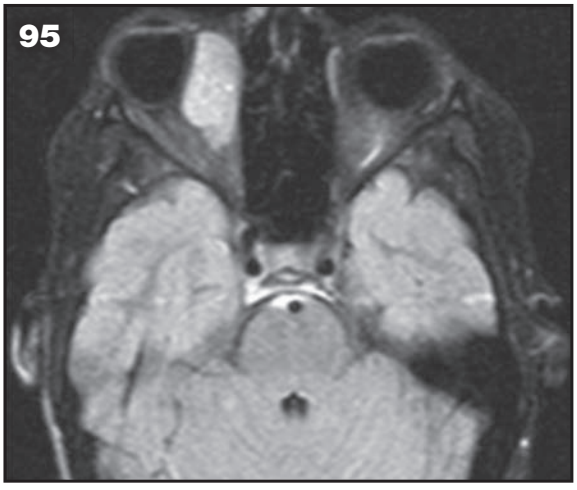

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ICD-10 Is Here: What You Need to Know Now

After several years of delay, ICD-10 will be implemented on October 1, 2015. What does this mean for your practice?

Q Will there be another delay in implementation, or will the ICD-10 diagnosis coding system be required on October 1, 2015?

A No further implementation delays are expected. The first implementation delay moved the deadline from 2013 to 2014. Then another delay was included in the Protecting Access to Medicare Act of 2014, delaying the start until 2015. All indications point toward a final date of October 1, 2015 requiring the use of ICD-10 codes on claims submitted for reimbursement.

Q Is the Center for Medicare & Medicaid Services confident that its systems are prepared to receive and process claims with ICD-10 codes beginning on October 1, 2015?

A Yes. Several claim testing weeks with CMS revealed high levels of acceptance of claims (>90 percent), with only a small number of denials due to an invalid ICD-10 code. CMS encouraged testing with clearinghouses and others to ensure a smooth transition.

Q Will CMS provide any latitude with code selection due to the newness of these codes?

A In a July FAQ, CMS published information about a one-year grace period associated with code selection. It stated:

While diagnosis coding to the correct level of specificity is the goal for all claims, for 12 months after ICD-10 implementation, Medicare review contractors will not deny physician or other practitioner claims billed under the Part B physician fee schedule through either automated medical review or complex medical record review based solely on the specificity of the ICD-10 diagnosis code as long as the physician/practitioner used a valid code from the right family.

CMS clarified that family of codes means "category," which is the first three digits of an ICD-10 code. CMS further clarified that the grace period is associated with a claim review and not with an initial claim submission.

Q Will CMS penalize physicians who apply incorrect ICD-10 codes as they relate to the quality reporting programs?

A CMS addressed this concern in its FAQ publication:

For all quality reporting completed for program year 2015 Medicare clinical quality data review contractors will not subject physicians or other Eligible Professionals (EP) to the Physician Quality Reporting System (PQRS), Value Based Modifier (VBM), or Meaningful Use 2 (MU) penalty during primary source verification or auditing related to the additional specificity of the ICD-10 diagnosis code, as long as the physician/EP used a code from the correct family of codes. Furthermore, an EP will not be subjected to a penalty if CMS experiences difficulty calculating the quality scores for PQRS, VBM, or MU due to the transition to ICD-10 codes. CMS will not deny any informal review request based on 2015 quality measures if it is found that the EP submitted the requisite number/type of measures and appropriate domains on the specified number/percentage of patients, and the EP's only error(s) is/are related to the specificity of the ICD-10 diagnosis code (as long as the physician/EP used a code from the correct family of codes).

In the subsequent clarification, CMS indicated that leniency will apply in the event of failure with the

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quality program and a subsequent appeal revealing that the failure was due to diagnosis codes.

Q Will CMS continue to update ICD-10 files on its website?

A Yes. The 2016 General Equivalence Mapping (GEM) files are currently available on the CMS website at cms.gov/Medicare/Coding/ICD10/2016-ICD-10-CM-and-GEMs.html. In addition, the 2016 ICD-10 files are also posted on the CMS website.

Q Some ophthalmic conditions that are coded per eye did not have a laterality designation in the 2015 ICD-10 manual. Will these change in 2016?

A Unfortunately, no. Based on the files published on the CMS website, there continues to be no laterality designation for primary open-angle glaucoma (H40.11x-); age-related macular degeneration (H35.31 – dry), (H35.32 – wet); and diabetes with ophthalmic manifestations (E1-.---). Additional examples may exist.

Q Will practices still relying on superbills or route slips be able to continue to use them after October 1, 2015?

A Yes. CMS addressed this question in June 2015:

Practices may continue to create superbills that contain the most common diagnosis codes used in their practice. ICD-10-CM-based superbills will not necessarily be longer or more complex than ICD-9-CM-based superbills. Neither currently used superbills nor ICD-10-CM-based superbills provide all possible code options for many conditions.

Practices should be able to cull their existing superbill down to the most commonly used codes to create one containing ICD-10 codes should they choose to continue to use a superbill.

Q Will CMS require the use of "external causes" codes on claims (e.g., V86.59xA – Driver of golf cart injured in non-traffic accident)?

A No. The CMS Medicare Learning Network (MLN Matters) article number SE1518 states the following:

Similar to ICD-9-CM, there is no national requirement for mandatory ICD-10-CM external cause code reporting. Unless you are subject to a State-based external cause code reporting mandate or these codes are required by a particular payer, you are not required to report ICD-10-CM codes found in Chapter 20 of the ICD-10-CM, External Causes of Morbidity. If you have not been reporting ICD-9-CM external cause codes, you will not be required to report ICD-10-CM codes found in Chapter 20 unless a new State or payer-based requirement about the reporting of these codes is instituted. If such a requirement is instituted, it would be independent of ICD-10-CM implementation. In the absence of a mandatory reporting requirement, you are encouraged to voluntarily report external cause codes, as they provide valuable data for injury research and evaluation of injury prevention strategies.

For example, CMS would accept the code for traumatic hyphema (S05.1- - -) and, although they exist, would not require submission of these additional codes on the claim:

V86.59xA–Driver of golf cart injured in non-traffic accident

W21.04xA–Struck by golf ball

Y92.39–Golf course as place of occurrence

Y93.53–Activity, golf

Q What other concessions is CMS making related to the implementation of ICD-10?

A CMS has plans in place to assist with implementation in a few additional ways:

1. CMS will establish an ICD-10 ombudsman to receive and triage physician and provider issues;

2. CMS will authorize advance payments if Medicare Administrative Contractors (MACs) are unable to process claims within established time limits due to ICD-10 issues. REVIEW

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

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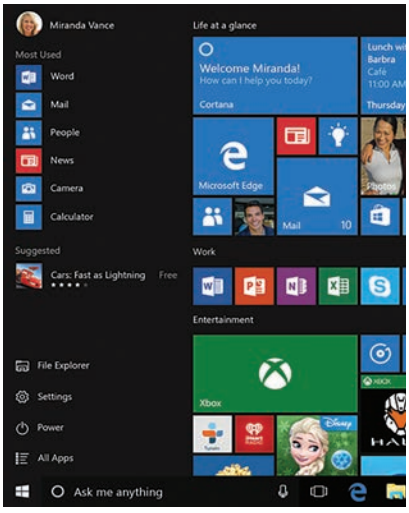
An Early Look at Windows 10

A revival of the Start menu on the desktop and enhanced security are some of the features of the new operating system.

Walter Bethke, Managing Editor

If you use a Windows computer at home or at your practice, you may be intrigued by the current rollout of Microsoft's latest operating system, Windows 10, especially since it's free for users of Windows 7 or 8.1 who upgrade before July 2016. Experience has shown, however, that rushing into a new operating system can cause more headaches than it cures. Here, information technology experts share their thoughts on potential pros and cons of the new operating system, and discuss considerations to take into account if you decide to upgrade your practice's computers.



Windows 10 sees the return of the Start menu, which is appreciated by many users.

"Start" It Up

Computer specialists say there are a couple new things in Windows 10 that users might welcome, not the least of which is the return of the popular Start button on the desktop, which was absent in Windows 8.

"From a usability standpoint, Windows 8 was ill-conceived," says Jeff Grant, a practice management consultant at Health Care Management and Automation Systems. "Microsoft was trying to make it so that everything worked the same: phone; tablet; and desktop. However, the way people work on their mobile device isn't the way they work at their desk. In Windows 10, they've taken a few things from Windows 8 but went back to other things before Windows 8, such as the Start menu.

"The benefit of having the Start button back is familiarity," Mr. Grant continues. "We humans say we want things to get better, but at the same time we don't want them to be different. Windows users were used to the Start button on the bottom left of the desktop, and when it was taken away for Windows 8, it made people crazy. With the Start button there, when the user wants to access available printers or open the control panel to adjust settings, all he has to do is move the mouse down there and click on the circle."

Windows 10 also has a modified version of a security feature called Bitlocker, which Microsoft first implemented in Windows 7 Professional Edition. IT experts say it can come in handy in a work environment where users are more mobile than ever. "I really like the fact that they've got Bitlocker in Windows 10," says Scott Peterson, director of IT at the Eye Center of Central Pennsylvania in Lewisburg, Pa. "Bitlocker actually encrypts the machine's hard drive completely. So, from a security standpoint, a HIPAA standpoint and a privacy standpoint, your hard drives are completely secure. If someone steals your laptop or desktop hard drive, for example, the drive is literally useless to them. They won't be able to decrypt it. It's a nice

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INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

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

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

REGENERON

05/2015
LEA-0760

EYLEA® (aflibercept) Injection For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

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

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

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

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

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

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

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

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

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

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

3 DOSAGE FORMS AND STRENGTHS

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

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

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

5 WARNINGS AND PRECAUTIONS

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

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

5.3 Thromboembolic Events. There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

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

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

Diabetic Macular Edema (DME). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

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

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

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

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

In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

8 USE IN SPECIFIC POPULATIONS

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

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

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

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

17 PATIENT COUNSELING INFORMATION

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

REGENERON

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

U.S. License Number 1760

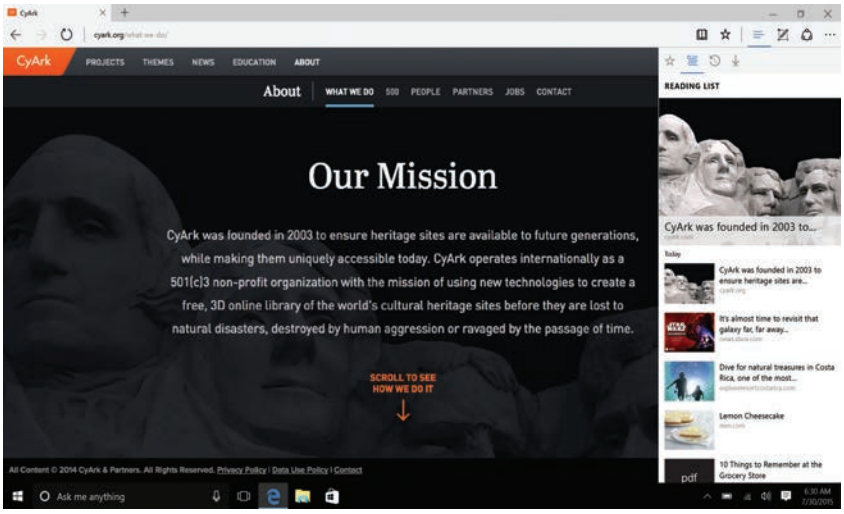
Issue Date: March 2015
Initial U.S. Approval: 2011

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

LEA-0721

feature for protecting patient information."

In addition to the return of the Start menu, another milestone marked by Windows 10 is the retirement of Microsoft's Web browser Internet Explorer, which had been a mainstay of the company's operating systems for 20 years. In its place will be a new browser called Edge. "Edge is supposed to integrate apps a little better," says Mr. Grant. "I've read that it has the ability to have the same look and feel as Explorer, but they've done work tightening up security holes associated with Explorer and its security patches. By taking the opportunity to start over with designing the browser, they were able to build it up better."



Windows 10 will come with Microsoft's new browser, Edge. Experts say the company tried to maintain some of Internet Explorer's appearance while also increasing security.

Upgrade Considerations

Of course, benefits such as increased usability and security of a new operating system come with the cost of ensuring that the applications you run will be compatible with the new system.

• ***Check with your vendors.*** From a practice standpoint, Mr. Peterson notes that what really drives the practice's computer system is the applications it can run. "Make a comprehensive list of your software vendors and then either call them directly or visit their websites to find out if they're Windows-10 certified," Mr. Peterson says. "Even if they're not certified, that doesn't mean they won't work with the operating system, but that they're not in a position to technically support them if you have a problem."

• ***Check Internet-based applications.*** Since Windows 10 will be using the new Edge browser, some of the Internet-based applications you or your patients use may not work properly. "I just got a call from one of our partner companies that does Web-based products, and he informed me that his company is evaluating all its code sets that run their websites to ensure that they'll work properly on Edge," says Mr. Peterson. "This is important because quite a bit of stuff has moved into the Internet realm; for instance, our time clock is cloud-based, and there are a lot of vision plans whose benefits and member information are also cloud-based. Make sure all of your partners' online products will work with Edge."

• ***Evaluate third-party PCs.*** Devices that often go overlooked when a practice upgrades its computers' operating system are the computers that came to the practice already connected to diagnostic machines, such as a PC connected to an optical coherence tomographer. "The computer with a diagnostic device is often part of the package that the practice purchased," says Mr. Grant. "In general, an office wouldn't be updating that computer, though there may be some instances in which a practice can do so. So, if you have a third-party device, such as a computer used to view diagnostic images, it will help to make sure that it will work after the update and check with its maker about its use with Windows 10. However, even if you can upgrade one of these machines, you may not be able to without voiding your warranty, so it will pay to check and find out if it's the equipment vendor's responsibility to do the upgrade."

• ***The small stuff.*** Experts say some businesses obsess over the big things when they do an upgrade and miss smaller items that can have almost as much of an impact. "Many practices take care of higher-level applications such as electronic health records when they make an upgrade, but forget to test the little things such as printers. For example, some EHRs require you to give a digital or printed summary of the patient's care, but you may find you can't print it with Windows 10 because you don't have the Windows 10 drivers for the printer. Other small but essential things to check are card scanners for scanning insurance cards or tablet computers that patients use to electronically provide their signatures."

For those users running Windows 8 computers, many of whom dislike that operating system, Mr. Grant says the decision to upgrade to Windows 10 will be easy. It's a tougher choice, however, for Windows 7 users. "If someone is on Windows 7 and things are running well, it will be a hard decision," he says. "To that user, I might point out that he's on an operating system whose life is about to end, and Windows 10 is the current upgrade path. Don't wait too long, or you'll miss the opportunity for the free upgrade." REVIEW

Using Today's Dry-Eye Diagnostic Tools

Christopher Kent, Senior Editor

Clinicians explain how the current crop of tests and instruments fit into the diagnostic picture.

The collection of signs and symptoms referred to as "dry eye" has been around as long as humans have had eyes. But like many areas in ophthalmology, dry eye didn't become a popular focus for doctors until effective ways to diagnose and treat the problem began to appear—along with the realization that dry eye can impact the outcome of refractive, cataract and disease-related surgeries. Avenues for managing dry eye are now proliferating, particularly in terms of diagnostic and evaluative options.

"More doctors are now paying attention to dry eye because there's more we can do about it," notes David R. Hardten, MD, director of refractive surgery for Minnesota Eye Consultants and Regions Hospital, and adjunct associate professor of ophthalmology at the University of Minnesota. "There are more diagnostic tests, more treatments and more evidence that appropriate management reduces some of the long-term disability that comes with the disease. We now have tests for factors such as MMP-9 and osmolarity, and ways to image and quantify the tear film and condition of the meibomian glands. These allow us to monitor any ongoing damage, as well as any response to our treatments.

"The problem is that there are now too many diagnostic tests relating to dry eye for us to do them all," he concludes. "It would take all day." That reality has led many surgeons to wonder which tests and devices they should be using, and in which circumstances. Here, to help address those questions, a number of doctors who are using these tests and instruments share their experiences and what they've learned from using them.

Measuring Factors in the Tears

Three of the recent tests that are becoming more widely used are the TearLab osmolarity test, the InflammaDry test from Rapid Pathogen Screening and the TearScan Microassay System from Advanced Tear Diagnostics. The TearLab test measures the concentration of electrolytes in a 50-µl sample of a patient's tears; higher levels indicate a reduced aqueous component in the tears. The InflammaDry provides a gross measurement of matrix metalloproteinase-9, an enzyme associated with the presence of inflammation. The TearScan system detects the level of the protein lactoferrin, which is produced in the acinar cells of the lacrimal glands, providing an indication of the level of aqueous tear production. The TearScan test

This article has no commercial sponsorship.

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.

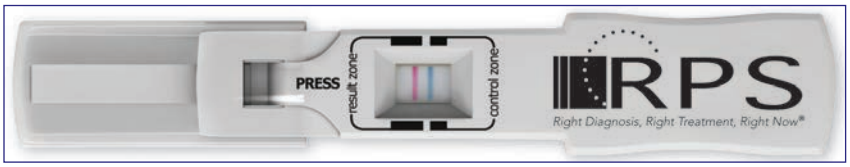
Risk of Secondary Infection

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



Two tests that are becoming more widely adopted for dry-eye testing are the TearLab osmolarity test (left) and the InflammaDry test from Rapid Pathogen Screening (above). The TearLab test provides a quantitative analysis of a tear sample's osmolarity; the InflammaDry provides a gross measurement of the inflammatory marker matrix metalloproteinase-9, indicating the level of inflammation present in a tear sample.

also measures the level of immunoglobulin E, an allergy-related marker.

Kenneth A. Beckman, MD, FACS, director of corneal services at Comprehensive EyeCare of Central Ohio, and a clinical assistant professor of ophthalmology at Ohio State University, notes that there are multiple forms of dry eye, so he uses different tests in different circumstances. "I use the osmolarity test on every patient that I'm evaluating for dry eye," he says. "It's a quantitative test. It's really good at detecting, grading and monitoring dry eye.

"For example, a patient may have a subjective complaint that isn't identified as dry eye, such as fluctuating vision, but not have a lot of systemic findings such as corneal staining," he says. "However, this test may reveal that the patient has high osmolarity, and we know that high osmolarity and a poor tear film will affect your vision. It also tells you how severe the patient's dry eye is, although it doesn't necessarily lead you down a particular path, such as indicating that this patient has evaporative dry eye or aqueous-deficient dry eye. To me, it's a 'vital sign' in a dry-eye exam, so I include it in every dry-eye check.

"It's also really good at monitoring response to treatment," he adds. "If I start a patient on Restasis and the patient's osmolarity goes down from 360 to 310 to 295, I know the patient is getting better. It's probably one of the best markers out there for monitoring treatment."

Dr. Beckman also uses the InflammaDry test. "InflammaDry tests for the inflammatory marker MMP-9, which is present in higher quantities in an eye with inflammation," he says. "I use this when I'm trying to determine how bad the inflammation is on the eye's surface. In an eye with a lot of inflammation I'll typically start the patient on Restasis, and maybe a steroid, too."

Dr. Beckman notes that he doesn't use the InflammaDry test at every dry-eye patient evaluation. "There are many situations in which I would use it, however," he says. "If the patient has been referred for dry eye, is scheduled for a dry-eye consult, and the patient's previous doctor has been dealing with this for a while and the patient is not getting better, I'll use the InflammaDry test at the initial visit. On the other hand, if someone just comes in for a regular eye exam and happens to mention dry-eye symptoms, my staff will do an osmolarity test on the spot, but we won't necessarily do an InflammaDry right away unless my clinical findings suggest it's appropriate. Typically, I may do it on the next visit.

"One of InflammaDry's most powerful applications is when I'm trying to decide whether I'm going to treat a problem with medications or punctal plugs," he continues. "In that situation I use both the InflammaDry and the Schirmer's test. I prefer not to put a punctal plug in an eye with a significant amount of inflammation, indicated by a positive MMP-9 result, especially with a high Schirmer's score. I don't want to conserve the tears if the tears are full of inflammation; that's like bathing in dirty bathwater. So before proceeding with punctal plugs I like to see a negative InflammaDry and a low Schirmer's score. It's worth noting, however, that if I get a high score on Schirmer's, I'll repeat the test later to make sure it was valid; you can get a lot of false negatives with the Schirmer's test."

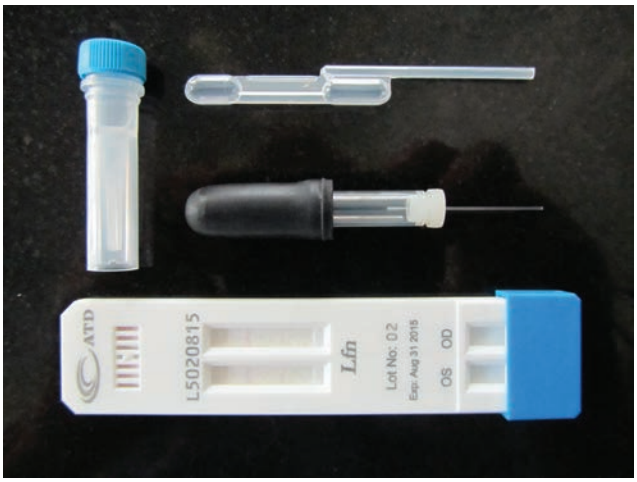
Dr. Beckman points out that MMP-9 levels don't change quickly. "For that reason, I don't do that test at every visit," he explains. "I may do it at the initial evaluation, and I may do it down the road to see how the patient has responded to treatment if he's not getting better and I think I need to do another type of intervention. In contrast, I use the osmolarity test more frequently."

Dr. Beckman adds that your staff has to know how to use the InflammaDry test. "As with most tests, you can get a false negative if the technician doesn't take a good sample," he says. "It's also important to make sure the patient didn't receive drops before this test was done. I've never seen a false positive, but I have seen eyes that looked really inflamed and had a false negative."

Young Choi, MD, medical director at InVision Ophthalmology in Homewood, Ala., has used the TearScan system, which indicates the level of aqueous production, for a couple of years. "I use this test in the initial workup and monitoring of dry-eye patients," he explains. "I'll also use this test in se-

lect LASIK patients to confirm good candidacy. Furthermore, I use this test for my allergy patients because it provides the IgE level.

"The lactoferrin level is a quantitative test, so not only does it confirm the existence of dry eye secondary to aqueous deficiency, more importantly it indicates the level of severity with an actual number," he continues. "This is very helpful. Patients like not only seeing an actual number indicating the severity of the aqueous deficiency, but also seeing that our treatment plan is changing that number—in other words, seeing that the treatment is working." In terms of the test's limitations, Dr. Choi notes that it doesn't help in cases of evaporative dry eye.



Advanced Tear Diagnostics' TearScan system measures levels of lactoferrin, associated with the level of aqueous tear production, as well as the level of IgE, an allergy-related marker. A sample is placed into the vial (left) for dilution; the pipette at the top tranfers the correct amount of fluid to the test cassette. The cassette is inserted into the TearScan Reader to get numeric results.

Mixing and Matching

Like many surgeons managing dry eye, Christopher J. Rapuano, MD, director of the cornea service and co-director of the refractive surgery department at Wills Eye Hospital, and professor of ophthalmology at the Sidney Kimmel Medical College at Thomas Jefferson University in Philadelphia, uses both the osmolarity test and the InflammaDry. "First, we often do the tear osmolarity test," he says. "If the osmolarity is on the high side, that supports the diagnosis of dry eye. If it's relatively normal, then I'll begin looking for other explanations.

We also sometimes use the MMP-9 test," he continues. "That's basically a litmus test; it turns pink or red if your tears contain a significant amount of MMP-9, which is an inflammatory marker. There is a midrange; if it's pink, it's mildly positive; if it's really red, it's very positive. If there's a lot of inflammation, then it's possible that topical steroids will be necessary to get the patient over the hump. If there's not much inflammation, then topical anti-inflammatories may not be the best way to go."

Some surgeons use the tests in the reverse order. "When new patients come in, we give them a questionnaire that includes questions about symptoms of dry eye," explains Francis Mah, MD, who specializes in cornea, external disease and refractive surgery at Scripps Health System in San Diego. "We can't really do testing without a complaint of dry eye, but if patients give a positive answer to one of those questions, then we'll start testing.

"First," he says, "we do the InflammaDry, which identifies most cases in which there is inflammation around the ocular surface by testing for MMP-9, a pretty specific marker for inflammation. The drawback is that elevated MMP-9 is not specifically diagnostic for dry eye; blepharitis, allergy and infection can all produce levels of MMP-9 that will set off the InflammaDry test. Nevertheless, if that test is positive and the patient does not have signs or symptoms of an active infection or the itching, redness and swelling associated with allergies, then I'll lean towards a diagnosis of dry eye.

"The next step is usually the Tearlab osmolarity test," he continues. "In general, the patients who have elevated osmolarity are more likely to have issues with their ocular surface and dry eye, so if the osmolarity is high, I look more closely at the meibomian glands and the aqueous. But like the inflammation test, we don't use the osmolarity test as a diagnostic tool; we use osmolarity more as a follow-up management tool, kind of like measuring a diabetic patient's blood sugar levels or a glaucoma patient's intraocular pressure. IOP isn't diagnostic for glaucoma, but there is likely to be a correlation, and the same is true for osmolarity. We don't live or die by the number at any given visit, but it is a guide."

"It's worth noting that these tests must be done before examining the patient, before giving him any drops and before checking his pressure," adds Dr. Rapuano. "So if I decide that a test is worth doing, I'll tell the patient to alert the technician that he needs this test as soon as he arrives for his next visit."

Dr. Mah points out that several companies are working on tests using other markers. "One promising idea is testing multiple markers at the same time," he says. "Combining some of these markers could potentially improve the yield in terms of the specificity and sensitivity of testing for ocular surface disease and dry eye. If two factors are shown to be abnormal, that significantly increases the likelihood of identifying and diagnosing an ocular surface disease."

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Biomarkers Measured in the Sjö Test Diagnostic Panel[1]

	Biomarker	Diagnostic Characteristics
Novel, proprietary	Salivary protein-1 (SP-1, IgA, IgC, IgM)	Provides high specificity and sensitivity for early Sjögren's syndrome
	Carbonic anhydrase (CA-6, IgA, IgC, IgM)	Offers additional sensitivity for an early diagnosis
	Parotic secretory protein (PSP, IgA, IgC, IgM)	Expressed early in disease course
Traditional	SS-A (Ro)	Expressed in about 70 percent of patients; typically appears later than the novel biomarkers
	SS-B (La)	Less frequently expressed than Ro; typically appears later than novel biomarkers
	Antinuclear antibody (ANA) by HEp-2	Expressed in about 60 percent of Sjögren's sydrome patients
	Rheumatoid factor (RF) levels (IgA, IgC, IgM)	Found in many rheumatic conditions—not unique to Sjögren's syndrome

According to Bausch + Lomb, the biomarkers measured by the Sjö test allow earlier identification of Sjögren's syndrome than previous tests. Clinicians say that earlier identification and treatment by a rheumatologist may also improve dry-eye symptoms.

Testing for Sjögren's

Another addition to the armada of dry-eye evaluative tests is the Sjö test, currently available from Bausch + Lomb. Dr. Beckman uses the Sjö test. "Sjögren's syndrome is an underdiagnosed disease that can not only cause dry eye but has other systemic manifestations such as lymphoma," he says. "If I'm treating for dry eye and the patient is not responding to conventional treatment as I would expect, I'll do the Sjö test. I'll also do the test if the patient mentions other symptoms that make me think of autoimmune disease, such as complaining about dry mouth or arthritis.

"I like the Sjö test better than traditional Sjögren's tests because it has early biomarkers that may pick up the disease much more quickly," he continues. "A number of my patients who suffered from dry eye for a long time and did not respond to conventional treatment had negative results when they took traditional Sjögren's tests. But when I did the Sjö test, they had positive biomarkers that led us to confirm the diagnosis and send them to a rheumatologist for management.

"This is valuable for a number of reasons," he points out. "By identifying the disease you can get the patient into the care of a rheumatologist. These patients are going to need to be monitored for life to watch for other systemic manifestations, including lymphoma. And although many rheumatologists used to think there wasn't much that could be done for these patients, that's no longer the case. There are medications that help with the saliva component, and anecdotally, I have a number of dry-eye patients who have been treated systemically for Sjögren's or other autoimmune diseases whose eyes are getting better. We don't typically put people on Plaquenil for dry eye, for example, but I have a number of Sjögren's patients who are being treated with Plaquenil, and they say their dry eye is improving. In our experience, getting the autoimmune disease under control can really help the dry-eye symptoms."

Dr. Rapuano also uses the Sjö test. "When it first came out, it was a fingerstick test that we did in the office," he recalls. "That was convenient in the sense that the patient didn't have to go elsewhere to take the test, but we had a very high percentage of 'insufficient quantity' results. So we'd stick patients, make them wait a week or two for the result, and then it would say 'no answer.' Patients were not very happy about that.

"The company has now gotten labs to agree to do the test using a blood draw," he continues. "Even with the pinprick version of the test we had some positive results, but we're getting more quality testing with the blood test. Most important, we always get an answer.

"I now use the Sjö test if I have a suspicion of Sjögren's—even a small suspicion," he says. "In addition to dry eye, the number one symptom I look for when I suspect Sjögren's is dry mouth. If a patient has that and dry eye, then I ask him or her about other rheumatoid-type symptoms. I explain what Sjögren's is, that it can be slow-onset and that lots of other systemic issues can go along with it, including dental issues, vaginal issues and cancer concerns."

Dr. Rapuano says that in the past, if he suspected Sjögren's syndrome, he would often tell patients to see their rheumatologist. "However, rheumatologists aren't that eager to see dry-eye patients if there's no diagnosis except 'dry eyes,' " he says. "They're much more willing to see these patients if they have a positive Sjö test. And a lot of the current blood tests, like SS-A, SS-B and rheumatoid factor, don't pick up Sjögren's very early. The Sjö test seems to pick it up earlier,

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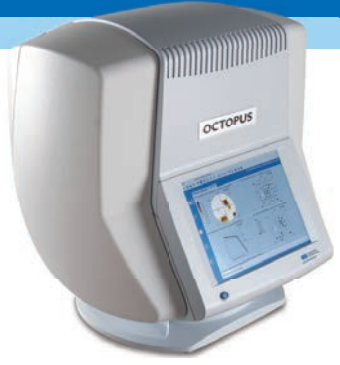

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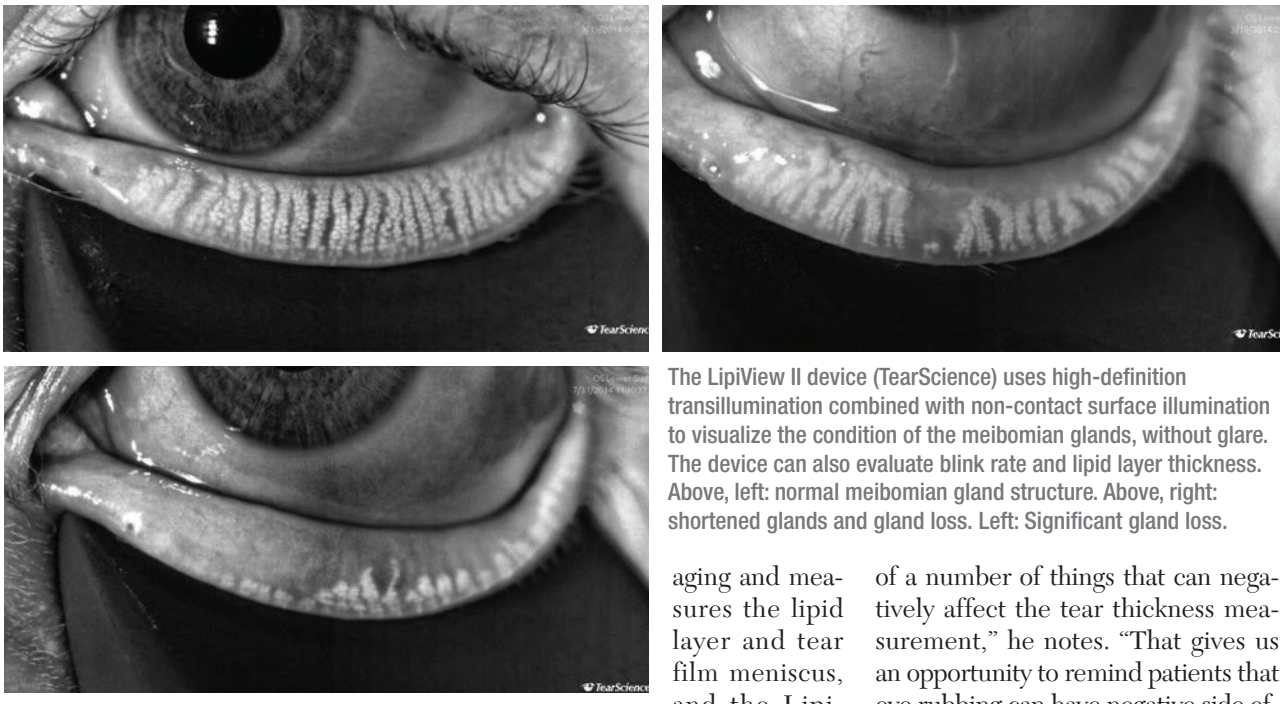

The LipiView II device (TearScience) uses high-definition transillumination combined with non-contact surface illumination to visualize the condition of the meibomian glands, without glare. The device can also evaluate blink rate and lipid layer thickness. Above, left: normal meibomian gland structure. Above, right: shortened glands and gland loss. Left: Significant gland loss.

and if you can pick it up earlier, then patients can seek treatment earlier. The earlier they get monitored, the better."

As far as downsides to the Sjö test, Dr. Beckman says he hasn't encountered many. "The test may not be covered by a patient's insurance, so there's a cost to it," he notes. "On the other hand, you're screening for a disease that can be life-threatening—at a minimum, it can be severely debilitating. And in many cases patients get relief simply knowing that they have a real condition; they finally understand why they're suffering from chronic dry eye. It gives them a little peace of mind. Patients are sometimes grasping for a diagnosis, and they don't like guesswork. So to have something objective is really nice."

Analyzing Other Factors

Several instruments now allow doctors to measure and analyze different aspects of the tears and eye that are relevant to managing dry eye. These include the Oculus Keratograph, which allows meibomian gland imaging and measures the lipid layer and tear film meniscus, and the LipiView system from TearScience.

"The LipiView instrument images and measures the patient's lipid layer thickness with sub-micron accuracy, and analyzes it's stability or early breakup," says Vance Thompson, MD, who practices at Vance Thompson Vision/Sanford Health in Sioux Falls, S.D., and is assistant professor of ophthalmology at the University of South Dakota School of Medicine. (Dr. Thompson addresses dry eye most often in the context of refractive and cataract patients. His practice uses the LipiView II—the most recent model.) "Having this objective measurement is helpful for both diagnosis and measuring treatment effect over time. It allows us to measure and document the patient's blink rate and behavior, and it also gives us, for the first time, a clinically useful way of imaging meibomian gland structure. LipiView has been a tremendous asset to our dry-eye center."

Dr. Thompson says that to ensure that LipiView provides accurate information, patients need to be educated about what not to do before the measurement. "Eye rubbing is one of a number of things that can negatively affect the tear thickness measurement," he notes. "That gives us an opportunity to remind patients that eye rubbing can have negative side effects. Patients are also instructed not to swim in chlorinated pools the day of the evaluation, since this can throw off the measurement. Certain ophthalmic drops can affect the accuracy of the measurement, so patients are instructed not to use oil-based drops like Restasis the day of the measurement, and not to instill ointments for at least 24 hours prior. It's also important for contact lens wearers to remove the lenses a minimum of four hours before the measurement. Cosmetics that are oil-based should also not be used around the eyes on the day of the measurement."

Dr. Rapuano's office currently uses the original LipiView I device. "It uses interferometry to look at the lipid layer of the tears," he notes. "Unfortunately, we haven't found that function to be especially helpful. However, the instrument also records a video of the eye during blinking, and we've found that rather useful for diagnosing partial blinkers. Of course, taking care of or resolving partial blinking isn't easy, but at least if you've diagnosed it you have something to go after when other things aren't working."

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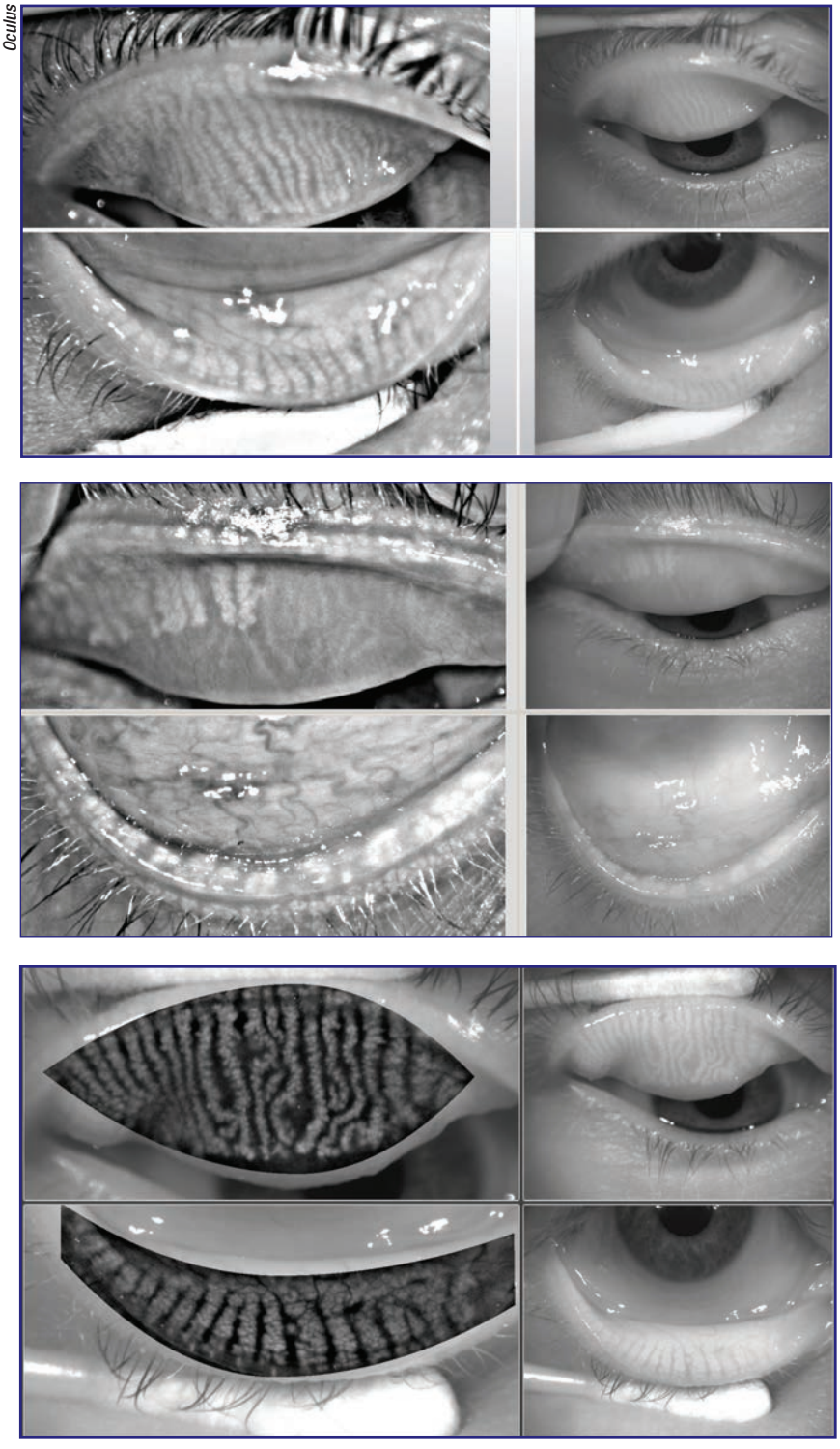

The Oculus Keratograph 5M is a corneal topographer with a built-in keratometer and a color camera optimized for external imaging; it can be used to measure tear-film breakup time and tear meniscus height, to evaluate the tear film's lipid layer and to visualize the meibomian glands, with or without digital enhancement. Above, top: Healthy meibomian glands imaged by the Keratograph; middle: severe meibomian gland dropout; bottom: digitally enhanced images of meibomian glands.

Dr. Rapuano believes the ability to look at the meibomian glands using the LipiView II should be helpful. "If the eye has very healthy meibomian glands, then the problem may not be a posterior blepharitis evaporative issue," he says. "If the eye has very unhealthy meibomian glands, then you know that you need to do as much as you can to save the glands that are working. And if you can show the patient a picture revealing that his meibomian glands are only 50 percent of what they should be, the patient may be a little more aggressive with his posterior blepharitis treatments."

How the Tests Fit in

Surgeons using these tests emphasize that they need to be used in the context of a broader evaluation, including the traditional approaches to evaluating the patient. "Being suspicious of dry eye in every surgical patient and making it a diagnosis of exclusion has helped my postoperative results tremendously," notes Dr. Thompson. "But since there is no single symptom, exam finding or test result that you consistently see when diagnosing dry eye, you have to rely on putting these factors together. You have to rely on the whole picture."

Dr. Beckman agrees. "All of the dry-eye tests work hand-in-hand," he says. "I still do Schirmer's, tear breakup time and cornea and conjunctival staining. You need to use all of them to come up with a good dry-eye assessment."

"Just sitting there and listening to your patient is one of the most powerful ways to diagnose dry eye," notes Dr. Thompson. "Even when I'm talking to patients I'm looking at their tear film reflectivity from a distance, looking for redness, assessing how much they blink during our conversation and even estimating their tear lake. I'm amazed how often you can be suspicious of dry eye before you

look with the slit lamp or do a single test. Nevertheless, we know that symptoms and an exam fail to uncover many dry-eye patients. That's why I appreciate the companies that have brought us testing for tear osmolarity, tear inflammatory markers and meibomian dysfunction. I wish I could use all of them on every patient, but for practical reasons we primarily do the TearLab osmolarity measurement. It's easy to do, fits well into our clinic flow and give us good data. But we do find value in having all three of the devices that we use. All of them play a major role."

Dr. Rapuano also sees the recent point-of-service tests as only one part of the dry-eye diagnostic process. "Over the years, we've learned that there are many different forms of ocular surface disease that can cause dry-eye symptoms," he says. "These can range from insufficient tear production to anterior or posterior blepharitis to conjunctival chalasis. So when faced with potential dry-eye patients, I begin by asking about their symptoms. Are they worse in the morning or do they get worse over the course of the day? Are they worse in windy conditions? Then I do a slit-lamp exam. That may reveal lashes poking in, entropion or ectropion or partial blinking. I look at the health of the cornea and conjunctiva and tear meniscus. I look for conjunctival chalasis. I check for corneal fluorescein staining, measure tear-film breakup time and often do a Schirmer's test. I may also do conjunctival staining with lissamine green.

"In most cases, this gives me a pretty good idea about what's going on with the patient, and I treat accordingly," he says. "But sometimes the patient will return for the next visit and not be doing as well as I expected. If that happens, I'll think I may not have made the right diagnosis; maybe I need a little bit more information. For me, that's when the point-of-service testing typically comes in."

Dr. Hardten notes that it's helpful to think of these tests as being short-term or long-term tests. "Dry eye is like glaucoma—it's an ongoing disease that fluctuates over time," he says. "It's hard to tell from one day to the next what's real. So, we use a combination of short-term and long-term testing. For dry eye we have short-term tests like osmolarity and long-term tests like examining the meibomian glands using tools such as the Keratograph or LipiView. These instruments allow infrared imaging of the meibomian gland structure, making it possible to follow the health

How Testing Impacts Patients

The recent crop of dry-eye tests clearly provides useful medical data relevant to diagnosis and treatment. However, the tests are also affecting patient attitudes in positive ways—particularly in terms of encouraging compliance and increasing patients' peace of mind.

Kenneth A. Beckman, MD, FACS, director of corneal services at Comprehensive EyeCare of Central Ohio, has noted that having objective dry-eye test data impacts patient compliance. "The osmolarity test is not only objective, it gives the patient a real number that he or she can follow," he says. "If you put a patient on Restasis and her osmolarity is 350, and she comes back three months later and says she doesn't feel any better, the test will allow me to show her that her osmolarity is down to 308. Granted, her symptomatic relief may be lagging behind the clinical signs, but I can say, 'You're getting better, you're just not feeling it yet. You are making progress. Once you get over the hump you'll probably notice it.' That patient is now more likely to stick with the treatment.

"If I didn't have any objective data that the treatment was working, she might stop using it," he adds. "I've seen that happen. By encouraging the patient to continue treatment, it helps ensure a positive outcome. The same is true in reverse with a positive InflammaDry test. It lets the patient know he needs to keep using the drops because he has documented inflammation on the surface of the eye that hasn't been resolved yet."

Vance Thompson, MD, who practices at Vance Thompson Vision/Sanford Health in Sioux Falls, S.D., agrees. He images the meibomian glands with the LipiView II instrument and finds this helps to motivate patients. "By showing our patients any structural changes, such as gland atrophy and/or dropout—and then showing them an example of someone who has end-stage changes—it is both a great way for us to monitor and document our treatment effect and a great patient educator that helps motivate patients to follow through with our guidelines and directions regarding quality lid hygiene."

Francis Mah, MD, who specializes in cornea, external disease and refractive surgery at Scripps Health System in San Diego, also has noted that these tests have advantages beyond their medical implications. "If a patient is coming in for a first or second opinion, these tests will help you educate him," he says. "A positive test also proves to the patient that this is a real issue—he or she is not going crazy. And initially, it's reassuring to the patient that we're doing the testing; it shows that we're taking this seriously, that it's not a psychological issue and we're not pushing it aside. That's especially true when we're providing a second or third opinion for the patient. And later, when we're monitoring something like osmolarity, it helps the patient to see whether the treatment is having an effect. It can also help patients understand why you're asking them to do therapy before refractive surgery. When you show them concrete evidence that an issue exists, they're more likely to comply.

"A significant number of patients that we see in our practice have been to two or three eye doctors who didn't feel the dry-eye problem was worth addressing," he adds. "It may be that the doctors just didn't want to deal with it, or didn't have the expertise, or they were too busy to manage or treat dry eyes. It could be that the symptoms hadn't reached a level that they felt compelled to treat. These patients will sometimes get multiple opinions because they know something is wrong and they want to make sure they're not going blind. They believe there must be something that can be done to improve their functioning and reduce the fluctuating vision and discomfort they're having. It's a relief to them that you're doing testing and taking the problem seriously."

—CK

of the glands long-term. This can help the eye-care provider analyze whether there is significant damage to the meibomian glands, helping to further distinguish evaporative tear-film deficiency from aqueous-deficient dry eye. Testing the short-term things, such as osmolarity, is like monitoring IOP in glaucoma. You check the intraocular pressure, but you also look at the optic nerve and visual field."

Finding the Best Option

Dr. Rapuano says no one test is currently sufficient to diagnose the cause of dry eye. "Diagnosis usually comes from evaluating symptoms, a thorough slit-lamp exam and some of these tests," he says. "They all go together. It would be nice to have one litmus test to give us a yes or no answer about the cause, but we don't have one. My guess is that we never will, because the causes of dry eye are not a single diagnosis. This is not a pregnancy test-type situation."

Dr. Mah agrees. "I think in dry eye we're talking about multiple entities," he says. "Until we can separate out all the ocular surface issues that are labeled dry eye, I don't think we'll have one single test that will be universally diagnostic."

Given those qualifications, if you're in the market for a dry-eye test, what is most likely to be clinically useful? Dr. Mah notes that companies tend to say that their test is the one every practice needs to use. "To determine the value of these tests, it helps to read the literature," he says. "Look at the information and clinical trials associated with a given test. Also, realize that while these tests are all helpful in some way, they all have limitations. You need to know what each test can and cannot do for you,

and use it accordingly. Finally, don't give up on using the time-honored clinical tests. They are still valuable."

"I think if you're making a commitment to treat dry-eye patients, you need to understand what's out there," says Dr. Beckman. "That includes the more traditional tests that don't require an instrument. From my perspective, if you're committed to treating dry eye, I'd say it's worth getting both the osmolarity test and the InflammaDry, because we use those tests all the time. If you're dealing with complicated patients, I think the InflammaDry test will give you a lot of information to help direct your treatment."

What about the cost factor? "The number of testing options you pursue will depend, in part, on how much money you're able to invest in this area," notes Dr. Rapuano. "The osmolarity test is probably the one that will give you the most bang for the buck. The MMP-9 test can also be helpful in some patients. Those tests involve very little up-front investment; you need to buy the tests, but you usually get reimbursed enough to cover the costs. You won't lose money."

Dr. Beckman agrees. "One of the good things about the more recent tests that do require equipment, like the osmolarity test, is that you can get the basic equipment for free; you just have to buy the cards," he says. "That cost is usually reimbursed by insurance. None of these tests has a huge profit margin, but that's not the point; they're there to provide you with information to help you make good decisions and treat the patient properly. Meanwhile, you're not going to lose money on them."

"The Sjö test doesn't cost the doctor anything, and it's usually covered by insurance," adds Dr. Rapuano. "Without insurance coverage it might cost a couple hundred dollars."

In terms of investing in one of the more expensive instruments that can help with dry-eye analysis, Dr. Rapuano says if he were looking for one new instrument to help analyze the ocular surface he would probably choose one that images the meibomian glands, such as the LipiView II or Oculus Keratograph. "The LipiView II is a much bigger investment," he admits, "but you can get reimbursed for imaging the meibomian glands." REVIEW

Dr. Beckman is a consultant for Tearlab, RPS and Bausch + Lomb. Dr. Rapuano is a consultant for Tearlab and TearScience, and has a minor stock ownership in RPS. Dr. Mah is a consultant for Tearlab; Dr. Hardten is a consultant for Allergan. Drs. Thompson and Choi have no financial ties to any of the dry-eye companies.

1. http://www.bausch.com/ecp/our-products/diagnostics/sjo#.VfMtT-n-P8s. Accessed 11 Septem-ber 2015.

Delving into the Dry-Eye Pipeline

Mark B. Abelson, MD, CM, FRCSC, FARVO, George Ousler, and Lisa Smith, Andover, Mass.

Novel compounds of all sorts, from anti-inflammatories to receptor inhibitors, are on the way.

After years of fits and starts, the often stalled but always prodigious machinery of the dry-eye pipeline appears to be moving forward. Thanks to improvements in designing clinical trials, monitoring patients' signs and symptoms and evaluating the performance of therapeutic agents, a number of drugs are making their way through the clinical trial process. These agents include new mucomimetics, receptor inhibitors and anti-inflammatories. Here's a comprehensive look at the dry-eye drugs you may be using in the coming years.

A Variety of Agents

Many different therapeutic entities are under investigation for the treatment of dry eye. Besides the continued efforts to improve polymers, more targeted mechanisms are also coming into focus, from secretagogues and mucomimetics to anti-evaporatives and hormonal and nutritional supplements. Here are the different classes of drugs being investigated.

• ***Hyaluronic acid.*** Hyaluronic acid has been intensely studied in the realm of artificial tears, primarily in Europe: 0.1% solutions in saline;[1] hypotonic and isotonic solutions of sodium hyaluronate;[2] sodium hyaluronate 0.4% and 0.25% in combination with chondroitin sulfate;[3] unpreserved, hypotonic 0.4% hyaluronic acid drops versus HPMC plus Dextran 70, 0.1% (Fermavisc);[4] and 0.18% sodium hyaluronate,[5,6] the last of which went the furthest down the pipeline before stalling.

Efforts to modify HA to increase its residence time on the ocular surface have provided us with improved compounds. A thiolated, carboxymethyl hyaluronic acid (CMHA-S) has been synthesized to form covalent disulfide cross-links, thus modulating the gelation of the formulation to enhance dwell time on the ocular surface. A similar formulation is already marketed worldwide for veterinary use (ReMend),[7] and clinical investigations by Jade Pharmaceuticals are forthcoming in the United States. Another modified hyaluronate is being developed by Seikagaku and is in the Phase II/III stage of clinical investigation.[8]

Yet another tear solution containing CMC, the osmoprotective erythritol L-carnitine and glycerin, was compared to a standard HA formulation in a Phase III non-inferiority study in Europe. Compared to HA, the osmoprotective CMC-containing tear was preferred by patients, and

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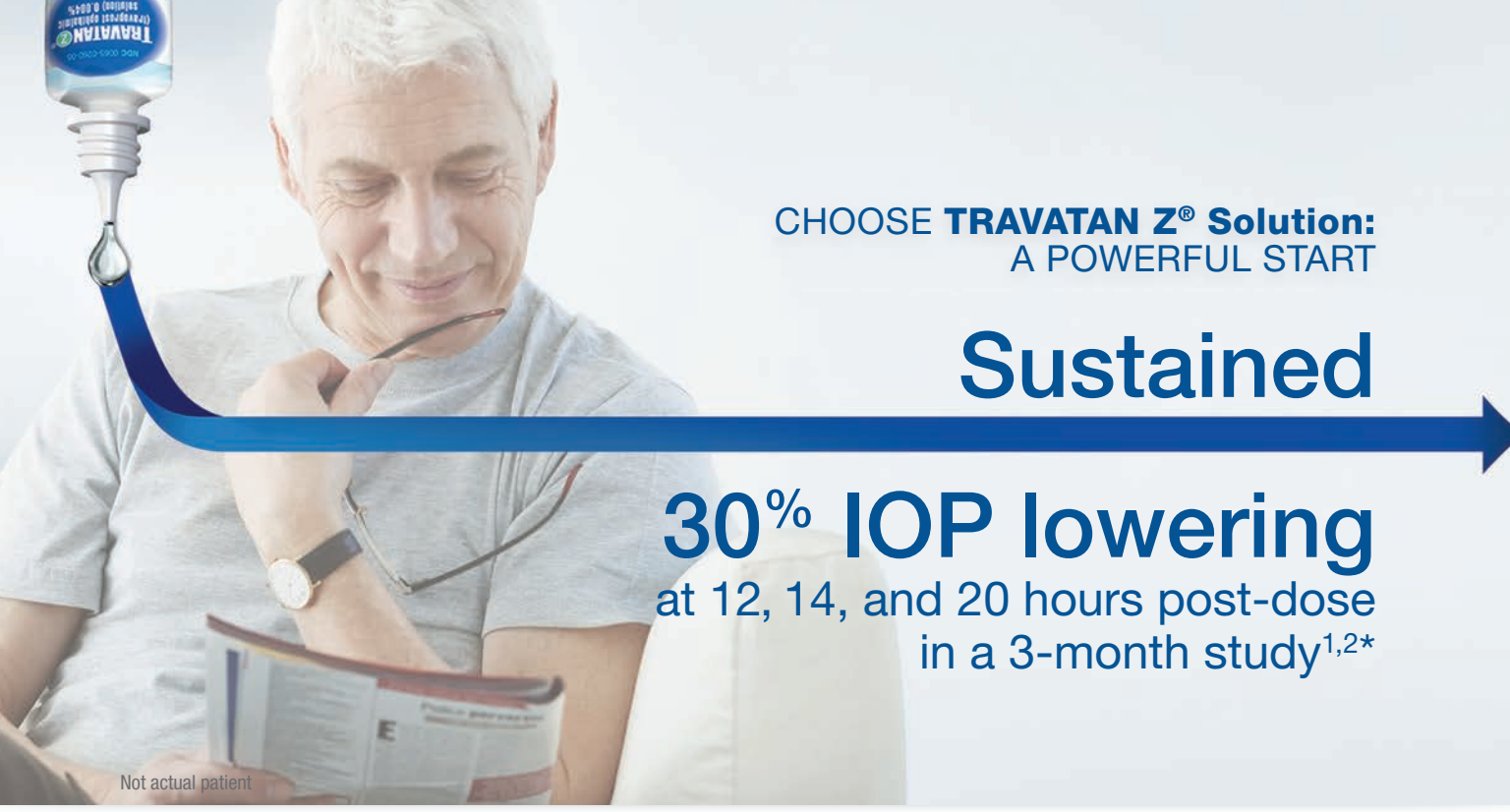

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30% IOP lowering

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

TRAVATAN Z® Solution has no FDA-approved generic therapeutic equivalent[3]

Help patients start strong and stay on track with the Openings®
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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. **3.** Drugs@FDA. FDA Approved Drug Products: TRAVATAN Z page. US Food and Drug Administration website. http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm. Accessed March 31, 2015.

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TRAVATAN Z®
(travoprost ophthalmic solution) 0.004%

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

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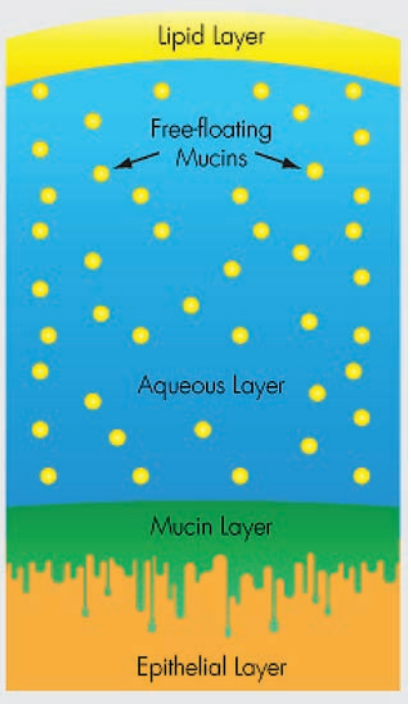
4/15 TRV15086JAD

was noninferior in terms of efficacy and safety.[9]

• ***Mucomimetic/mucogenic agents***. Tamarind seed polysaccharide is a mucomimetic, mucoadhesive pseudoplastic with a structure similar to mucin 1, a transmembrane glycoprotein thought to play an essential role in ocular surface wetting. This has been evaluated alone and with HA in Europe, and is a component of Visine Intensiv 1% EDO eyedrops, available commercially in Europe.[10] However, a 2014 paper demonstrated it was equivalent to an eye drop containing the barrier polymer carmellose, and as such, tamarind seed polysaccharide might end up being just an ingredient in improved tear substitute formulations rather than an active therapeutic.[11]

Mucomimetic agents continue to be developed in Japan, but the programs are stalled in the United States. The compounds approved in Japan are rebamipide (Otsuka/Acucela), a quinolone that enhances mucosal defense and scavenges free radicals,[12,13] and diquafosol (Santen), a G-protein coupled, P2Y2 purinogenic receptor agonist.[14,15] Studies of these agents primarily assessed change or improvement from baseline in signs and symptoms over the time treated. In one study designed to assess noninferiority, patients were treated for four weeks with either rebamipide 2% or 0.1% sodium hyaluronate.[13] All endpoints showed noninferiority of rebamipide to hyaluronate, although rebamipide was superior for lissamine green staining.

Diquafosol 3%, approved in Japan in 2010, was also shown to be noninferior to HA in a similar trial run in Japan, and was superior to HA for rose bengal staining.[14] Another study that compared diquafosol to HA therapy found that the mucogenic was superior for tear-film breakup time, fluorescein staining, rose bengal staining and symptoms. A more recent study compared diquafosol plus HA to either HA alone or diquafosol alone, and the combination therapy was found to be the most effective.[15] So there appears to be a benefit to these mucogenic agents. Despite this, it doesn't appear that dry-eye patients in the United States will benefit from these anytime soon.



Mucin helps stabilize the tear film, and is the subject of several research studies investigating new therapies.

• ***Autologous serum.*** Eyedrops composed of autologous serum are being tested on a regular basis, and publications in the past 15 years have been numerous.[16-18] Twenty percent serum in saline or sodium hyaluronate has been evaluated in severe dry eye or in dry eye associated with graft-versus-host disease.[16] By instilling up to 10 times daily, symptoms and signs were significantly improved. Punctal plugs may be used in conjunction with serum eyedrops to heighten their efficacy. While there is understandably not much impetus from pharmaceutical companies on this front, if an allogeneic serum eyedrop were developed, preserved and in some way formulated in a patentable fashion, patients might benefit from this technology.

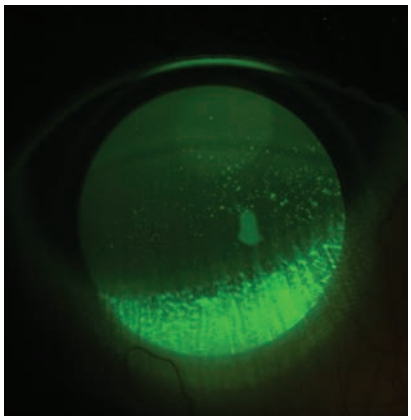
• ***Antioxidant therapy.*** Scavenging free radicals is the role of every antioxidant, and these molecules are in high demand in all avenues of medicine and nutriceuticals. One promising antioxidant with a somewhat different mechanism is SkQ1, a mitochondria-specific plastoquinone-containing reactive oxygen species scavenger. In Phase II testing of 91 dry-eye subjects exposed to a controlled adverse environment challenge, improvements in central fluorescein and lissamine green staining, lid margin redness and the symptoms of discomfort, dryness and grittiness were all significant after one month of treatment with SkQ1.[19] The ophthalmic formulation was approved in Russia as Visomitin in 2012 for treatment of dry eye.

• ***Receptor inhibition.*** Mimetogen is developing a dry-eye therapeutic, MIM-D3, that has an innovative mechanism of action. Conjunctival mucin gene expression and secretion, as well as goblet cell differentiation, are stimulated by nerve growth factor action at the tyrosine kinase A receptor. MIM-D3 is a partial TRKA receptor agonist that demonstrates activities similar to NGF, and also acts by potentiating suboptimal concentrations of NGF. Although it didn't meet its pre-specified primary endpoints, after four weeks of treatment in a Phase II trial, MIM-D3 significantly improved total corneal fluorescein staining when assessed as the change from pre- to post-exposure in the CAE chamber.[20] Inferior corneal fluorescein and lissamine green staining revealed improvements after 14 and 28 days of treatment. The four-week treatment with MIM-D3 also significantly improved diary-reported ocular dryness (p=0.034). In-office assessment of symptoms

also showed improvements in CAE-induced stinging at day 14 (p=0.029) and at day 28 (p=0.013). Furthermore, in patients with more severe symptoms at baseline, diary-reported symptoms of dryness (p=0.015) and worst symptom scores (p=0.036) were significantly improved in the 1% MIM-D3 group, and ocular discomfort was significantly improved in the 5% MIM-D3 treatment group (p=0.014). This drug is now in Phase III development.

A thymosin beta-4 antagonist has completed Phase II development with publication of results in the CAE model. As frequently occurs, neither of the primary endpoints showed a significant difference between treatment and placebo groups; however, a number of secondary endpoints demonstrated significant treatment benefits. In a single-center study of 72 subjects treated with RGN-259 (0.1% Tβ4) for 28 days, discomfort scores in the CAE were significantly improved, as were central and superior corneal fluorescein staining.[21] The newly formed company RegenTree is planning an upcoming Phase III study in the United States and Korea that will take this drug to the next level. The company is a joint venture in the United States between RegeneRx Biopharmaceuticals, which originally developed Tβ4 for multiple indications, and the Korean company G-treeBNT.[22]

• ***Oculeve tear stimulator.*** An innovative intranasal device from Oculeve that stimulates tearing will continue clinical testing this year.[23] This is similar to an intraoral electrostimulating device used to treat xerostomia.[24] Allergan has acquired Oculeve's device, which has shown safety and efficacy in four clinical studies in more than 200 patients. Allergan plans to conduct two additional pivotal trials prior to FDA submission, which is expected in 2016.[25] This creative solution to dry eye will be interesting to watch for, and teaches us yet again to think outside of the box for dry-eye therapeutics.



In its Phase III study, lifitegrast significantly reduced total fluorescein staining.

The Anti-Inflammatory Pipeline

Treating inflammation has always been a mainstay for dry-eye therapy, with cyclosporin A (Restasis, Allergan) leading the way, and several other promising agents coming up fast. Here's a look at what's making its way to the clinic.

• ***Lifitegrast.*** In the lead in the race to approval is Shire's lifitegrast, the lymphocyte function antigen-1 (LFA-1) antagonist and a first-in-class integrin anti-inflammatory agent specifically engineered for ophthalmic indications. Activation and homing of lymphocytes to the ocular surface is central to the chronic dry-eye process and under the control of T-cell activators like LFA-1, which binds to intercellular adhesions molecule-1 (ICAM-1) expressed on the cell surface of the inflamed epithelium. Lifitegrast acts as an ICAM decoy, preventing binding of LFA-1 to ICAM.[26]

Lifitegrast has been the subject of three clinical trials involving b.i.d. treatment for 84 days. The first dose-response Phase II trial in 230 subjects used the CAE challenge to enrich the study population with subjects who had a modifiable, moderate degree of inferior corneal staining. Mean change from baseline to day 84 in inferior corneal staining was statistically significant (p=0.0208). Furthermore, the proportion of patients with an increase in inferior staining greater than one at day 84 compared to baseline was 16.1 percent for placebo, 3.6 percent for 1% and zero for 5% lifitegrast. The Ocular Surface Disease Index and the vision-related OSDI showed significant improvements, as did Ora scale-measured ocular discomfort (p=0.0442) in the per-protocol population. Improvements in tear production (p=0.0392) and symptoms were also seen as early as day 14. A reduction in burning/stinging was also found after 84 days of treatment when assessed as change from baseline (p=0.0496).[27]

The first Phase III study of lifitegrast was conducted with the same study design but with greater power due to an increased number of subjects. Again, mean change from baseline in inferior corneal staining as measured by the Ora scale was highly significant, this time with the p-value going from p=0.0208 to p=0.0007. It also significantly reduced superior and total fluorescein staining, as well as conjunctival lissamine green staining. The co-primary endpoint of OSDI symptoms wasn't met. Secondary symptom scores for Ora-scale measured discomfort (p=0.0273) and dryness (p=0.0291) were significant, however.[28]

The OPUS-2 study has been completed in 718 subjects, and the company has announced success with symptom endpoints. While this study failed in the co-primary corneal fluorescein staining endpoint, symptoms won big across the board in primary (p=0.001), secondary and tertiary symptom outcomes.[29]

• ***Cyclosporine A derivatives.*** In recent years, researchers have attempted various changes in the for-

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mulation of cyclosporine in order to facilitate manufacturing and improve tolerability. Aqueous solutions of cyclosporine at 1% were shown to be superior to 0.5% in improving the major signs of dry-eye disease as early as 21 days after initiation of treatment.[30] It will be interesting to see if anyone succeeds in getting another cyclosporine on the market either as a generic or as a new patentable entity with its structure or formulation significantly modified. Recent Phase IV studies of Restasis have shown that it significantly slows or prevents disease progression from mild to moderate or severe dry eye.[31]

A unique 0.1% unpreserved cyclosporine cationic emulsion (Cyclokat) is in Phase III development by Santen, and has now been recommended for approval by the European Medicines Agency. In Europe, a six-month study showed statistically significant improvements in fluorescein and lissamine green staining at months one, three and six. Post-hoc analyses revealed better outcomes in groups with higher staining scores (~3) at baseline; however, for complete corneal clearing of staining, Cyclokat was superior in patients with grade 2 staining at baseline. This higher concentration appears to be focusing on severe keratitis associated with dry eye. It will be interesting to see if Santen attempts to bring Cyclokat across the ocean.[32]

Novaliq in Germany is also developing a novel formulation of cyclosporine (CyclASol) that's entering Phase II development. CyclASol is a novel, patented, non-aqueous and preservative-free formulation of cyclosporine. EyeSol is Novaliq's proprietary drug delivery technology based on the chemically and biologically inert semi-fluorinated alkanes. These compounds have extraordinary spreading properties that optimize drug distribution on the corneal surface, and aid in the solubility of poorly water-soluble compounds such as cyclosporine. As such, CyclASol is the first clear, non-emulsion, multidose, preservative-free solution of this immunosuppressive, promising greater tolerability, less stinging and superior pharmacokinetics. Phase I results were positive and the Phase II program is under way.[33]

• ***Steroids and NSAIDs.*** Anti-inflammatories don't end with cyclosporine. Steroid use has been studied, both alone and as an adjunct to cyclosporine. Ocular Therapeutix has a slow-release, biodegradable dexamethasone punctal plug that's being investigated for both allergy and dry eye.[34] Investigators have evaluated a 30-day treatment with twice-daily, low-concentration 0.1% clobetasone butyrate eyedrops in a 2% polyvinylpyrrolidone vehicle compared to vehicle alone. They found the therapy to be safe, with no intraocular pressure or fundus changes. Patients treated with just PVD vehicle showed a statistically significant improvement in symptoms and a reduction in HLA-DR expression, a dry-eye marker. Patients treated with clobetasone showed statistically significant improvements in corneal and conjunctival staining versus baseline and versus the vehicle group. The symptom scores were also significantly better compared to both baseline and vehicle, as were the HLA-DR expression and epithelial cell area. These results, both compared to baseline and to parallel vehicle control, are a powerful testament to the efficacy of a 30-day treatment of low-concentration steroid in a disease that we commonly think of as not steroid-responsive.[35]

In another recent report, researchers studied the effect of loteprednol

The Dry-Eye Pipeline

Molecule	Company	Mechanism of Action	Status
Cyclokat	Santen	Immunosuppressive	Phase III/ Recommended for approval by EMA
Lifitegrast	Shire	LFA-1 antagonist	Phase III
MIM-D3	Mimetogen	Selective TrkA receptor agonist	Phase III
SI-614	Seikagaku	Modified hyaluronate	Phase III
SkQ1	Mitotech	Mitochondria-targeted antioxidant	Phase II/III
RGN-259	ReGenTree	Thymosin beta-4	Phase II/III
Intranasal neurostimulatory device	Oculeve-Allergan	Tear stimulation	Phase II/III
EBI-005	Eleven Biotherapeutics	IL-1 antagonist	Phase III
Cis-UCA	Herantis	Anti-inflammatory; cytoprotective effect in response to UVB stress	Phase II
CycloASol	Novaliq	Immunosuppressive	Phase II
Cross-linked hyaluronic acid	Jade Pharmaceuticals	Modified hyaluronate barrier function, enhanced dwell time	Phase II

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Ways to Streamline the Pipeline

What's behind the current number of advances in the pipeline of dry-eye therapy? It turns out that several enhancements to trial design are making it possible to guide a drug through the process more effectively than ever before.

First, there are without a doubt improvements in clinical trial execution within the field of dry eye. At our research firm, Ora, the pitfalls of conducting dry-eye trials have been well-defined over the past 10 years. Recognition of the seasonality of dry eye and the importance of conducting a study in as short a period as possible rather than a four- or six-season period, was critical. Seasonal and geographic constraints add a layer of complexity to conducting a dry-eye trial that makes it best to complete the trial within one season.[1-4]

Another challenge to running a successful dry-eye trial is the placebo effect. Any placebo vehicle solution will ameliorate a desiccated ocular surface, and this benefit will narrow the differences between the study treatment and the placebo. Most of our clinical trials involve prescreening subjects with placebo and eliminating anyone who responds to its lubricating effects. Thus, the population that remains will more effectively reveal any drug effect.[1]

In addition, we now have tools that screen for a greater likelihood of response, such as a significant increase in staining with the controlled adverse environment challenge or other more subtle matching of sign/symptom characteristics with the mechanism of action of the drug. By selecting patients based on their response to an artificial challenge [controlled adverse environment (CAE)], and not based on a potentially anomalous threshold level of naturally presenting signs and symptoms, regression to the mean should be minimized. Even though finding the right patient might result in a higher rate of non-eligibility, the considerably smaller pool of subjects is more homogeneous and provides cost-containment and greater statistical power.

The trial endpoints themselves have also benefited from improvements. The most critical areas of the cornea have been redefined to home in on dry eye, the techniques for conducting tear-film breakup time and staining have been recalibrated and precise scales for assessments of staining and discomfort have been developed. Similarly, calibration, both initially and continuously through the education of investigators, minimizes "investigator-drift," and tightens the dataset across sites. Educating dry-eye investigators and patients about how to use the sign and symptom scales is vital for maintaining data consistency.[1]

In terms of future modifications to clinical trials, there's been some consideration of looking for sign efficacy and symptom efficacy in separate trials. The published literature might corroborate this approach, since signs and symptoms of dry eye have often been shown to have no correlation.[5]

— M.B.A.

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etabonate 0.5% administered two weeks before initiation of cyclosporine in 118 patients. When compared to subjects treated with cyclosporine alone, the steroid group had significantly less cyclosporine-induced stinging, and more importantly, loteprednol-treated subjects had significantly better OSDI scores and Schirmer's test scores, as well as fluorescein and lissamine staining.[36] While this demonstrates a more rapid onset of effect when boosting with a safe steroid, it's not known if the benefits of steroid pre-treatment could be maintained over time periods longer than 60 days. Nevertheless, our dry-eye subjects will certainly be happier if their improvement in signs and symptoms kicks in earlier.

In China, investigators compared the nonsteroidal anti-inflammatory 0.1% pranoprofen in a sodium hyaluronate drop to viscoelastic alone in 115 patients. Gradual improvements in symptom scores, fluorescein staining and TFBUT were shown, with statistical significance for the latter two at day 14. This anti-inflammatory was well-tolerated with 28 days of dosing.[37] Fluorometholone 0.1% plus 0.1% HA was tested in clinical trials in China, comparing the combination to cyclosporine. After eight weeks of treatment, mean staining, OSDI scores, conjunctival cell density and redness were all significantly improved in both groups compared to baseline. However, fluorometholone + HA was superior to cyclosporine for mean staining at week two, OSDI scores and redness at week four and TFBUT at week eight.[38] The positive effects of these various steroids for treatment of dry eye are worth exploring in creative ways with our patients, particularly when a worsening of symptoms—brought on by abrupt environmental changes, certain activities or factors such as medication change—causes our patients to fall into an acute dry-eye crisis. *(See the Therapeutic Topics in the May 2015 issue of* Review *for a discussion of acute dry eye.)*

Another anti-inflammatory on the horizon for dry eye has a unique mechanism and origin. Cis-urocanic acid is an endogenous small molecule component of human and animal skin. It's formed in the upper layers of the skin, and is constantly present in the human body at micromolar levels, and in millimolar levels

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in the epidermis after exposure to sunlight. This molecule has anti-inflammatory effects due to inhibition of c-Jun N-terminal kinase (JNK) signaling; a notable effect is that activation of the mitogen-activated protein kinase (MAPK) cascade is thought to be central to dry-eye inflammatory events. The Phase I safety and pharmacokinetics of 0.5% and 2.5% cis-UCA eyedrops were recently published.[39] In the EU, cis-UCA is being developed as a dermal cream for treatment of psoriasis and atopic dermatitis.[40] A Phase II study has been completed and is listed on clinical trials.gov, and we look forward to hearing of its progress.[41]

IL-1 is a key inflammatory and immune mediator in many inflammatory diseases, and Eleven Biotherapeutics is developing an IL-1 antagonist (EBI-005) for treatment of ocular allergy and/or dry eye. The fate of Eleven's research programs is not yet clear, but both Phase II and Phase III studies are listed on clinicaltrials.gov, and the company has completed a Phase III study in 669 patients at more than 40 clinical sites. In a press release, the dry-eye study results were described as failing to show significant efficacy in any primary or secondary endpoints, so the second Phase III study was shelved.[42] The allergy indication remains the company's focus for 2015-2016.

Potentially effective therapeutic agents deserve a rigorous clinical study program based on an understanding of corneal physiology, disease pathology and epidemiology, as well as pharmacology and pharmacokinetics. Having spent more than 20 years refining the precise operational execution of dry-eye clinical trials, and having had the opportunity to work with many therapeutic agents, it's gratifying to the clinical achievements that finally hold the promise of greater choice for treating our dry-eye patients. REVIEW

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

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What to Expect from Your Dry-Eye Device

Walter Bethke, Managing Editor

Results from devices used in-office that take the treatment onus off of the patient.

Some ophthalmology practices are approaching meibomian gland dysfunction-related dry eye in keeping with the old adage, "If you want something done right, do it yourself." They're opting to treat these patients in their office rather than send them home with a regimen of remedies that the patients may not adhere to. However, as these new non-invasive, external treatment devices have begun appearing in practices, some physicians wonder how well they work. This article takes a look at studies using these treatments, and hears from doctors who have worked with them to give you an idea of the results you can expect if you choose to offer them in your practice.

LipiFlow

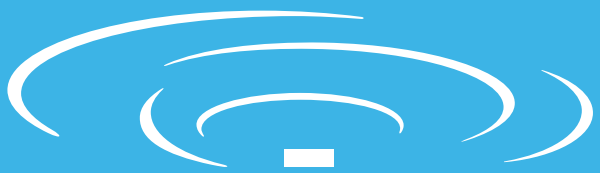
TearScience's LipiFlow, also known as thermal pulsation, was the first device aimed specifically at MGD-related evaporative dry eye. It combines heat with physical massage to liquefy and express the meibomian gland contents in an effort to get the lipid layer of the ocular surface back to normal again.

The device consists of a small piece that looks like a scleral contact lens that slides beneath the lids and over the globe. Some physicians administer

LipiFlow combines heat from beneath the lid with mechanical squeezing.

one or two drops of topical anesthetic before fitting the device beneath the lid, for patient comfort. This lens-like piece emits heat outward, to the lids, while at the same time protecting the eye itself from the heat. The second part of the device, which is connected to the shield, sits outside the eye on the lids and provides a pulsatile squeezing of the lids to try to open the gland orifices and express the oil that's being warmed and liquefied by the heat. The treatment takes 12 minutes.

Jack Greiner, DO, PhD, of the Schepens Eye Research Institute, has conducted a long-term study of LipiFlow, following patients for up to three years. In the study, 40 eyes of 20 patients with MGD and dry-



LACRISERT®

(hydroxypropyl cellulose ophthalmic insert)

BAUSCH + LOMB

US/LAC/14/0008b

ATON PHARMA Lawrenceville NJ 08648 USA

STERILE OPHTHALMIC INSERT

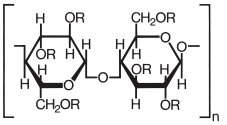
LACRISERT®

(HYDROXYPROPYL CELLULOSE OPHTHALMIC INSERT)

DESCRIPTION

LACRISERT* (hydroxypropyl cellulose ophthalmic insert) is a sterile, translucent, rod-shaped, water soluble, ophthalmic insert made of hydroxypropyl cellulose, for administration into the inferior cul-de-sac of the eye.

The chemical name for hydroxypropyl cellulose is cellulose, 2-hydroxypropyl ether. It is an ether of cellulose in which hydroxypropyl groups (-$CH_2CHOHCH_3$) are attached to the hydroxyls present in the anhydroglucose rings of cellulose by ether linkages. A representative structure of the monomer is:



$$R = CH_2CHCH_3 \quad (OH)$$

The molecular weight is typically 1×10^6.

Hydroxypropyl cellulose is an off-white, odorless, tasteless powder. It is soluble in water below 38°C, and in many polar organic solvents such as ethanol, propylene glycol, dioxane, methanol, isopropyl alcohol (95%), dimethyl sulfoxide, and dimethyl formamide.

Each LACRISERT is 5 mg of hydroxypropyl cellulose. LACRISERT contains no preservatives or other ingredients. It is about 1.27 mm in diameter by about 3.5 mm long.

LACRISERT is supplied in packages of 60 units, together with illustrated instructions and a special applicator for removing LACRISERT from the unit dose blister and inserting it into the eye. A spare applicator is included in each package.

CLINICAL PHARMACOLOGY

Pharmacodynamics

LACRISERT acts to stabilize and thicken the precorneal tear film and prolong the tear film breakup time which is usually accelerated in patients with dry eye states. LACRISERT also acts to lubricate and protect the eye.

LACRISERT usually reduces the signs and symptoms resulting from moderate to severe dry eye syndromes, such as conjunctival hyperemia, corneal and conjunctival staining with rose bengal, exudation, itching, burning, foreign body sensation, smarting, photophobia, dryness and blurred or cloudy vision. Progressive visual deterioration which occurs in some patients may be retarded, halted, or sometimes reversed.

In a multicenter crossover study the 5 mg LACRISERT administered once a day during the waking hours was compared to artificial tears used four or more times daily. There was a prolongation of tear film breakup time and a decrease in foreign body sensation associated with dry eye syndrome in patients during treatment with inserts as compared to artificial tears; these findings were statistically significantly different between the treatment groups. Improvement, as measured by amelioration of symptoms, by slit lamp examination and by rose bengal staining of the cornea and conjunctiva, was greater in most patients with moderate to severe symptoms during treatment with LACRISERT. Patient comfort was usually better with LACRISERT than with artificial tears solution, and most patients preferred LACRISERT.

In most patients treated with LACRISERT for over one year, improvement was observed as evidenced by amelioration of symptoms generally associated with keratoconjunctivitis sicca such as burning, tearing, foreign body sensation, itching, photophobia and blurred or cloudy vision.

During studies in healthy volunteers, a thickened precorneal tear film was usually observed through the slit-lamp while LACRISERT was present in the conjunctival sac.

Pharmacokinetics and Metabolism

Hydroxypropyl cellulose is a physiologically inert substance. In a study of rats fed hydroxypropyl cellulose or unmodified cellulose at levels up to 5% of their diet, it was found that the two were biologically equivalent in that neither was metabolized.

Studies conducted in rats fed ^{14}C-labeled hydroxypropyl cellulose demonstrated that when orally administered, hydroxypropyl cellulose is not absorbed from the gastrointestinal tract and is quantitatively excreted in the feces.

Dissolution studies in rabbits showed that hydroxypropyl cellulose inserts became softer within 1 hour after they were placed in the conjunctival sac. Most of the inserts dissolved completely in 14 to 18 hours; with a single exception, all had disappeared by 24 hours after insertion. Similar dissolution of the inserts was observed during prolonged administration (up to 54 weeks).

INDICATIONS AND USAGE

LACRISERT is indicated in patients with moderate to severe dry eye syndromes, including keratoconjunctivitis sicca. LACRISERT is indicated especially in patients who remain symptomatic after an adequate trial of therapy with artificial tear solutions.

LACRISERT is also indicated for patients with:

- Exposure keratitis
- Decreased corneal sensitivity
- Recurrent corneal erosions

CONTRAINDICATIONS

LACRISERT is contraindicated in patients who are hypersensitive to hydroxypropyl cellulose.

WARNINGS

Instructions for inserting and removing LACRISERT should be carefully followed.

PRECAUTIONS

General

If improperly placed, LACRISERT may result in corneal abrasion (see DOSAGE AND ADMINISTRATION).

Information for Patients

Patients should be advised to follow the instructions for using LACRISERT which accompany the package.

Because this product may produce transient blurring of vision, patients should be instructed to exercise caution when operating hazardous machinery or driving a motor vehicle.

Drug Interactions

Application of hydroxypropyl cellulose ophthalmic inserts to the eyes of unanesthetized rabbits immediately prior to or two hours before instilling pilocarpine, proparacaine HCl (0.5%), or phenylephrine (5%) did not markedly alter the magnitude and/or duration of the miotic, local corneal anesthetic, or mydriatic activity, respectively, of these agents. Under various treatment schedules, the anti- inflammatory effect of ocularly instilled dexamethasone (0.1%) in unanesthetized rabbits with primary uveitis was not affected by the presence of hydroxypropyl cellulose inserts.

Carcinogenesis, Mutagenesis, Impairment of Fertility

Feeding of hydroxypropyl cellulose to rats at levels up to 5% of their diet produced no gross or histopathologic changes or other deleterious effects.

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 following adverse reactions have been reported in patients treated with LACRISERT, but were in most instances mild and transient:

- Transient blurring of vision (See PRECAUTIONS)
- Ocular discomfort or irritation
- Matting or stickiness of eyelashes
- Photophobia
- Hypersensitivity
- Edema of the eyelids
- Hyperemia

DOSAGE AND ADMINISTRATION

One LACRISERT ophthalmic insert in each eye once daily is usually sufficient to relieve the symptoms associated with moderate to severe dry eye syndromes. Individual patients may require more flexibility in the use of LACRISERT; some patients may require twice daily use for optimal results.

Clinical experience with LACRISERT indicates that in some patients several weeks may be required before satisfactory improvement of symptoms is achieved.

LACRISERT is inserted into the inferior cul-de-sac of the eye beneath the base of the tarsus, not in apposition to the cornea, nor beneath the eyelid at the level of the tarsal plate. If not properly positioned, it will be expelled into the interpalpebral fissure, and may cause symptoms of a foreign body. Illustrated instructions are included in each package. While in the licensed practitioner's office, the patient should read the instructions, then practice insertion and removal of LACRISERT until proficiency is achieved.

NOTE: Occasionally LACRISERT is inadvertently expelled from the eye, especially in patients with shallow conjunctival fornices. The patient should be cautioned against rubbing the eye(s) containing LACRISERT, especially upon awakening, so as not to dislodge or expel the insert. If required, another LACRISERT ophthalmic insert may be inserted. If experience indicates that transient blurred vision develops in an individual patient, the patient may want to remove LACRISERT a few hours after insertion to avoid this. Another LACRISERT ophthalmic insert maybe inserted if needed.

If LACRISERT causes worsening of symptoms, the patient should be instructed to inspect the conjunctival sac to make certain LACRISERT is in the proper location, deep in the inferior cul-de-sac of the eye beneath the base of the tarsus. If these symptoms persist, LACRISERT should be removed and the patient should contact the practitioner.

HOW SUPPLIED

LACRISERT, a sterile, translucent, rod-shaped, water-soluble, ophthalmic insert made of hydroxypropyl cellulose, 5 mg, is supplied as follows:

NDC 25010-805-68 in packages containing 60 unit doses (each wrapped in an aluminum blister), two reusable applicators, and a plastic storage container to store the applicators after use.

Storage

Store below 30°C (86°F).

Distributed by:
ATON PHARMA, INC.
Lawrenceville, NJ 08648, USA

Manufactured by:
DPT Lakewood, Inc.
Lakewood, NJ 08701 USA

Issued August 2008
Printed in USA

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eye symptoms underwent a LipiFlow treatment at Dr. Greiner's office. The outcomes were measured in terms of meibomian gland secretion score (determined by grading three sets of five glands on the lower lid on each gland's ability to secrete healthy, clear oil [a grade of 3] down to nothing [a grade of zero]) and tear-film breakup time. Patients also rated their symptoms on the Ocular Surface Disease Index and Standard Patient Evaluation of Eye Dryness questionnaires.

In the study, MGS scores increased from 4.5 at baseline to 12 at one month ($p \leq 0.001$). This improvement continued at three years (score: 18.4). TFBUT at baseline was 4.1 seconds, and improved to 7.9 seconds at one month ($p \leq 0.05$). However, the difference between TFBUT at three years wasn't statistically significant (score: 4.5 seconds). The average OSDI score improved significantly from a 26 at baseline to 14.7 at one month ($p \leq 0.001$), but returned to baseline levels at three years (22.5; $p > 0.05$). The SPEED scores, however, remained improved at both one month and three years: The average SPEED score improved from a 13.4 at baseline to 6.5 at a month ($p \leq 0.001$), and the improvement continued at three years (9.5; $p \leq 0.001$).[1]

"At the 12-month time point, the tear breakup time dropped out as being statistically significant," says Dr. Greiner. "When you get to the two-year time point, the OSDI score dropped out as being significantly better than baseline. In terms of adverse events, after the treatment, there's some minor irritation that's usually gone in an hour. Sometimes the vessels on the lid margin, which are very tiny, will be more fragile on people with various skin textures and you'll see some subcutaneous hemorrhaging along the lid margin. However, if you look at that patient in a day or two, the hemorrhage signs are gone."

LipiFlow isn't for every patient, however, and in one study around 20 percent of the subjects didn't report an overall improvement in symptoms.[2] Because of this, doctors say patients should fit a certain profile to ensure success with the procedure. "You can't just put anyone in LipiFlow treatment," says Dr. Greiner. "The patient can have a severe amount of dry eye but you need some glands that are capable of being opened. What we're usually looking for is someone with at least six glands in his lower lid that are open to some degree before we'll do LipiFlow. If there aren't this many, we might do lid expression for a few weeks or months ahead of the LipiFlow treatment, as well as have him do warm compresses and lid therapy at home." Another factor some surgeons say may be important is the occurrence of incomplete blinking. If a patient has persistent incomplete blinks,

surgeons say, it's a problem that will always be there and LipiFlow might not be successful in such a patient.

In the right patient, Dr. Greiner has been pleased with the results. "Looking at this technology, for me it was completely unexpected that it would last this long," he says. "When we could get an eye drop to last six or eight hours, we were excited, but we never expected to see something last nine months or a year."

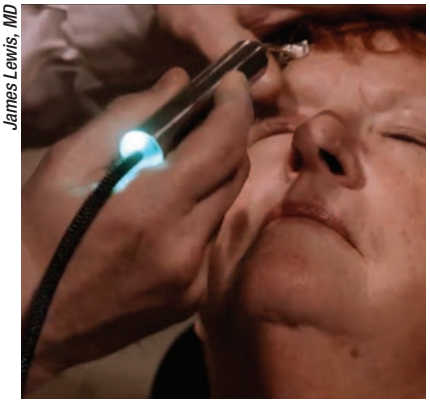
ThermoFlo

ThermoFlo is another in-office treatment performed by either the doctor or a staff member that takes aim at MGD-related dry eye. Like LipiFlow, it combines pressure and heat, but in a fashion that differs slightly from LipiFlow's approach.

The ThermoFlo is essentially an electric handpiece with two small pads on the end. The user spreads some ultrasound gel on the pads, then applies them to the patient's closed lids. The pads heat to 108 degrees F to loosen the material in the meibomian glands and the pressure necessary to express the contents is provided manually by the user. The treatment takes 12 minutes and doesn't require anesthesia.

ThermoFlo hasn't been studied as formally as LipiFlow, but anecdotal reports seem to show it's at least as good as warm compresses, without the need for patient adherence with the compress regimen. "In virtually every patient, the treatment lasts a week," says Elkins Park, Pa., ophthalmologist James Lewis. "By two weeks after their first treatment, about half of the patients feel that another treatment is needed. Three or four ThermoFlo treatments, two weeks apart, are usually enough to evacuate the remaining healthy glands, and patients seem to do considerably better then. We usually don't need to do a fifth or sixth treatment."

James Lewis, MD



The ThermoFlo device heats the oil glands from outside the lid. Periodic pressure for expressing the glands' oil is applied by the practitioner holding the device.

In his practice, Dr. Lewis studied 45 patients referred to him for dry-eye treatment. All were currently using treatments such as warm compresses, lid hygiene, Restasis, non-preserved artificial tears, temporary or permanent punctal occlusion and/or low-dose ocular steroids, but hadn't gotten satisfactory relief from them. Two weeks after the ThermoFlo treatment, the patients completed a questionnaire, and 89 percent reported some improvement in their symptoms. "In my practice, after ThermoFlo we've noticed improved Schirmer's testing results, improved osmolarity and improved TFBUT as measured by the Oculus Keratograph," Dr. Lewis avers. "We're having TFBUT extend as much as five seconds after a ThermoFlo treatment."

In everyday practice, Dr. Lewis doesn't use ThermoFlo alone, but instead makes it part of patients' dry-eye regimen. "In clinical practice, we rarely do a treatment unassociated with other therapies, and will accompany it with topical steroids, the use of punctal occlusion and sometimes the addition of Restasis," he explains.

Intense Pulsed Light

The treatment known as intense pulsed light is actually a repurposing of a device used in the dermatology field for skin treatments.

IPL for treatment of dry eye was initiated by Memphis surgeon Rolando Toyos. Dr. Toyos received a research grant from the American Society of Cataract and Refractive Surgery to study IPL for evaporative dry eye, and eventually developed a laser for the treatment with the device company Dermamed. His approach using this device for ocular indications is now being taught to various ophthalmology clinics and practices via lectures and training courses.

In July 2015, Duke Eye Center surgeon Gargi Vora co-authored a retrospective study of IPL to get a sense of its efficacy. "For an ocular IPL treatment, we first apply ultrasound jelly to the area under the lower lid/lateral canthal area and the upper cheek," she says. "IPL is only used to treat the lower lid/lateral canthal area, not the upper lid, because light directed at the upper lid could penetrate it and damage the eye itself. We also put special eye shields on the ocular surface itself, and have the patient close his eye over them, to make sure no light energy enters the eye. Alternatively, some practitioners place shields over the lids. For the treatment, the patient receives 10 to 15 treatment spots on the upper cheek and lateral canthal area, and the physician makes two passes. To the patient, it's similar to facial skin treatments, with little zaps to the skin. Patients can feel some warmth during the procedure and the zaps can be a little uncomfortable, so we use the jelly to help soothe the skin. After the second pass, the shield and jelly are removed, and the patient receives warm compresses over his lid to soothe it as well as help the oils in the glands melt a little.

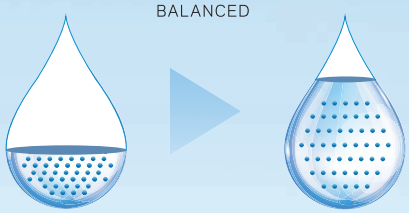
"We then take the patient to the slit lamp and decompress the meibomian glands and scrape out the oil from the lid margin using a cotton-tip applicator," Dr. Vora continues. "Patients are then prescribed a mild

IT'S ENOUGH TO MAKE ANYBODY'S EYES FEEL DRY, GRITTY & UNCOMFORTABLE

A high salt concentration can disrupt the osmolarity balance within the tear film. Elevated tear film osmolarity (osmolarity imbalance or hyperosmolarity) is one of the primary causes of dry eye symptoms.[1]

TheraTears® Dry Eye Therapy with Osmo-Correction™ corrects osmolarity imbalance to restore comfort with a unique hypotonic and electrolyte balanced formula that replicates healthy tears.

THERATEARS® DRY EYE THERAPY
WITH
OSMO-CORRECTION™
HYPOTONIC & ELECTROLYTE BALANCED



HYPEROSMOLARITY

Increased concentration of the tears leads to irritation and potential damage to the ocular surface.

HEALTHY TEAR

TheraTears® Dry Eye Therapy replicates the electrolyte balance of natural tears to restore comfort.

RESTORE + CLEANSE + NOURISH

thera tears®
THERAPY FOR YOUR EYES™

DRY EYE THERAPY

Restores Eyes Natural Balance™

theratears.com

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

AKORN Consumer Health

steroid such as one drop of fluorometholone or loteprednol b.i.d. for two to three days."

In the Duke study, Dr. Vora and her colleague Priya Gupta, MD, administered at least three IPL treatments to evaporative dry-eye patients. Drs. Vora and Gupta report a significant decrease in the level of lid margin edema, facial telangiectasia and lid margin vascularity, as well as an improvement in meibum quality score ($p<0.001$ for all measurements). There was also a significant increase in oil flow score and TFBUT ($p<0.001$). Subjective symptoms improved, with a statistically significant decrease in OSDI scoring ($p<0.001$). The patients had relief for several months, and maintenance treatments were necessary every six to 12 months.[3]

Dr. Vora says the improvements grew over time. "In our study, there was a range of three to six treatments per patient, with an average of four," she explains. "Each treatment was separated by three to six weeks, the scheduling of which wasn't really symptom-based but more about when the patient could come in. We noticed that patients saw improvement by the second treatment, which was also the date of the second follow-up—after the visit on the day of the procedure—which was about three weeks after the initial IPL treatment."

Ophthalmologists are still curious about the exact mechanism of action involved with IPL. "In dermatology, IPL is used for rosacea and to reduce telangiectasia," Dr. Vora says. "Then, in 2002, Dr. Toyos found that dermatology patients also had improvement in meibomian gland dysfunction and dry-eye disease. We're not 100-percent sure of how IPL works in dry eye. The way it works in rosacea cases, at least as believed by dermatologists, is that oxyhemoglobin in the blood vessels absorbs the light energy and then converts it to heat, which causes a coagulation or closing of the vessels. Patients with meibomian gland dysfunction often have abnormal vessels at the lid margin or ocular rosacea, so we're assuming that the oxyhemoglobin is absorbing the energy from the IPL and closing off the vessels, preventing inflammatory mediators from reaching the meibomian glands and allowing them to become inflamed.


Gargi Vora, MD

Intense Pulsed Light manages to get an effect in the meibomian glands of the lower lid, and sometimes the upper lid, by treating blood vessels in the lower lid/lateral canthal area.

"Another theory of how it works is that, due to a kind of local heating effect, it's similar to LipiFlow in that it's causing a melting of the oils in the glands to let them be secreted more smoothly," Dr. Vora continues. "We think that the heating effect might also decrease the bacteria in the lid margin, decreasing the inflammatory burden on the meibomian glands. The Demodex parasite on the lid margin is partially treated, as well. Ultimately, we don't know exactly what IPL does, but I imagine it's a mix of these three things that results in improvement."

Blephex

Blephex (RySurg; Palm Beach, Fla.) is a new in-office tool for use on patients with blepharitis, and, as such, it appears to also ease the signs and symptoms of evaporative dry eye associated with blepharitis.

The Blephex is a handheld tool similar in appearance to an electric screwdriver. The doctor or technician affixes a small disposable pad to the rotating end of the Blephex, and puts a small amount of lid cleaning soap on the pad. As the cleaning pad rotates at high speed, it's used to scrub away debris from the lid margins under topical anesthesia. From the dry-eye perspective, debriding the margins can open up the meibomian gland orifices, allowing the oil to return to the ocular surface.

Charles Connor, OD, PhD, professor at the Rosenberg School of Optometry at the University of the Incarnate Word in San Antonio, co-authored a prospective study of Blephex in 20 patients with meibomian gland dysfunction. *(Connor C, et al. IOVS 2015;56:ARVO E-Abstract 4440)* At baseline and four weeks after treatment, the investigators used the Efron scale for grading the level of MGD, and the patients also underwent TFBUT measurement and answered the OSDI questionnaire. At four weeks, MGD on the Efron scale improved from 1.65 to 0.76 ($p=0.01$), and TFBUT improved from 3.31 to 5.47 seconds ($p=0.05$). Symptom scores on the OSDI improved from an average of 43.74 to 20.33 ($p=0.01$).

Dr. Connor and his colleagues say Blephex appears to be an alternative for patients who are non-compliant

with lid scrubs and warm compresses at home. "If the meibomian gland is still viable when you debride the thickened tissue on top of it, it will secrete and the patient will have a positive response," Dr. Connor says. "The cleaner used on the Blephex pad is basically the type of cleaner we've been using for years to clean lids; it's a soap designed to not induce a lot of irritation in the eye. In addition to cleaning off the thickened tissue on the lid margins, the soap will kill bacteria there too. Blephex lasts about three to six months before requiring a retreatment.

"The Blephex treatment isn't an unpleasant experience for the patient, provided you use a little stronger anesthetic," Dr. Connor continues. "If you use proparacaine, it's a little too weak and patients feel the vibration more. But with tetracaine patients have less sensation, so when you run the Blephex across the lid margins the patient gets less irritation. We haven't had any patients say the treatment is painful, with the worst complaint being that it's mildly uncomfortable or that it tickled. My gut feeling is that the old traditional treatments also work, but patients don't really want to do them because it's one more thing they have to add to their daily routines. They either forget, or get lackadaisical about doing them. I don't know if Blephex works better than therapies we've done traditionally, but what's nice about it is I know that it's been done. I or my staff can do it, get a result, and not have to worry about the patient going home and doing anything." REVIEW

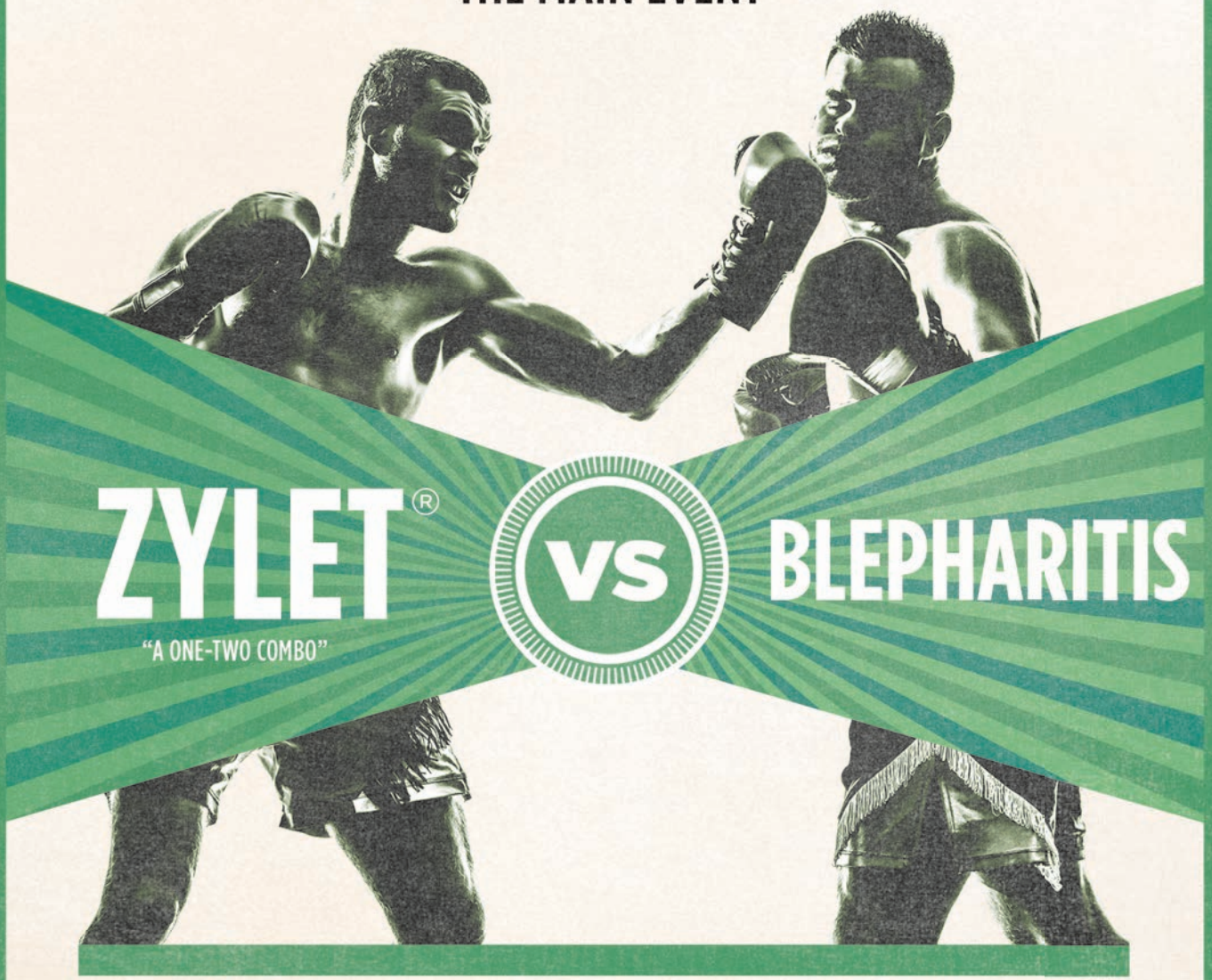
Charles Connor, OD, PhD

Blephex removes scales and debris from the lid margin using a rotating head, which opens up meibomian gland orifices.

Dr. Greiner has performed studies funded by TearScience. Dr. Lewis is a stockholder in Mibo. Drs. Vora and Connor have no financial interest in any product mentioned in the article.

1. Greiner JV. Long-term (3 year) effects of a single thermal pulsation system treatment on meibomian gland function and dry-eye symptoms. Eye Contact Lens 2015 Jul 28. [Epub ahead of print]
2. Lane S, DuBiner H, Epstein R, et al. A new system, the lipiflow, for the treatment of meibomian gland dysfunction. Cornea 2012;31:4:396-404.
3. Vora GK, Gupta PK. Intense pulsed light therapy for the treatment of evaporative dry-eye disease. Curr Opin Ophthalmol 2015;26:4:314-8.

★ ★ ★ THE MAIN EVENT ★ ★ ★



HELP PUT RELIEF IN YOUR CORNER

INDICATIONS AND USAGE

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

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

INDICATIONS AND USAGE (continued)

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

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

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

IMPORTANT SAFETY INFORMATION

- ZYLET® is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.
- Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. Steroids should be used with caution in the presence of glaucoma. If this product is used for 10 days or longer, intraocular pressure should be monitored.
- Use of corticosteroids may result in posterior subcapsular cataract formation.
- The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification such as a slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infections. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Employment of corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Most common adverse reactions reported in patients were injection and superficial punctate keratitis, increased intraocular pressure, burning and stinging upon instillation.

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

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

BAUSCH+LOMB

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

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

Initial U.S. Approval: 2004

DOSAGE AND ADMINISTRATION

2.1 Recommended Dosing

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

2.2 Prescription Guideline

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

CONTRAINDICATIONS

4.1 Nonbacterial Etiology

Zylet, as with other steroid anti-infective ophthalmic combination drugs, is contraindicated in most viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal diseases of ocular structures.

WARNINGS AND PRECAUTIONS

5.1 Intraocular Pressure (IOP) Increase

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

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

5.2 Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

5.3 Delayed Healing

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

5.4 Bacterial Infections

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

5.5 Viral Infections

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

5.6 Fungal Infections

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

5.7 Aminoglycoside Hypersensitivity

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

ADVERSE REACTIONS

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

Zylet:

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

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

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

Loteprednol etabonate ophthalmic suspension 0.2% - 0.5%:

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

In a summation of controlled, randomized studies of individuals treated for 28 days or longer with loteprednol etabonate, the incidence of significant elevation of intraocular pressure (≥10 mm Hg) was 2% (15/901) among patients receiving loteprednol etabonate, 7% (11/164) among patients receiving 1% prednisolone acetate and 0.5% (3/583) among patients receiving placebo.

Tobramycin ophthalmic solution 0.3%:

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

Secondary Infection:

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

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

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

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

8.3 Nursing Mothers

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

8.4 Pediatric Use

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

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

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

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

8.5 Geriatric Use

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

NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

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

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

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

PATIENT COUNSELING INFORMATION

This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the suspension. If pain develops, redness, itching or inflammation becomes aggravated, the patient should be advised to consult a physician. As with all ophthalmic preparations containing benzalkonium chloride, patients should be advised not to wear soft contact lenses when using Zylet.

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How to Take on Strabismus in Adults

Michelle Stephenson, Contributing Editor

Often mislabeled a childhood disease, strabismus can be treated in adults, with visual and psychosocial benefits.

Strabismus, whether it is new-onset or a reappearance of childhood strabismus, can usually be successfully treated in adults. Surgical and non-surgical treatment options are available, and treatment choice is typically based on the severity of the strabismus.

Although it is often considered a childhood condition, the incidence of strabismus is actually higher in adults. "Approximately 1 percent of children have strabismus," says David Stager Sr., MD, who is in private practice in Plano, Texas. "In adults, the incidence is probably closer to 4 percent. Many of these cases are completely new entities, but, occasionally, it can be a recurrence of a childhood problem. I frequently tell parents that chances are 80 percent that it is fixed for a lifetime, but it's not 100 percent. Many times, it can be decades before they start having a problem again."

If an adult has new-onset strabismus, it is typically the result of a disease process or trauma. "There are myriad causes of adult strabismus, and the treatment often relates to the cause," says Stephen P. Christiansen, MD, from Boston University School of Medicine. "It's not uncommon for childhood strabismus to reappear in adults. Strabismus that patients were either able to control on their own or that was corrected with previous surgery may redevelop. Or, some patients may develop a problem for the first time that is related to their childhood misalignment. That's a common scenario. Then, of course, adults are often prone to acquired forms of strabismus just because of the varying impact of disease and disease processes, such as thyroid eye disease. These are patients who have dysfunctional thyroid or abnormal thyroid function and then develop thickening and inelasticity of the extraocular muscles. Then, they develop vertical, horizontal or torsional strabismus."

Additionally, there are patients who have strokes or ischemic disease that cause misalignment of the eye by affecting the cranial nerves that innervate the extraocular muscles, and these patients can have various forms of paralytic or paretic strabismus. "Then, there are patients who have trauma, and sometimes that trauma is iatrogenic," says Dr. Christiansen. "For example, patients who had cataract surgery with various forms of retrobulbar anesthesia can develop muscle dysfunction and need realignment. There are patients who have had glaucoma surgery and have had seton implantation or scleral buckle placement that impacts the extraocular muscle rotation and function. Those patients

Figure 1. An adult strabismus patient pre- and postoperatively.

may also develop strabismus."

David Stager Jr., MD, who is in practice with his father, says the number of adult patients being treated for strabismus is on the rise. "In my practice 10 to 15 years ago, maybe 5 percent or 10 percent of my surgical strabismus patients were adults," he says. "Now, about 70 percent of the patients on my surgery schedule are adults with strabismus, and my father is approaching 100 percent of the patients on his surgery schedule. Without a doubt, there is much more attention being given to adults with this problem than ever before, and I think there is good reason. If you really look at the population and the demographics, if the incidence is 4 percent in the adult population, the magnitude of that problem ends up being four or five times more than it is in kids."

He notes that the success rate of treatment is extremely high and offers vision improvement and psychosocial benefits. "Strabismus is not a cosmetic problem so much, because we usually think of a cosmetic condition as something normal that you would just prefer to change," he says. "Strabismus is not a normal condition. We now know that there are functional benefits to treating strabismus that are not cosmetic. Many of these patients will develop binocular vision or depth perception. There has been a tremendous amount of work done also on the psychosocial benefits. A lot of these patients have improved self-esteem, chances at work and chances at marriage. They are very much negatively impacted by strabismus, and correcting strabismus can offer tremendous improvement in all of those areas." According to a paper by Burt Kushner, MD, "Strabismus surgery in adults achieves satisfactory alignment with one operation in approximately 80 percent of patients, depending on the specific nature of the problem. Risks of adult strabismus surgery are relatively low, and serious complications are anecdotal and rare. Even if the strabismus has been long-standing, most adults will experience some improvement in binocular function after strabismus surgery. Consequently, adult strabismus surgery should not be considered merely cosmetic in most cases. In esotropic patients, this improvement typically takes the form of an expansion of binocular visual fields; however, some patients may also regain stereopsis. There are many psychosocial benefits to adult strabismus surgery. This is reflected in the finding that the majority of adults surveyed with strabismus would trade a portion of their life expectancy to be rid of their strabismus."[1]

Non-Surgical Treatments

The treatment of strabismus depends on the severity, and management options range from observation to surgery. According to Michael Repka, MD, who is in practice at the Johns Hopkins Children's Center in Baltimore, "For small amounts of strabismus, prism correction and other optical approaches would be attempted first. If that doesn't work, depending on many factors or the situation for that patient, surgical approaches may be employed."

Dr. Christiansen agrees. "Oftentimes, adults will develop small vertical or horizontal strabismus," he says. "These patients can sometimes be best managed with either observation, if it's not especially symptomatic, or with small amounts of prism placed in the glasses. If patients start developing a need for larger and larger amounts of prism to correct the alignment, they may develop spectacle distortion that they don't like, and then you need to start thinking of other forms of treatment. My rule of thumb is that if they need more than 10 prism diopters in their glasses, they are probably going to be a surgical candidate at some point."

Dr. Stager Jr. notes that certain types of orthoptic exercises or orthoptic training can be used to help give the patient better fusion. "Sometimes, we will just have to patch the eye to avoid diplopia if the patient is not a good can-

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didate for other treatments. Often, in patients who are not good candidates for these other treatments, surgery can be an excellent option," he says.

According to Dr. Christiansen, botulinum toxin A (BTX-A) is a fairly recent advance in strabismus surgery. "It can be used alone in some cases or, more commonly, as adjunctive treatment with standard muscle surgery," he says. "BTX-A results in muscle paralysis that lasts for up to three months; however, the change in alignment of the eye may last much longer. There are certain forms of strabismus that can be successfully treated with BTX-A. More recently, bupivacaine has been proposed as a means of treating patients with strabismus. It is a local anesthetic that actually makes muscles bigger and stiffer. It is not widely used in the United States, but that may change if efficacy can be shown."

In a recent study conducted in Brazil, a change in ocular motility was observed after 180 days of intramuscular injection of bupivacaine and botulinum toxin in horizontal extraocular muscles.[2] In both botox- and bupivacaine-injected muscles, there was an increase of muscle thickness after 30 days of injection when measured by ultrasonography. This change was greatest on lateral rectus muscles after bupivacaine injection.

This study included eight patients (eight amblyopic eyes) in whom ocular motility was measured prior to injection and one, seven, 30 and 180 days after one injection of 2 mL of 1.5% bupivacaine and 2.5 U of botulinum toxin A in agonist and antagonist muscles, respectively. Muscle thickness was measured prior to injection and on days one, seven, and 30 after injection using 10-MHz ultrasonography.

The mean change in alignment was 10 prism diopters after 180 days. Using ultrasonography, an average increase of 1.01 mm in muscle thickness was observed after 30 days of bupivacaine injection, and an average increase of 0.28 mm was observed after BTX-A injection. A mean increase in muscle thickness of 1.5 mm was seen in lateral rectus muscles injected with bupivacaine.

Surgical Treatments

If the abovementioned treatment strategies do not achieve the desired result, surgery is the next step. "Surgical techniques to treat adults and children are largely the same," Dr. Repka says. "However, many surgeons use adjustable sutures in adults that are not used in children. Adjustable sutures provide the ability to postoperatively fine-tune the alignment to the desired position."

However, outcomes can be less predictable in adults than they are in children. "Most often, the techniques we use in adults are the same that we use in children," says Dr. Christiansen. "However, in some cases, adult strabismus is complicated by abnormal extraocular muscle function, either because of inelasticity or because of paralysis. So, we have to adjust our techniques to the underlying pathology. Because of the unique pathology, and because many adults who have strabismus have had previous surgery, outcomes may be less predictable than in children. In hopes of improving outcomes in these situations, many surgeons use the adjustable suture technique, which allows the surgeon to position the operative muscle where it seems most appropriate. But, rather than securing the muscle permanently, the suture is tied in a temporary fashion, often with a slipknot that can be undone. The muscle position can be readjusted when the patient awakens from surgery. This adjustment can be done from six hours after surgery up to 24 hours after surgery and sometimes longer, depending on the adjustable suture technique. One potential drawback is that this technique requires a cooperative patient, so it is not often used in children."

He adds that adult patients can usually expect a successful surgical outcome. However, there are some patients who have either such complex strabismus or have had a history of head injury that precludes adequate binocularity, and double vision can result. "As a whole, however, well over 80 percent of adult strabismus patients can be treated successfully," says Dr. Christiansen. "Goals of surgery and definitions of success need to be discussed carefully with the patient preoperatively. For example, patients with paralytic or restrictive strabismus may not recover normal ocular rotations after surgery, which means that they will have some misalignment of the eyes in some positions of gaze."

The goal for patients with the more complex forms of strabismus is to get them to fuse with a single image in a straight-ahead position and in the reading position. "That allows them to read, drive, and walk without double vision in these critical gaze positions," Dr. Christiansen says. "Even with double vision in side gaze, however, many patients learn to adjust their head position, so that they can see singly. I counsel patients ahead of time that double vision may be treated successfully, but not completely. These patients learn to adjust pretty quickly and are much happier having straight eyes both for the cosmetic appearance and for the functionality of the depth perception they can re-establish."

A number of studies have shown the efficacy of adjustable sutures in adults. For example, a recent Canadian study found that achieving the immediate target angle is the most significant factor in the success of strabismus surgery for exotropia and that adjustable suture surgery results in a larger number of patients achieving this target angle.[3]

The study included 353 patients who were older than 12 years and who

(continued on page 70)

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PVR: An Update on Prevention & Management

We have learned much about the pathogenesis of PVR but have a lot of ground to cover to effectively treat this devastating disease.

Christopher J. Brady, MD, Baltimore, and Richard S. Kaiser, MD, Philadelphia

In spite of advanced surgical techniques and instrumentation, proliferative vitreoretinopathy is the biggest obstacle to successful retinal reattachment surgery, with a cumulative risk of approximately 5 to 10 percent of all retinal detachment repairs, accounting for approximately 75 percent of all primary surgical failures.[1] PVR is characterized by growth and migration of preretinal or subretinal membranes. Contraction of these membranes causes foreshortening of the retina, leading to stretch holes or traction, and recurrent detachment of the retina.

The pathogenesis is far from being completely understood. In general, processes that increase vascular permeability are more likely to increase the probability of PVR formation. Specific risk factors that have been identified include: uveitis; large, giant, or multiple tears; vitreous hemorrhage, preoperative or postoperative choroidal detachments; aphakia; multiple previous surgeries; and large detachments involving greater than two quadrants of the eye.[1,2]

The PVR process is thought to be analogous to the anomalous wound healing that leads to skin keloid formation.[3] It is thought the most important cell types in PVR pathogenesis are the retinal pigment epithelial cells, which are believed to migrate through retinal breaks, de-differentiate and proliferate on the retinal surface. Retinal glial cells and macrophages may also play important roles, perhaps by providing a scaffold for membrane formation and/or by releasing trophic factors.[3,4] This process appears to be driven by and modulated by numerous growth factors[5] (e.g., platelet-derived growth factor,[6] vascular endothelial growth factor,[7] tumor growth factor-beta, epidermal growth factor, tumor necrosis factor-alpha and fibroblast growth factor[8]) and cytokines (e.g., interleukin-1, -6, -8 and -10, and interferon-gamma[9]). Despite a growing understanding of the molecular underpinnings of PVR, prevention of the clinical phenomenon is still not possible.

Surgery

The mainstay of the management of PVR is surgical, with pars plana vitrectomy with membrane peeling being the primary procedure.

The surgical approach for PVR is generally the same for primary retinal detachments without membranes. The principal difference is that there is significantly more retinal traction in PVR, which is caused by membranes and bands rather than vitreous gel alone. As such, different techniques may be employed to dissect these membranes to allow the retina to flatten.

Additionally, if a scleral buckle was not used at the time of the primary retinal detachment repair, it can be advantageous to place one during the PVR vitrectomy procedure. However, if an extensive inferior retinectomy is likely to be performed, a scleral buckle is likely not needed.

The primary surgical goal in PVR surgery is to remove the membranes from the retinal surface and from beneath the retina (if necessary). Because these membranes may be tightly adherent to the underlying tissue, it is frequently advantageous to use bimanual surgical techniques,

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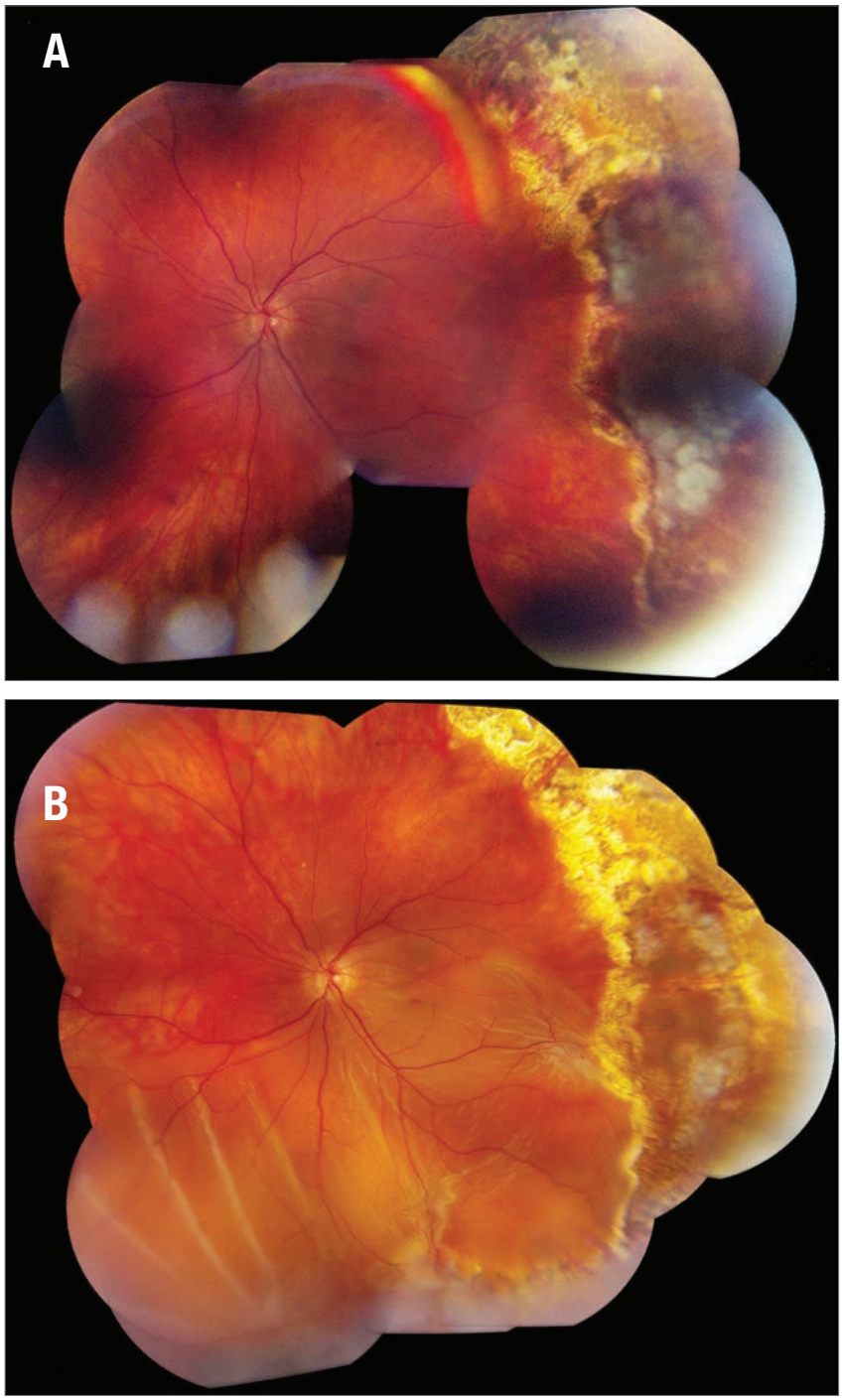


Figure 1. Following primary retinal detachment repair, this patient initially had a good result (A). Several weeks later, following a decline in vision, a proliferative vitreoretinopathy re-detachment was noted, with membranes seen temporally and inferiorly (B). *(See p. 66 for Figures 1C and D.)*

with both hands using surgical instruments to manipulate the retina and associated membranes. Typically, silicone oil is instilled for longer lasting tamponade, though perfluoropropane (C3F8) gas may also be used for eyes with less-extensive disease.[10,11]

Medical Prevention/Treatment

Significant basic science and animal research effort has been directed towards elucidating the pathobiology of PVR with the aim of preventing retinal re-detachment. Unfortunately few human studies conclusively provide guidance on the optimal means of doing so. Historically, three main categories of pharmacologic prevention have been explored: anti-inflammatory; anti-proliferative/neoplastic; and anti-growth factor.[9]

Corticosteroids were among the first agents tested in the prevention of PVR. The rationale for their utility stems from the observation that PVR seems to be an inflammatory event clinically, and this has been validated with proteomic analysis.[12] Their effectiveness was suggested in animal experiments,[13] but this has not translated to long-term success in humans.[14,15] A randomized controlled trial of systemic steroids for the prevention of epiretinal membrane following primary RD repair showed a lower rate of ERM in the experimental group, but no difference in visual acuity outcomes.[16] One retrospective series that achieved good outcomes involved 2 mg triamcinolone acetate administered intravitreally at the end of vitrectomy surgery with silicone oil tamponade.[17] However, a randomized trial in eyes with at least Grade C PVR that compared 4 mg triamcinolone injection following silicone oil infusion with no triamcinolone found no significant difference in anatomic success rate, visual acuity or PVR recurrence at six months.[18] If access to compounded medication becomes more restricted, the dexamethasone intravitreal implant might be

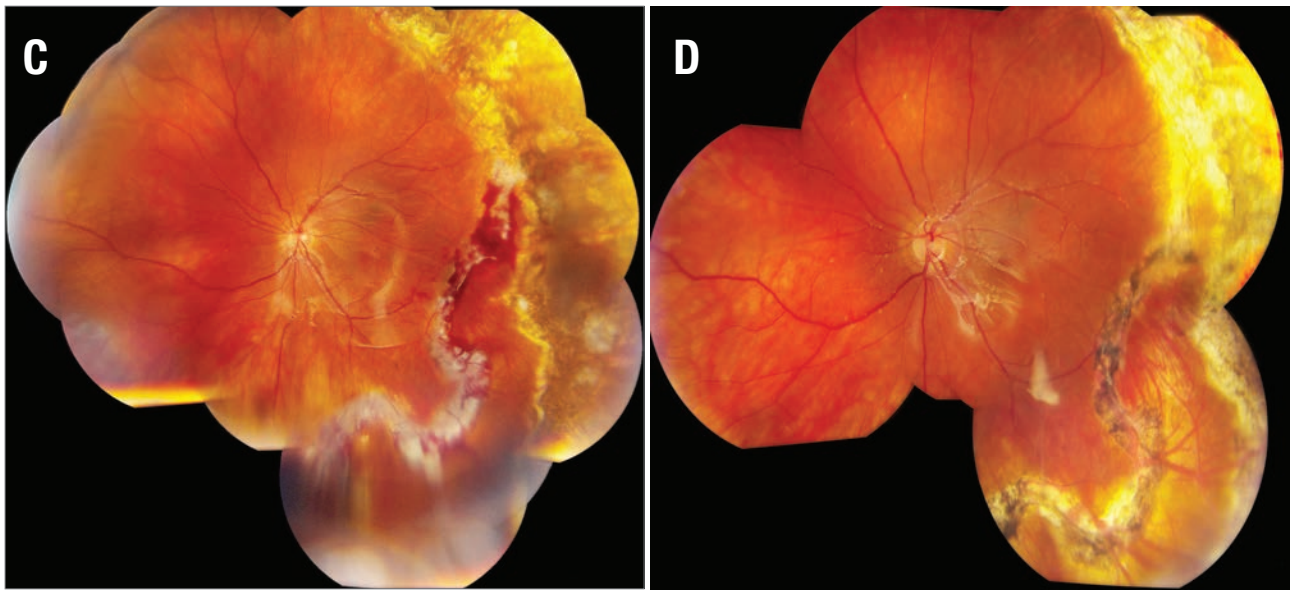


Figure 1. *(See p. 65 for Figures 1A and B.)* Immediately following re-operation, the retina is flat under silicone oil tamponade. Note the margins of the retinectomy temporally and inferiorly (C). Several months later the retina is still attached under oil (D).

another experimental option.[19]

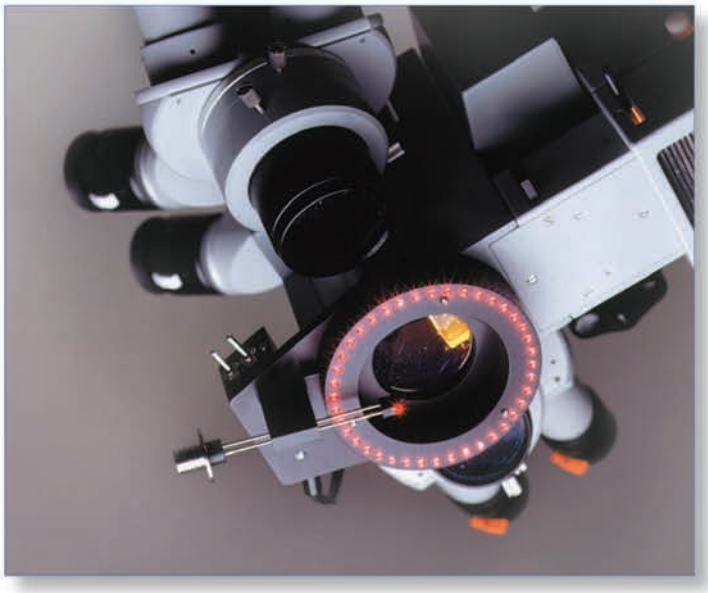
Anti-proliferative agents also seem to be good candidates for activity against PVR given the de-differentiation of mature cell lines and proliferation of the cellular membranes. One of the most tested compounds for PVR has been 5-fluorouracil.[9] 5-FU is frequently used in glaucoma surgery to prevent the scarring associated with filtration procedures, so it has a pre-existing safety profile, albeit externally. Two prospective, randomized studies have been conducted of 5-FU in combination with low molecular weight heparin,[20,21] which were then the subject of a meta-analysis given their differing results.[22] A benefit was shown in subjects at higher risk of PVR,[23] but not in an unselected population,[21] which led the authors of the meta-analysis to urge that further research be conducted only in high-risk individuals.[22]

Retinoic acid, in the form of 13-cis-RA (isotretinoin), has also been tested in several trials. While commonly used by dermatologists for the treatment of acne, isotretinoin was originally developed as an anti-proliferative agent for the treatment of basal cell carcinomas. In a prospective randomized trial of 35 patients,[24] those who received 20 mg daily had higher rates of retinal re-attachment, lower rates of epiretinal membrane formation and higher rates of ambulatory vision after at least one year of follow-up. Additionally, a randomized, placebo-controlled trial is currently under way at the Wills Eye Hospital evaluating the use of isotretinoin for the prevention of PVR in eyes with a primary retinal detachment at high risk for developing PVR as well as in eyes that have already failed primary surgery due to the development of PVR.

Daunorubicin, which inhibits DNA and RNA synthesis, has been tested in a large multicenter, prospective, randomized trial. Anatomical success rates were similar between the Daunorubicin and control groups, and there was no difference in best-corrected visual acuity.[25] Some animal studies suggested a benefit of colchicine in models of PVR, but this was not borne out in a clinical trial in humans.[26] Ribozymes are small RNA molecules that bind and cleave specific target mRNA sequences. One such molecule, VIT100, was tested in a trial of 134 patients with Grade C PVR undergoing vitrectomy, but it was not found to be effective.[27]

Perhaps the most vibrant current research involves attempting to inhibit growth factor pathways, though few human trials have been published.[9] Ranibizumab, well-known to retinal specialists in angiogenic disease processes, has been shown to prevent PVR in rabbit models of disease.[7] Kinase inhibitors work downstream at the intracellular signaling level and may block PVR processes caused by various upstream signals. In the near term, viral vectors may be able to insert genes for soluble receptors to block factors, and commonly used medications like N-acetlycysteine (NAC) may help block indirect platelet-derived growth factor activation through its antioxidant activity,[28] though human data is lacking as yet.

We have learned a great deal about the pathogenesis of PVR over the past decades, but are still unable



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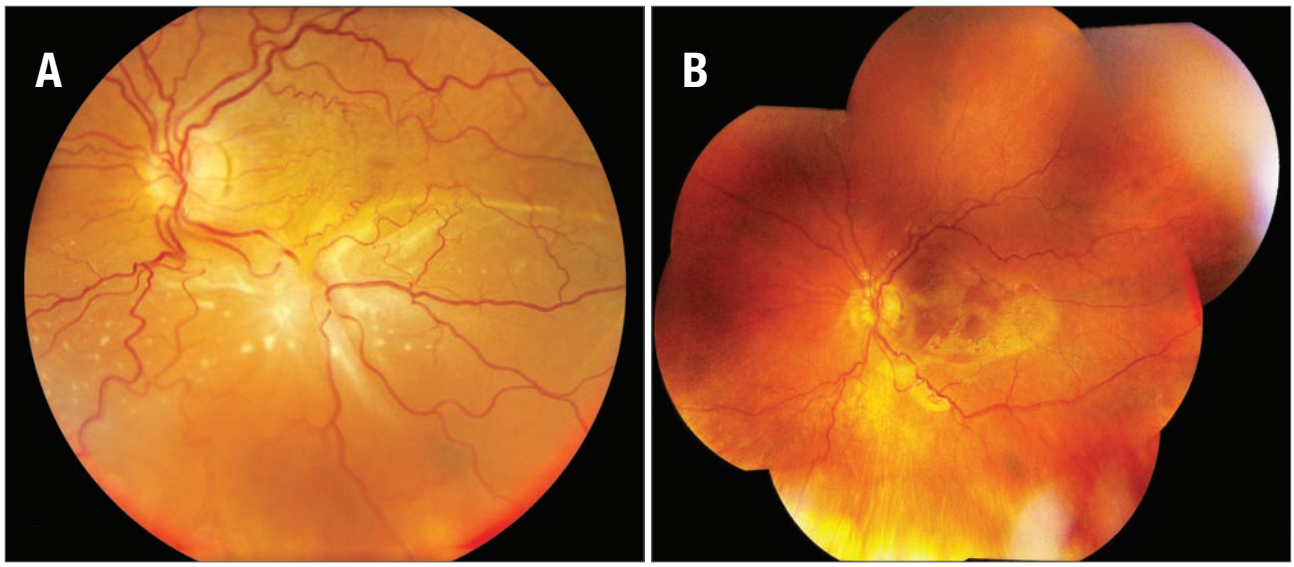

Figure 2. A typical example of a fixed "star" fold preoperatively (A). Postoperatively, the retina is flat under silicone oil (B).

to reliably prevent its occurrence. At the current time, surgery is our only option for dealing with PVR; we do not have any proven surgical adjuvants or medical therapies. Many drugs have been tested and some clinical studies are ongoing, but we have a lot of ground to cover to more effectively treat this devastating disease process. REVIEW

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(continued from page 62)

underwent strabismus surgery with either adjustable or non-adjustable sutures. Mean follow-up was 13.9 months (range: four to 132 months). Patients who achieved the target angle immediately postoperatively had a higher success rate (83.6 percent) than patients who did not (63.7 percent), and when the target angle was achieved, the success rate was similar with adjustable (84.8 percent) and non-adjustable (80.9 percent) sutures. However, it is important to note that patients who underwent adjustable surgery obtained the target angle more often than those who underwent non-adjustable sutures (75.5 percent compared with 54 percent). The success rate for exotropia surgery was significantly higher when the immediate target angle was achieved (86.4 percent) than when it was not achieved (58.7 percent). However, a similar beneficial effect was not shown.

Additionally, a recent review of a large national private insurance database found that adjustable sutures were associated with significantly fewer reoperations in the first postoperative year for horizontal muscle surgery. Additionally, they were associated with more reoperations for vertical muscle surgery, but this observation was not statistically significant in the primary analysis after controlling for age.[4]

In this review, 526 of 6,178 surgical patients required and underwent a reoperation (8.5 percent). Of these reoperations, 8.1 percent were performed in patients who underwent adjustable suture surgeries and 8.6 percent were performed after conventional suture surgeries.

Of the 4,357 horizontal muscle surgeries, reoperations were performed after adjustable suture surgeries in 5.8 percent of cases and after conventional suture surgeries in 7.8 percent of cases. Of the 1,072 vertical muscle surgeries, reoperations were performed after adjustable suture surgeries in 15.2 percent of cases and after conventional suture surgeries in 10.4 percent of cases. Younger age (18 to 39 years) was associated with a lower reoperation rate, and significant multivariable predictors of reoperation for horizontal surgery were adjustable sutures, monocular deviation, complex surgery and unilateral surgery on two horizontal muscles. Adjustable sutures were not significantly associated with reoperation rates after vertical muscle surgery. REVIEW

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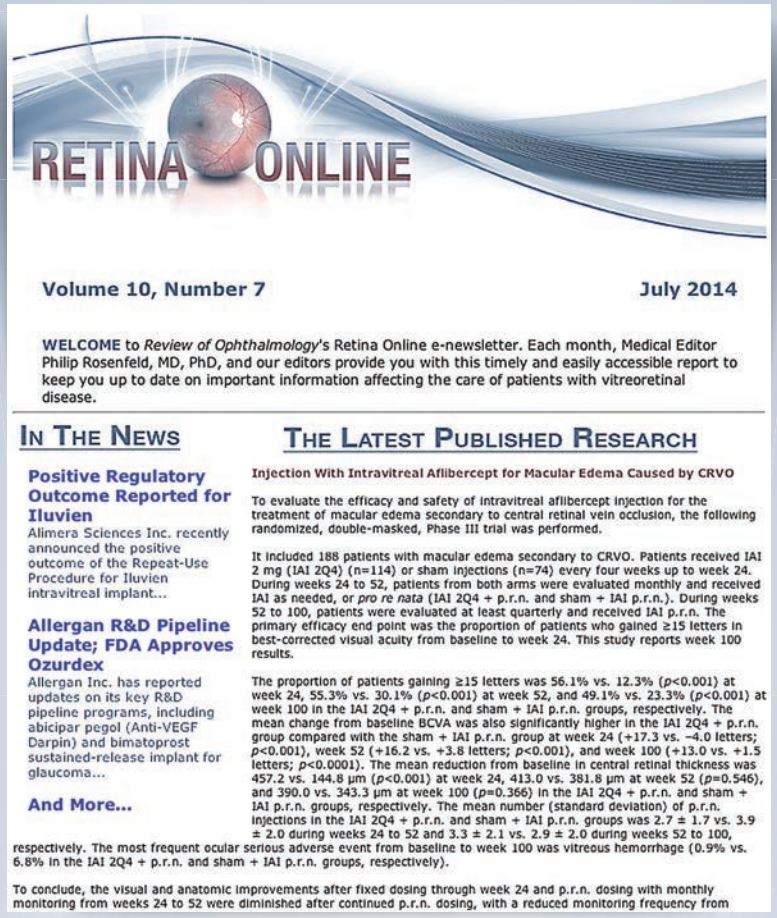

RETINA ONLINE

Volume 10, Number 7 July 2014

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

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THE LATEST PUBLISHED RESEARCH

Injection With Intravitreal Aflibercept for Macular Edema Caused by CRVO

To evaluate the efficacy and safety of intravitreal aflibercept injection for the treatment of macular edema secondary to central retinal vein occlusion, the following randomized, double-masked, Phase III trial was performed.

It included 188 patients with macular edema secondary to CRVO. Patients received IAI 2 mg (IAI 2Q4) (n=114) or sham injections (n=74) every four weeks up to week 24. During weeks 24 to 52, patients from both arms were evaluated monthly and received IAI as needed, or *pro re nata* (IAI 2Q4 + p.r.n. and sham + IAI p.r.n.). During weeks 52 to 100, patients were evaluated at least quarterly and received IAI p.r.n. The primary efficacy end point was the proportion of patients who gained ≥15 letters in best-corrected visual acuity from baseline to week 24. This study reports week 100 results.

The proportion of patients gaining ≥15 letters was 56.1% vs. 12.3% (p<0.001) at week 24, 55.3% vs. 30.1% (p<0.001) at week 52, and 49.1% vs. 23.3% (p<0.001) at week 100 in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean change from baseline BCVA was also significantly higher in the IAI 2Q4 + p.r.n. group compared with the sham + IAI p.r.n. group at week 24 (+17.3 vs. −4.0 letters; p<0.001), week 52 (+16.2 vs. +3.8 letters; p<0.001), and week 100 (+13.0 vs. +1.5 letters; p<0.0001). The mean reduction from baseline in central retinal thickness was 457.2 vs. 144.8 µm (p<0.001) at week 24, 413.0 vs. 381.8 µm at week 52 (p=0.546), and 390.0 vs. 343.3 µm at week 100 (p=0.366) in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively. The mean number (standard deviation) of p.r.n. injections in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups was 2.7 ± 1.7 vs. 3.9 ± 2.0 during weeks 24 to 52 and 3.3 ± 2.1 vs. 2.9 ± 2.0 during weeks 52 to 100, respectively. The most frequent ocular serious adverse event from baseline to week 100 was vitreous hemorrhage (0.9% vs. 6.8% in the IAI 2Q4 + p.r.n. and sham + IAI p.r.n. groups, respectively).

To conclude, the visual and anatomic improvements after fixed dosing through week 24 and p.r.n. dosing with monthly monitoring from weeks 24 to 52 were diminished after continued p.r.n. dosing, with a reduced monitoring frequency from

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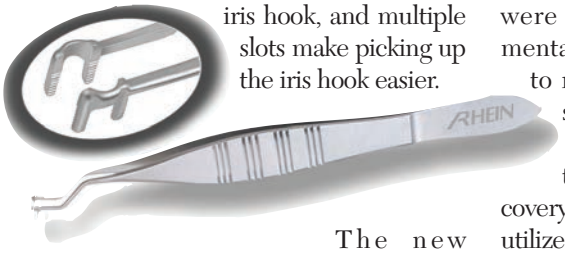
REVIEW® of Ophthalmology

New Surgical Options and Automated Hysteresis

Rhein Medical has introduced two additions developed in coordination with Lawrence R. Goldberg, MD, to its line of surgical instruments.

The new Goldberg Iris Hook Forceps (Product #8-01635) have micro slots in the inner jaws designed to grasp iris hooks for easier and more controlled insertion. These slots are married to the outer diameter of the iris hook, and multiple slots make picking up the iris hook easier.



The new Goldberg Silicone Oil Extractor (Product #91-8052) is designed to remove oil located in the vitreous during cataract surgery due to a retinal detachment repair. The oil migrates to the anterior chamber, where the instrument is used to aspirate it.

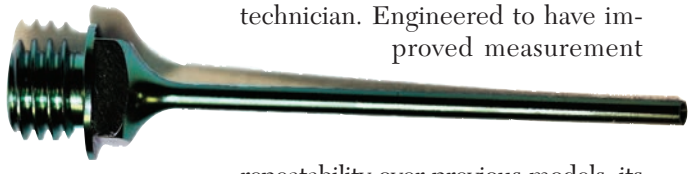
Both instruments are reusable, guaranteed for life, and available for a 30-day surgical evaluation without obligation. Contact Rhein at (727) 209-2244 or rheinmedical.com and enter the product number to see a video of the instrument being used in surgery.

B + L: 23-Ga. Fragmentation Needle for Stellaris

Bausch + Lomb announced the availability of a 23-ga. fragmentation needle for the Stellaris PC Vision Enhancement System. This new ultrasonic needle design is used during vitreoretinal procedures to effectively remove the lens material from the posterior chamber of the eye with balanced irrigation and aspiration through 23-ga. incisions providing enhanced intraoperative control and efficiency.

Prior to its introduction, surgeons were required to use larger fragmentation needles (20-ga.) in order to remove lens fragments during surgery, creating the need for increased incision size, suturing of the wounds and lengthened recovery time. Surgeons are now able to utilize the 23-ga. fragmentation needle to help balance the inflow and outflow in the eye and achieve a sutureless wound closure.

When combined with the Stellaris PC with 23-ga. valve Entry Site Alignment system, this advancement will provide surgeons: use of the existing cannula wound architecture to insert the 23-ga. fragmentation needle into the eye; fluidic and intraocular pressure stability during lens nucleus removal, due to the consistency in gauge sizes for inflow and outflow of fluid; and easy replacement of the original valved cannula in the same wound for completion of the procedure.



For more information on the Stellaris PC Vision Enhancement System, visit bausch.com.

Automated Corneal Hysteresis

Reichert Technologies has launched the Ocular Response Analyzer G3, the only tonometer capable of measuring corneal hysteresis, a superior predictor of glaucoma progression. The instrument also provides the patented Corneal Compensated IOP measurement, which Reichert calls a better indication of the true pressure than Goldmann or other methods of tonometry.

This third-generation Ocular Response Analyzer offers fully automated alignment and unique chinrest-less design for a fast and simple measurement that can be delegated to a trained technician. Engineered to have improved measurement repeatability over previous models, its ability to connect to electronic medical record systems makes patient record-keeping easy and worry-free. A CPT code for corneal hysteresis measurement was authorized effective January 1, 2015. Consult a billing specialist for more information.

Contact Reichert at (888) 849-8955, or visit reichert.com/ora. REVIEW

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The Hows and Whys of Pharmacokinetics

Simple attributes, such as how much drug can reach its target and how long it stays there, make a big difference in outcomes.

Mark B. Abelson, MD, CM, FRCSC, FARVO, Andover, Mass.

We tend to think about drugs as magic bullets, the keys for the locks, chemical agents on a quest. But, as in life, in therapeutics sometimes the most important thing is just showing up—and hanging around for a while. The mundane issues of drug absorption, distribution, metabolism and elimination have been discussed to death, but they are often the factors that determine treatment success or failure.

Ophthalmologists make decisions every day about whether to prescribe a solution, suspension or ointment; whether the route of administration should be topical, injected or systemic; or whether the dosing regimen can be once-daily, more than once a day or through an extended-release platform. These decisions are as key to the treatment plan as the choice of medication, and are informed by a fundamental understanding of ocular pharmacokinetics (PK).

This month we examine the principles that underlie these therapeutic decisions. In an upcoming column we'll examine how the modulation of drug PK behavior has become a factor in the development of new drugs.

Pharmacokinetics Explained

Pharmacokinetics seeks to understand what the body does to a drug in order to establish a quantitative relationship between administered dose and dosing regimen and the concentration of the drug in plasma and/or in tissue.[1] This relationship allows maximal efficacy to be balanced against minimal toxicity. The studies that provide PK data for drug approvals are strictly controlled and provide a generalizable result to guide prescribing physicians. Given that each patient who presents in the clinic is unique and has a disease etiology that's likely to be unique as well, the treating physician must be prepared to apply his understanding of how the drug works to each case.

As the name implies, pharmacokinetics is about time, but it is also about dose, and the relationship between the two. For every drug or formulation, there is a relationship between dosing and drug exposure. The sum total of that exposure, or the "area under the curve" of the concentration versus time curve, dictates that exposure and the opportunity for drug efficacy.

All drugs targeting ocular tissues, regardless of their route of administration, must contend with anatomical and physiological barriers to deliver a safe and effective dose to the target tissue.[2,3] How those drugs overcome those barriers has implications for patient adherence to treatment, which, in turn, affects treatment success.

Systemic Administration

Systemically administered drugs, particularly those administered orally, are subjected to first-pass metabolism by the liver, where the concentration of the drug is reduced prior to entering the bloodstream. Following transport in the bloodstream, a drug seeking to reach target ocular tissues encounters the blood-retinal barrier. Composed of retinal capillary endothelial cells and retinal pigment epithelium cells, the blood-retinal barrier restricts the flow of drugs from the blood to the posterior segment. The outer layer of the barrier, which consists of the RPE, restricts intercellular permeation due to its tight junctions.[2] While drugs can easily enter the choroid due to its high vasculature, the tight junctions of the RPE restrict drug from further trans-

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port into the retina. Less than 2 percent of the systemically administered drug reaches the target ocular tissue following the first-pass metabolism and permeation of the blood-retinal barrier.[2]

Systemically administered ophthalmic drugs benefit from high patient treatment adherence due to the relative simplicity of the dosing regimen in terms of frequency, ease of administration and non-invasiveness.[2,4] Despite this considerable benefit, systemically administered drugs must compensate for the loss in concentration experienced during absorption, metabolism, distribution and excretion. Consequently higher dosages of the drug have to be administered, which also increases the risk of systemic toxicity, making the option less desirable.[5]

Topical Administration

At a weight of approximately 8 g, the eye is a relatively small target for systemic drug delivery.[6] Topical ocular drugs have the advantage of directly targeting the eye, while avoiding first-pass metabolism. Despite this, other sophisticated barriers exist to impede delivery of drug to ocular tissue.

Upon instillation, topical ocular drugs must contend with spillage, dilution, blinking and drainage, as well as basal and reflex lacrimation. The eye can hold approximately 10 to 15 µl, which is considerably smaller than the typical eye drop volume of 40 µl. This imbalance results in an initial loss of drug to overflow. Any drug remaining on the surface is diluted by the tear film where albumin and other proteins may bind to the drug, further reducing drug concentration. Within a few minutes, the healthy tear film turns over, replacing itself entirely, so whatever drug is not absorbed by the cornea and conjunctiva drains down the nasal lacrimal duct. Consequently, the contact time of the drug with the cornea, conjunctiva and sclera is brief.

If a patient can suppress her blinking for four to six seconds prior to instilling a drop, the breakup of the tear film that results can give the drop better access to the ocular surface.

The cornea is the primary path for drugs to penetrate from the tear film to the anterior segment. The corneal epithelium is highly lipophilic, posing a significant barrier to topically administered hydrophilic drugs, and the superficial epithelial cells are surrounded by tight junctional complexes that permit only small-molecule drugs to permeate transcellularly from the tear film.[2,7,8] The stroma is the next barrier, and it is hydrophilic, restricting further permeation of highly lipophilic drugs passing from the epithelium. Additionally, enzymes present in the cornea act to metabolize drugs before they further penetrate into the eye. The combination of precorneal and corneal barriers results in less than 5 percent of the instilled drug penetrating the cornea and reaching intraocular tissues.[9]

Though the conjunctiva also has tight junctions, the intercellular spaces are slightly larger than those in the cornea.[3] While this allows better penetration by larger molecules, the presence of conjunctival blood capillaries lowers bioavailability of drug through elimination via systemic blood circulation.[2]

Drug that permeates these barriers must continue through the blood-aqueous barrier, which is composed of the endothelial cells in the uvea. Similarly to the cornea and conjunctiva, the blood-aqueous barrier is controlled by tight junctions. Drug that diffuses into the aqueous humor is then eliminated by aqueous turnover and by the blood flow of the anterior uvea.

Due to the direct targeting, eye drops result in a higher bioavailability than systemically administered drugs, especially in the anterior chamber. Drops that require no more than q.d. or b.i.d. dosing promote patient treatment adherence through a simplified treatment regimen, lower toxicity and fewer side effects.[9] However, if instillation of a drop is challenging or if it's associated with transient effects such as stinging or blurring of vision upon instillation, treatment adherence can be detrimentally affected.

Injections

Topical eye drops can effectively impact anterior segment targets, but barriers limit their ability to reach posterior segment targets. As a result, delivery of drug to posterior segment targets often involves subconjunctival, sub-Tenon's and peribulbar injection or comparatively more invasive administration via intravitreal injection. These methods avoid many of the barriers posed by topical and systemic routes, but effective delivery of the drug in this manner isn't obstacle-free.

Drug can be injected into the subconjunctival, sub-Tenon's or peribulbar space to create a depot for extended drug release, which bypasses the barriers posed by the tear film and corneal-conjunctival barriers. Upon release, however, the drug must pass through the sclera, choroid and RPE and it must contend with elimination by blood and lymphatic circulation, which rapidly lowers the bioavailability of the drug.[10,11] Drugs injected intravitreally must diffuse through the vitreous to the retina, where they must permeate the retina and the RPE to reach the choroid. The retina limits the passage of macromolecules, while

the tight junctions of the RPE further restrict passage of hydrophilic compounds.[3,12] Larger molecules are primarily eliminated via the annular gap between the lens and the ciliary body, while smaller or lipophilic molecules are eliminated by the retina-choroid-sclera membrane.[13]

When compared to systemic and topical delivery, periocular and intravitreal injections are efficient methods of delivering drug to the posterior segment at sustained drug levels.[2] But while these methods require fewer doses over time, they are associated with more complications, such as subconjunctival hemorrhages, endophthalmitis, traumatic cataract, rhegmatogenous retinal detachment and RPE tears associated with intravitreal injections.[14] These complications can discourage patient treatment adherence when prolonged treatment regimens of repeated doses are required.

Treatment Considerations

Bioavailability of drug in the eye is negatively affected by barriers to penetration, drainage, dilution and metabolism. To overcome these obstacles the clinician needs to consider methods to improve bioavailability by selecting drugs or treatment methods that enhance penetration to the target tissue or that increase dwell time. Patient acceptance of the chosen drug and treatment method is a significant consideration as well. If the safety profile of a drug raises patient concerns about its risk/benefit ratio, or if the treatment regimen is too complicated or challenging, then treatment adherence is at risk and may render the most effective drug ineffective in practice.

Historically, topical ocular drugs have been the most convenient treatment for anterior chamber diseases, with choices ranging from solutions, emulsions and suspensions to ointments and gels.[7] Compared to solutions, emulsions and suspensions, ointments and gels increase bioavailability through prolonged ocular contact time. However, the increased viscosity tends to also lead to temporary discomfort and transient blurring of vision. Even temporary and minor side effects such as these can reduce patient adherence.

Within the last decade researchers have explored several novel drug-delivery approaches aimed at reducing the need for frequent dosing. Prodrugs and cyclodextrins have been studied as a means to improve ocular penetration of drug, while various colloidal delivery systems have been studied as a means to prolong the duration of drug action.[7] These developments are significant and are likely to change how we treat ocular disease. We will explore these developments in the near future.

As researchers continue to look for effective ways to deliver drugs to target tissues, there are some practical tips for the clinician to consider when prescribing topical drops. First, consider manual punctal occlusion. Since a significant amount of drug in an eye drop drains through the nasolacrimal ducts, manually occluding the puncta increases contact time of the drug with the ocular surface and minimizes systemic absorption, which is an important consideration where systemic side effects are of concern. Second, consider recommending the patient hold the eye open for a few seconds before administering a drop. This allows the average tear film to break apart, reducing the effectiveness of the pre-corneal barrier and allowing the drug to penetrate more quickly. Third, properly instruct patients on how and why they should instill their medication. Treatment adherence is not only taking medication when one is supposed to but also taking it in the specified manner. Eye drops can be challenging to self-administer, especially for elderly patients. This may result in the unintended result of patients taking more than the specified number of drops. Patients may also believe that taking more drops is better. In both instances, given the restricted volume of the lacrimal lake, additional drops are wasteful and could lead to contact dermatitis from excess spillage. Also, if more than one topical ocular drug is prescribed, patients should wait several minutes before instilling the second medication to avoid washing out the first.

Treatment success is often a matter of drug selection and treatment adherence. Ophthalmologists who understand basic ocular pharmacokinetics can make the most informed choices about drug formulation, mode of instillation and dosing schedule as they relate to the specific requirements of the patient. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at the Harvard Medical School, and emeritus surgeon at the Massachusetts Eye and Ear Infirmary.

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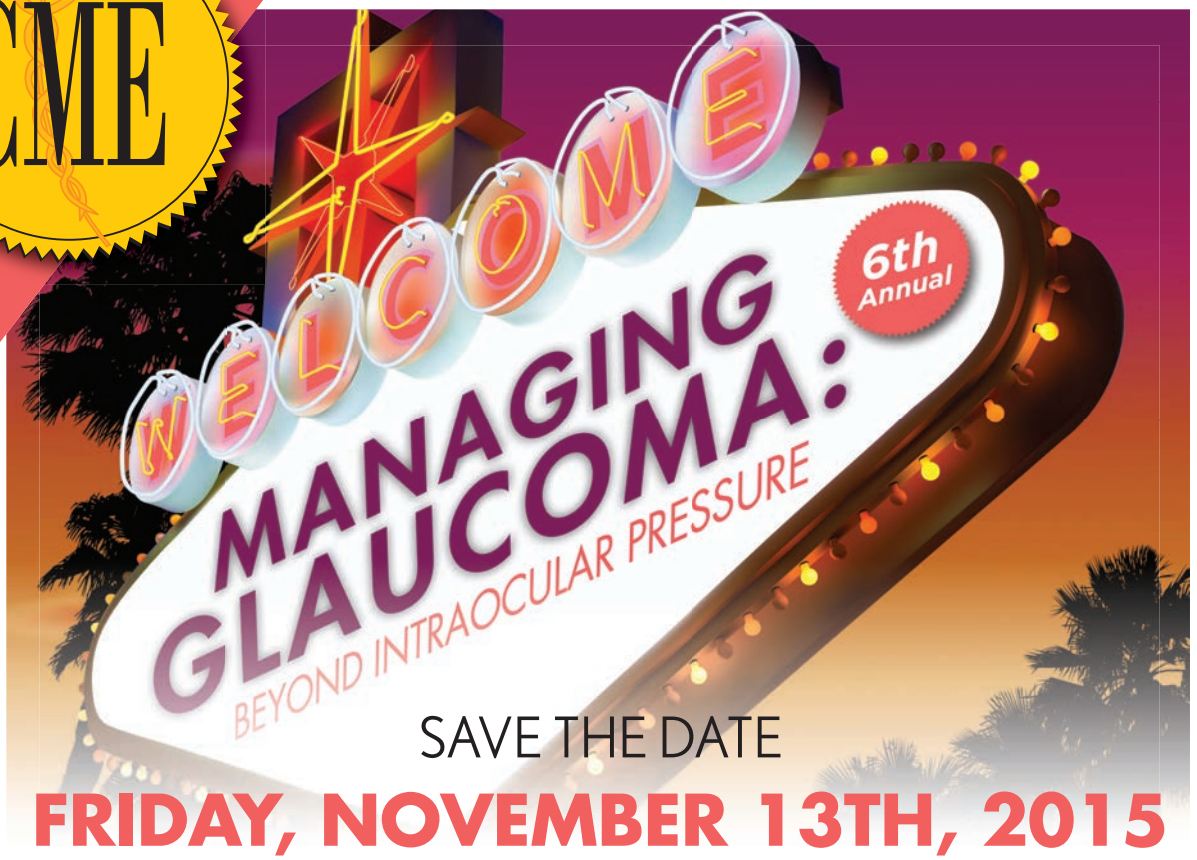

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Glaucoma Surgery 101: Tips and Pearls

Sometimes small changes can make surgery go more smoothly. One surgeon shares some of what she's learned.

Michele C. Lim, MD, Sacramento, Calif.

As glaucoma surgeons, each of us has had a unique set of experiences. Partly for that reason, it's useful to trade ideas and techniques that we've picked up along the way. I was recently asked to share some of the things I've learned in my years as a surgeon, and in that spirit, I'd like to share a few of the pearls that came to mind.

Surgical Exposure

Good exposure of the surgical area is crucial for success. If you don't take the time to get good exposure, the rest of the case becomes difficult because it's hard to see, and hard to gain access with your instruments.

Two key exposure-related factors will affect your surgery:

• ***Choice of eyelid speculum.*** The eyelid speculum you choose will make a big difference in the amount of exposure you can achieve. Most cataract surgeons use a standard wire speculum; that's fine for cataract surgery because you don't need a great deal of exposure for that type of surgery. However, in glaucoma surgery you may be working 8 to 9 mm posterior to the limbus. My eyelid speculum of choice is the Lieberman lid speculum, which is adjustable and can be widened to achieve the access you want.

• ***The traction suture.*** This is placed into the cornea to provide leverage to pull the eye downward so that we can access the superior part of the globe, which is the area of interest when placing glaucoma drainage devices or in limbus-based trabeculectomies. I use a double-armed 7-0 vicryl suture for the traction suture; I pass the needle through the cornea superiorly.

The key caveat when placing a traction suture is to make sure that you stay in the corneal stroma and avoid passing the needle too deep, which can lead to penetration of Descemet's membrane, creating an opening into the anterior chamber. It's not always easy to avoid this. Sometimes you can see that you've punctured Descemet's or you can feel a little pop, but you can't always see it or feel it. I always take a Weck-Cel sponge and dab the entry and exit point of my traction suture to see if aqueous is leaking.

If you realize that you've punctured Descemet's, you can take the traction suture out and place it somewhere else. But if you don't recognize it, the globe will soften and the anterior chamber will shallow as you proceed with the surgery. If that happens, you'll need to remove the traction suture, and you may need to make a paracentesis incision to reform the anterior chamber.

When handling the conjunctiva it's important to avoid using forceps with teeth. Three safe options are (left to right) Hoskins forceps; Lim conjunctival forceps; and tying forceps.

Block With Caution

Although topical anesthesia can be used in many surgical situations, anesthesia can also

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be achieved via a retrobulbar block. However, if you do choose to go with a block, be careful when deciding what volume you'll inject into the orbit. When I was a resident doing cataract surgery, I would usually inject 5 or 6 ccs of anesthetic. What I didn't initially realize was that different people have different-size orbits; Asians, for example, may have smaller orbits than Caucasians. One of my patients who received anesthetic retrobulbar block had a very long, proptotic, myopic eye; at the end of the case we couldn't close his eyelids. We ended up having to do a lateral canthotomy.

Today, I look carefully at each patient's anatomy and titrate the block accordingly. If the patient has a small or shallow orbit or tight eyelids, I minimize the amount of block I push. (Feeling the eye to get a tactile sense of the orbital pressure can help avoid injection of too much anesthetic.) I usually end up infusing about 3 cc into this type of orbit, or I switch to topical anesthesia.

Respect the Conjunctiva

Respecting the conjunctiva means handling it very gently. As a glaucoma surgeon, you should avoid handling the conjunctiva using forceps that have teeth. 0.12 forceps are commonly used for many purposes in ophthalmology, but they have sharp teeth at the end for grabbing; you can punch a hole in the conjunctiva if you use forceps like that, and doing so will pretty much ruin your surgery.

The picture on the facing page shows three types of non-toothed forceps that can safely handle conjunctiva. Hoskins forceps have a very fine tip with a little notch at the end that helps you grab tissue without poking a hole in it. Another option is a pair of conjunctival forceps I designed during my fellowship, called the Lim conjunctival forceps. They have a thicker tip with a crisscross pattern that helps you grip suture or conjunctiva without making a hole. The third option is tying forceps, which you might find in any tray of surgical instruments. They have very tapered, thin ends, with no teeth or pattern. In general, the main concern is to avoid toothed forceps.

One other point: When you're using forceps to move tissue around, or holding the conjunctiva for exposure, don't jerk on the tissue or pull it too hard; you can tear it or buttonhole it.

When holding conjunctiva or other tissue during surgery, keep looking into the microscope when you're passing off or receiving instruments from your scrub tech. Looking at the technician or your hand can cause your body to shift, potentially tearing the tissue you're holding.

Handoff at the Microscope

When you're passing off instruments or a suture to the scrub tech, don't turn away from the microscope to look at the scrub tech. Turning to look is the natural impulse, but you want to keep your eyes on the surgical field through the microscope. In a normal social situation, this would be rude, but in the OR it's expected; it's something all very efficient surgeons do. The scrub tech will take the instrument out of your hand. *(See picture, above.)* When you ask for the next tool—and in many cases a good tech will already know what you need—he or she will place the tool in your hand without you having to look up.

There are two good reasons for doing it this way. First, it's more efficient and fluid to not look away; you're not wasting time looking and stopping and looking and stopping. Second, it's a safety issue. When you need to hand off or receive a tool, your other hand may be holding the conjunctiva or the trabeculectomy flap or some part of the eye that's delicate. If you look away from the scope, your body will tend to shift with you, and you could inadvertently tear the tissue as your body moves.

A good analogy is bicycling down a road. If you're looking straight in front of you, the bike travels straight down the road. But if something on the side of the road catches your interest and you look at it, your bike will veer off-course.

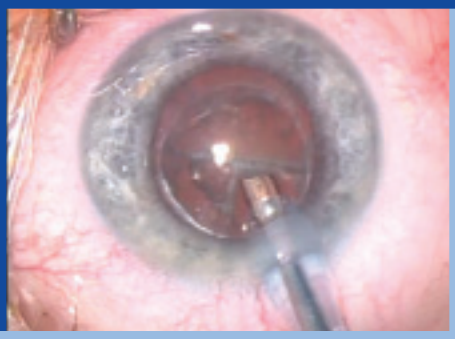
Fortunately, like athletes, surgeons are usually well-aware of the location of their bodies in space, and where things are in relation to them. Achieving a smooth handoff is a goal all surgeons should strive for.

Incisions: Fornix vs. Limbus

When performing trabeculectomy surgery, the surgeon must decide whether to use a fornix- or limbus-based incision. It's important for people doing glaucoma surgery to consider the differences between these options, because each has pros and cons.

First, it's important to define the terminology, which unfortunately is confusing. When the incision is made at the limbus, it's referred to as a fornix-based conjunctival incision, or peritomy. This type of incision involves dissecting a pocket posterior to the incision. It's called a fornix-based conjunctival incision because the base of the flap is in the fornix.

The converse of that is the limbus-based conjunctival incision, in which



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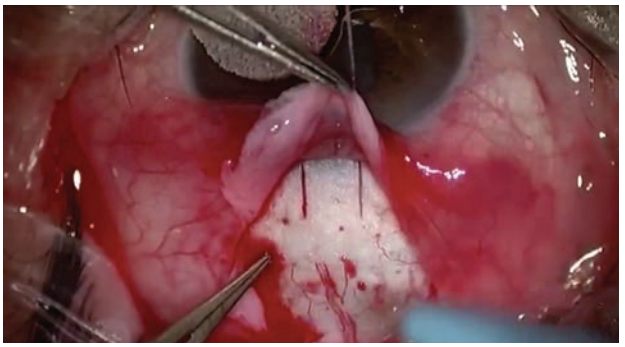
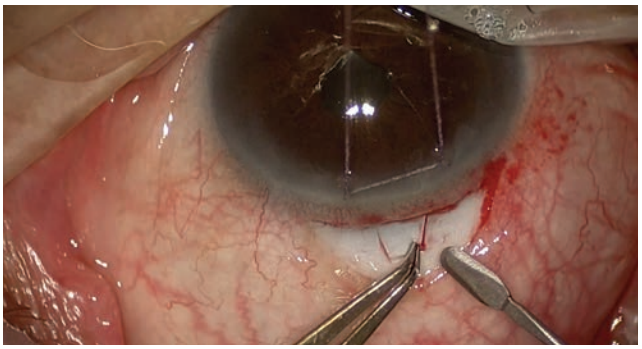




Limbus-based flaps (left) and fornix-based flaps (right) have different advantages and drawbacks. Limbus-based flaps require more dissection and help from an assitant but minimize the chance of postoperative leakage and are more comfortable for the patient. Fornix-based flaps are faster and easier to make, but are less comfortable for the patient and more prone to leakage.

you make the incision 8 or 9 mm back in the fornix. Here, you make the cut in the conjunctiva and dissect forward toward the limbus. It's called a limbus-based conjunctival incision because the base of the flap is at the limbus. *(See examples, above.)*

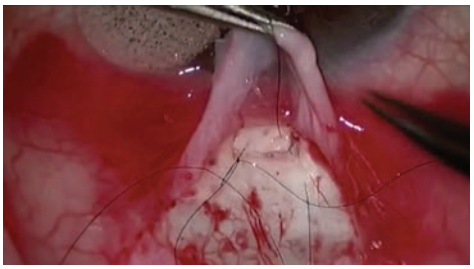
The benefits of using a fornix-based incision are that you have better exposure at the limbus to dissect your scleral flap, so it's a faster dissection of the conjunctiva and you don't need a lot of assistance. The cons include that it's harder to close this type of incision because you're right at the limbus. If the conjunctiva is fragile, you have to be careful; if you punch a hole in it, it will leak. And even if you do get good closure, sometimes you'll get a leak at the closure site postoperatively.

The benefits gained with a limbus-based incision include the absence of any problem with leakage postoperatively, unless you buttonhole the tissue, because the closure is way back in the fornix away from where the eye is exposed. There's more comfort for the patient because you don't have sutures right at the limbus where the patient can feel them. The downside of a limbus-based incision is that it requires a little more dissection of the conjunctiva for good exposure, and it requires you to have an assistant to hold the conjunctiva out of the way while you dissect the scleral flap for the trabeculectomy. You have to weigh the benefits and the drawbacks when deciding which approach to use. (After placing the lid speculum, a quick check of the exposure with calipers can help guide the decision for the type of incision. If the exposure is less than 8 to 9 mm, the choice is limited to a fornix-based flap, with the incision at the limbus.)

Suture Knot Technique

Two techniques can help you avoid problems when making knots in your suture.

First: Throw the needle off the field. I learned this technique from Paul Palmberg, MD, PhD, at Bascom Palmer. Many surgeons pass the needle through the tissue, pull the suture through and then drop the needle on the field close to where they're working. The drawback to this is that it allows the suture to curlicue onto itself on the field. It becomes all bunched up. Then, when you go to do your next throw or knot, the suture gets tangled up. I've watched residents struggle with this when suturing. Throwing a knot with a tiny suture is frustrating enough by itself; if you allow the suture to get bunched up on itself, it's much more difficult.

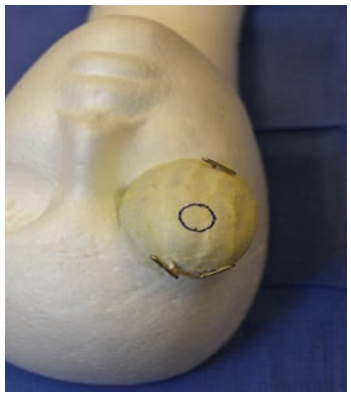


After pulling the needle through the tissue, set it down away from the field, pulling the suture straight. This prevents suture tangling (see above) which makes tying a knot more difficult.

Throwing the needle off the field means that once you pull the needle through, you set it down away from the field, pulling the suture straight. Then, when you make your next move, the suture goes the way you want it to go; it doesn't tangle up on itself. This is a very simple concept, but it works. (You can see a video illustrating this technique at https://www.youtube.com/watch?v=b91iKGnm9og.)

Second, learn to make a slipknot. When you tie a monofilament suture like 10-0 nylon into a slipknot, it doesn't lock down immediately. This is an advantage when performing trabeculectomy. You make a flap and a little incision into the anterior chamber to allow aqueous to come out; then you close the flap with a suture. But you don't want to tie the flap down very tight, because you'll get no flow. With a slipknot, you can adjust the tension of the suture on the flap until you get the flow you want. Then you can finish tying the knot and make it permanent. (You can see a video of this technique on YouTube at https://www.youtube.com/watch?v=bMzXAPOCg98.)





Practicing surgery on animal or cadaver eyes may not duplicate the feel of surgery on live human sclera. The white rind of a lime is closer to the correct texture, making it ideal for this purpose. After the green skin is removed, a circle marks the "cornea" for reference during practice.

Consider Injecting MMC

Mitomycin-C is commonly used during trabeculectomy surgery because of its ability to reduce scarring, which can undo the beneficial effects of the surgery by blocking the new outflow path the surgery has created. The traditional way of delivering mitomycin-C is by sponge, but at our practice we now deliver MMC by injection. Although this method is still not widely used, our surgical results have been just as good as when applying MMC in the traditional way, and this approach has some significant advantages over the Weck-Cel sponge method.

The first advantage is time; sponges soaked with MMC must be allowed to sit on the eye for several minutes. Injecting MMC takes about 30 seconds, which is a significant amount of time-savings during surgery. Second, there's no danger of losing sponges or having sponge material retained in the eye, which has been reported in the literature. Third, you know exactly what dose of MMC you're delivering because you know the volume and concentration you've injected. Fourth, the MMC can be spread as diffusely as you wish, helping to create a low-profile, diffuse bleb.

For more about this technique, see *Mitomycin-C: The Injection Alternative* in the October 2014 issue of *Review*. You can also watch a video of this technique on YouTube at: https://www.youtube.com/watch?v=LxmHd136FOs.

Practice Makes Perfect

Especially for beginning surgeons, practicing techniques outside of the OR is crucial. But for practice to be most helpful, it's important to create conditions that are very similar to those you'll encounter during real surgery. Usually when residents and fellows practice their technique in a wet lab, they work on pig eyes, sheep eyes or cadaver eyes. But those tissues are dead; they don't always react the way living tissue does. Amazingly, some food items do, leading to what I call the "whole foods approach" to glaucoma surgical practice.

For example, to practice scleral surgery, you can use what I call the "Lim lime" technique. The white rind of a lime has a texture very close to that of a human sclera. To practice your surgical technique, find a lime that has a good thick rind on it; peel off the green skin, leaving as much white rind underneath it as possible. Then tack the lime down so it can't move. (We place the lime into the eye sockets of the foam heads in our resident practice lab.) If you have an operating microscope to use, that's great; otherwise you can use a pair of loupes.

Once you're set up, you can practice cutting trabeculectomy flaps in the lime. We take a marker pen and draw a circle the size of a cornea; residents cut their trabeculectomy flap using the marked circle as their starting point. They use practice surgical instruments just as they would in the OR, and they can practice their moves over and over. (Needless to say, the practice area smells much better when practicing on a lime than when practicing on pig or sheep eyes. And when the session is over, you have the option of using the lime to make a margarita.)

The other thing we do as part of the whole foods practice approach is to use raw chicken parts that have their skin still on. We make incisions in the chicken skin that mimic the patterns of conjunctival incisions we make during glaucoma surgery. We use bigger suture material with the chickens, just because we're working on a more macroscopic scale.

It's All in the Details

All of the suggestions in this article are very small, easy, practical things that can be employed right away to make your next case a smooth one. As the great John Wooden, legendary basketball coach of the UCLA Bruins, said, "It's the little details that are vital. Little things make big things happen." REVIEW

Dr. Lim is professor of ophthalmology and vice chair and medical director of the UC Davis Health System Eye Center in Sacramento.

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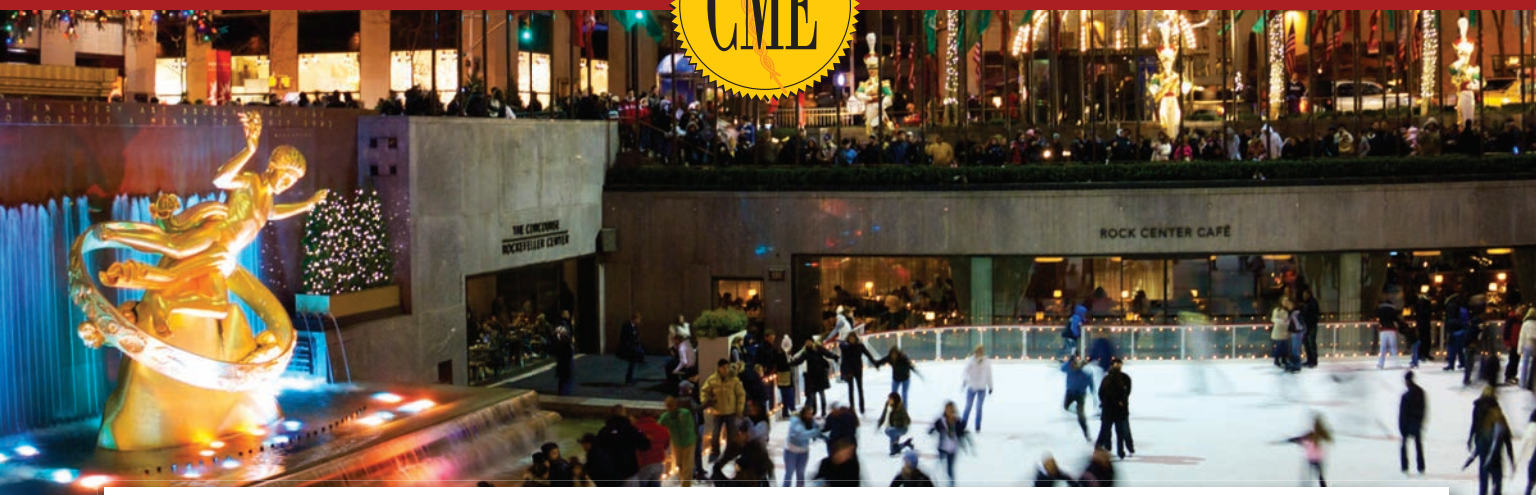

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Tackling Toric Lenses After PK Surgery

In properly selected transplant patients with astigmatism that's not too irregular, toric lenses can yield good results.

Walter Bethke, Managing Editor

The predictability that makes toric intraocular lenses so popular for run-of-the-mill cataract patients also makes them useful in certain post-penetrating keratoplasty eyes, since astigmatic keratotomy can be unpredictable in these patients. The key to getting good results, however, lies in selecting the right patient, setting expectations and then taking the appropriate steps during surgery. Here, surgeons well-versed in placing toric lenses in PK patients discuss what you need to know.

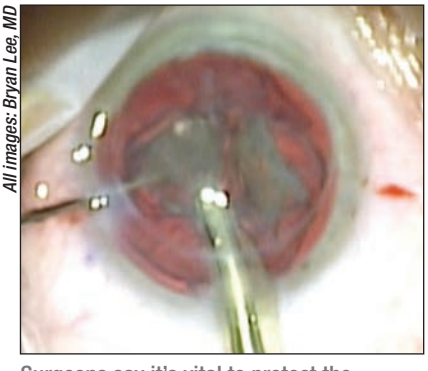
The Preop Process

Implant surgeons say that proper patient evaluation and education increase the odds of a good outcome.

The first consideration that needs to be dealt with is the inherent differences between the type of astigmatism the patient has and the type of astigmatism the toric lenses were designed to correct. "Toric lenses are useful for treating regular corneal astigmatism," says Kevin Miller, MD, chief of comprehensive ophthalmology at the Jules Stein Eye Institute at the University of California, Los Angeles. "When a post-PK patient has symmetrical astigmatism and the astigmatism is stable—and that's a big issue with these corneas—then a toric lens might be appropriate if there is a significant amount of astigmatism."

Bryan Lee, MD, of Los Altos, Calif., says it may take some time for the eye to become stable, but it's a crucial element to achieving success. "The patient should be one in whom the transplant appears to be able to last a while, you know you're not going to have to do anything with the sutures and the cornea looks really good," he says. "Ideally, the sutures should be out for three months or so, though that's not a hard-and-fast rule. If you're unsure, repeat your measurements to make sure they're stable. Also, the patient must have realistic expectations and know that your biometry beforehand will be limited and that you're doing something with the IOL that's off-label, since patients post-corneal transplant have, by definition, irregular astigmatism, and the toric lens is labeled for patients with regular astigmatism."

All images: Bryan Lee, MD



Surgeons say it's vital to protect the corneal graft in the post-PK patient undergoing cataract surgery.

Matthew Wade, MD, assistant clinical professor of cataract, cornea and refractive surgery at the Gavin Herbert Eye Institute, University of California, Irvine, says it's important to inform the patient about possible complications. "Have a frank discussion with the patient regarding the risks of intraocular surgery to the graft." he says. "The patient should be informed that if the graft needs to be repeated in the future, the spherical and cylindrical power of the lens likely won't match the new cornea and the lens may need to be exchanged. "If a graft fails, keep in mind that a DSAEK or a DMEK graft can be placed underneath it. This preserves the same anterior surface

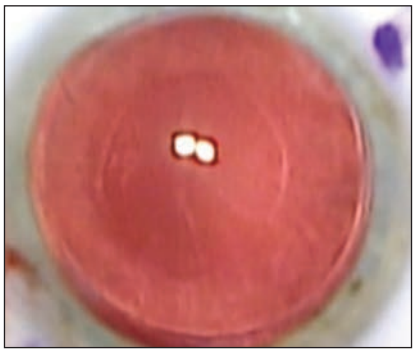
astigmatism that the toric IOL is treating. We haven't seen any graft failures yet in our cohort of patients with PKPs who have received toric IOLs."

Surgeons say the ultimate goal isn't to get a hyper-accurate correction of the astigmatism, but simply to knock down the bulk of it so the patient can be comfortable wearing spectacles. "If there's so much irregularity or irregular astigmatism in the cornea postop that the spectacle correction of their remaining cylinder won't be satisfactory, and therefore the patient will have to go back to—or start—wearing a rigid contact lens that's the rub," says Dr. Miller. "This is because when putting a toric lens in an eye to correct the corneal cylinder, that toricity will show through into the spectacle plane when you cover the cornea and nullify the corneal astigmatism with the rigid contact lens. So, the patient will be really unhappy if you correct the cylinder inside the eye and he has to wear a rigid contact lens as well as spectacles to correct the astigmatism that you put in the eye with the toric lens."

Dr. Miller says you can catch some clues as to who will be happy with his result postop. "If a patient has just had a transplant and is wearing a rigid contact lens to get the best vision, and thinks the quality of vision from spectacles is too low, that patient is highly likely to appreciate and demand really crisp vision after his cataract comes out," he says. "He may not be a good candidate for a toric lens. However, if someone has dry eye and isn't going to wear a contact lens no matter what, he is an ideal candidate for a toric IOL even if he's got a fair amount of irregular astigmatism."

Tips for Surgery

Surgeons say the cataract extraction and IOL implantation actually proceed in a fairly standard fashion with these patients, though the presence of the graft needs to be accounted for.



Cataract incisions in graft patients should be peripheral, well away from the graft incision, surgeons say.

Dr. Wade says maintaining visibility is important in these cases. "Visibility through the graft can often be difficult so I have a low threshold for using trypan blue," Dr. Wade says. "One nice way to keep the trypan away from the endothelium is to place it under Healon 5. During phaco I use extra viscoelastic to protect the endothelium. I place corneal cataract incisions as far away from the graft as possible. Also, I always place a suture in these patients as the corneal biomechanics are altered due to the corneal transplant. I'll leave the suture in for a few weeks."

Dr. Lee says the choice of viscoelastic may be a factor in certain cases, and that a dispersive type is probably best. "One consideration is, if you're using the ORA intraoperative aberrometer, mixing viscoelastics and probably even using a dispersive viscoelastic may affect the accuracy," he says. "I'd probably still use a dispersive viscoelastic though, because I think it's more important to protect the transplant."

Results to Expect

Even though these eyes have issues, and the bar for sharp vision isn't as high as in a normal eye, surgeons have found that the results can still be more than satisfactory in the right patient.

Dr. Wade and his colleagues reviewed cases of toric IOLs in post-PK patients and found that the predictability of postoperative manifest astigmatism correction was good.[1] "We had 21 eyes in the study, and 16 were 1 D or closer to the predicted postop manifest astigmatism," he says. "The predicted astigmatism tries to take into account that we can only treat 4 D at the corneal plane with the toric IOLs we have available to us in the United States. The 4-D limit is one limitation of using toric IOLs to correct post-PK astigmatism."

In another paper, this one from a group in New Zealand, researchers retrospectively analyzed 26 post-PK eyes that received either an Alcon AcrySof toric lens or a Rayner T-flex. At a follow-up of 14 months, the mean spherical equivalent decreased significantly from -3.67 to -0.58 D, and the astigmatism decreased significantly from -5.49 to -2.61 D. The surgeons were able to correct greater amounts of astigmatism since they had access to higher cylindrical lens powers that aren't available in the United States.

In terms of vision results, in the study there was a significant improvement in the average uncorrected distance acuity from 1.12 to 0.45 logMAR (a little worse than 20/200 to just worse than 20/50). The best-corrected distance acuity improved from 0.70 to 0.15 logMAR (20/100 to a little worse than 20/25).[2]

In the right patient, Dr. Wade says that a toric lens offers benefits that an incision can't match. "When you place a toric IOL in a post-PK patient," he says, "you're not only correcting the astigmatism, but the spherical refractive error, as well." REVIEW

Dr. Miller is a consultant for Alcon. Drs. Wade and Lee have no financial interest in the products mentioned.

1. Wade M, Steinert RF, Garg S, et al. Results of toric intraocular lenses for post-PK astigmatism. Ophthalmology 2014;121:3:771.
2. Lockington D, Wang E, Patel D, et al. Effectiveness of cataract phacoemulsification with toric intraocular lenses in addressing astigmatism after keratoplasty. J Cataract Refract Surg 2014;40:12:2044-9.

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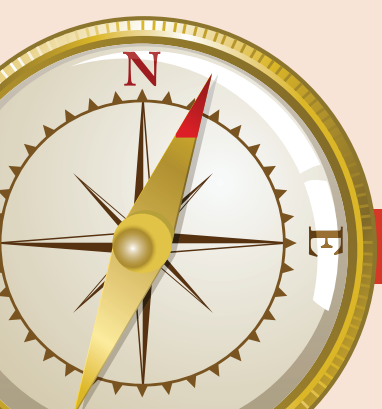

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Effects of Cataract Surgery on Wet AMD

A retrospective review of cataract surgery patients with wet age-related macular degeneration suggests that cataract surgery leads to vision improvement and does not appear to contribute to worsening of wet AMD. However, anatomic changes based on optical coherence tomography analysis suggest a subclinical susceptibility to postoperative cystoid macular edema or exacerbation of choroidal neovascularization.

The review was performed on consecutive patients with wet AMD (n=40) who underwent cataract surgery at the midpoint of a one-year study window. A control arm (n=42) included wet AMD eyes treated with anti-vascular endothelial growth factor injections that did not undergo cataract surgery for the one-year period. Best-corrected visual acuity, number of anti-VEGF injections and OCT features were compared between the control and trial arms.

Best-corrected visual acuity was equivalent in the first half of the study and became significantly better in the surgical group vs. the non-surgical group (0.23 ±0.65 vs. 0.11 ±0.59 logMAR improvement, p=0.049). There was no change in the number of injections given six months before vs. after the midpoint in the surgical group (p=0.921). The mean OCT central retinal thickness became greater in the postsurgical eyes compared to nonsurgical eyes (265.4 ±98.4 µm vs. 216.4 ±58.3 µm, p=0.048).

Am J Ophthalmol 2015;160:3:487-492.
Saraf S, Ryu C, Ober M.

A New Botulinum Toxin A Forehead Lift

A study investigating the safety and efficacy of microdroplet cosmetic periocular botulinum toxin A used to treat eyebrow depressors while leaving brow elevators untreated has concluded that the treatment results in an aesthetic improvement to the face and periocular area without the forehead paralysis associated with conventional treatment.

Patients were treated with 33 U onabotulinum toxin injected in microdroplets of 10 to 20 µl. Sixty to 100 injections of microdroplets were needed to complete a treatment pattern concentrated at the brow, glabella and crows feet area. The forehead was not treated. Patients who returned between 10 and 45 days were studied with image analysis.

There were 563 consecutive microdroplet treatments on 227 unique patients (female: n=175, mean age: 46 ±4 years; male: n=52, mean age: 44 ±8 years). The incidence of ptosis was 0.2 percent and transient. Forty-nine patients returned for a follow-up visit between 10 and 45 days and were included for image analysis to compare the before and after results of treatment. Photonumeric scales for forehead lines, brow ptosis and brow furrow all showed statistically significant improvements.

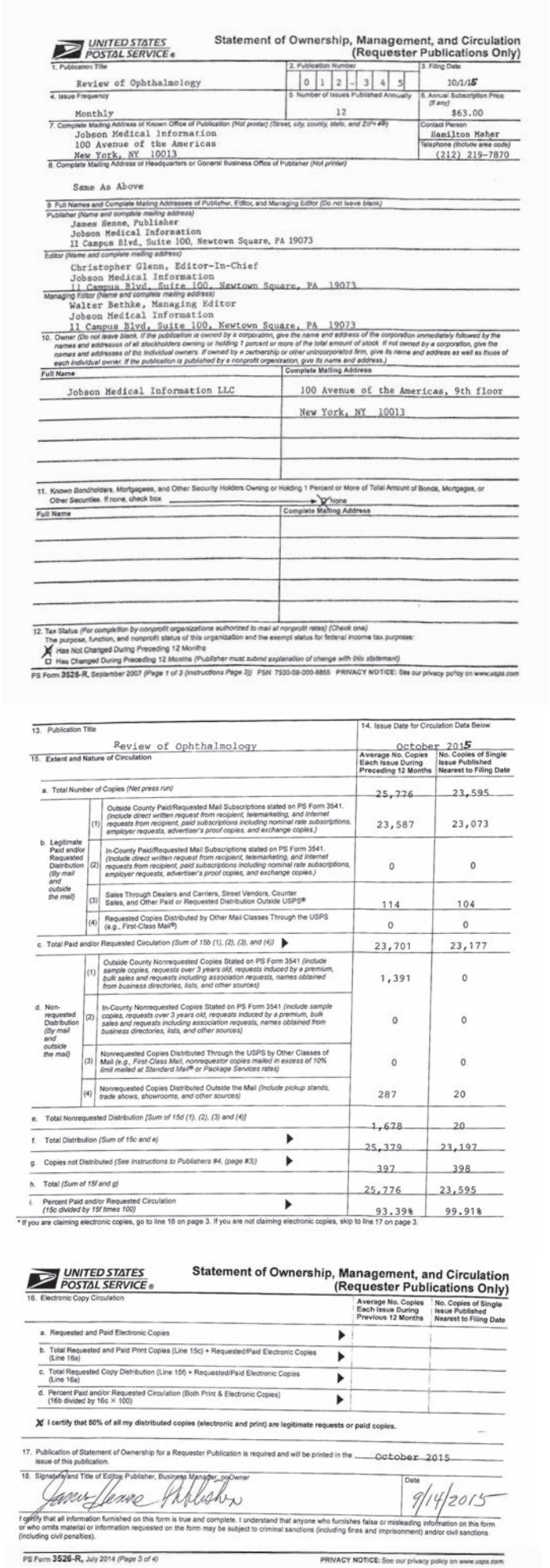
Ophthal Plast Reconstr Surg 2015;31:263-268.
Steinsapir K, Rootman D, Wulc A, Hwang C.

Medicare Payment and Service Volume for Retina Procedures

New York researchers found no evidence suggesting an association between Medicare payment and service volume for the three highest-volume retina procedures from 2005 through 2009.

The researchers used Medicare Part B carrier data for all 50 states and the District of Columbia, controlling for time-invariant carrier-specific characteristics, national trends in service volume, Medicare beneficiary population, number of ophthalmologists and income per capita. The main outcome measures were Medicare payment-service volume elasticities, defined as the percentage of change in service volume per 1 percent change in Medicare payment for the three highest volume retina procedures: intravitreal injection (Current Procedural Terminology code 67028); laser treatment for retinal edema (CPT code 67210); and laser treatment for proliferative retinopathy (CPT code 67228).

This article has no commercial sponsorship.



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For all three retina procedures, the regression coefficients representing the Medicare payment-service volume elasticity were non-significant: intravitreal injection elasticity, -0.75 (95 percent confidence interval, -1.62 to 0.13; p=0.09); laser treatment for retinal edema elasticity, 0.14 (95 percent CI, -0.38 to .065; p=0.59); and laser treatment for proliferative retinopathy elasticity, 0.05 (95 percent CI, -0.26 to 0.35; p=0.77).

Ophthalmology 2015;122:1609-1614.

Gong D, Jun L, Tsai J.

Effects of Personalized Diabetes Risk Assessment During Ophthalmic Visits

Researchers investigating whether or not point-of-care measurement of hemoglobin A1c (HbA1c) level and personalized diabetes complication risk assessments improved glycemic control determined that there was no intervention benefit compared with usual care over the span of a year.

Investigators in ophthalmology offices at 42 sites were randomly assigned to provide either study-prescribed augmented diabetes assessment and education or the usual care. Adults with type 1 or 2 diabetes were enrolled into two cohorts: those with a more-frequent-than-annual follow-up (502 control participants and 488 intervention participants) and those with an annual follow-up (368 control participants and 388 intervention participants). Enrollment in the clinical trial was from April 2011 through January 2013.

The study-prescribed augmented diabetes assessment intervention included point-of-care measurements of HbA1c; blood pressure and retinopathy severity; an individualized estimate of the risk of retinopathy progression derived from the findings of ophthalmologic visits; structured comparison and review of past and current clinical findings; and structured education with immediate assessment and feedback regarding participant understanding. These interventions were performed at enrollment and at routine ophthalmic follow-up visits scheduled at least 12 weeks apart. The main outcomes and measures were mean change in HbA1c and level from baseline to one-year follow-up. Secondary outcomes included body mass index, blood pressure and responses to diabetes self-management practices and attitudes surveys.

In the cohort with more-frequent-than-annual follow-ups, the mean (SD) change in HbA1c level at one year was -0.1 percent (1.5 percent) in the control group and -0.3 percent (1.4 percent) in the intervention group (adjusted mean difference, -0.09 percent [95 percent confidence interval, -0.29 percent to 0.12 percent], p=0.35). In the cohort with annual follow-ups, the mean (SD) change

in HbA1c level was 0.0 percent (1.1 percent) in the control group and -0.1 percent (1.6 percent) in the intervention group (mean difference, -0.05 percent [95 percent CI, -0.27 percent to 0.18 percent], p=0.63). Results were similar for all secondary outcomes. These data suggest that optimizing glycemic control remains a substantive challenge requiring interventional paradigms other than those examined in this study.

JAMA Ophthalmol 2015;133:8:888-896.

Aiello L, Ayala A, Antoszyk A, Arnold-Bush B, Baker C, et al.

Index to Estimate the Efficiency Of an Ophthalmic Practice

California researchers developed and evaluated an efficiency index that estimates the performance of an ophthalmologist's practice as a function of cost, number of patients receiving care and quality of care. This metric provides a broad overview of performance for a variety of ophthalmology specialties as estimated by resources used and a preliminary measure of quality of care provided.

The adjusted number of patients, adjusted costs, quality and efficiency index were calculated via a retrospective review of data from 36 ophthalmology subspecialty practices at a university-based eye institute from October 2011 to September 2012. The efficiency index (E) was defined as a function of adjusted number of patients (N_a), total practice adjusted costs (C_a) and preliminary measure of quality (Q). Constant b limits E between zero and one. Constant y modifies the influence of Q on E. Relative value units and geographic cost indices determined by the Centers for Medicare & Medicaid Services for 2012 were used to calculate adjusted costs. The efficiency index is expressed as the following: $E=b(N_a/C_a)Qy$. Independent, masked auditors reviewed 20 random patient medical records for each practice and filled out three questionnaires to obtain a process-based quality measure.

The median adjusted number of patients was 5,516 (interquartile range: 3,450 to 11,863), the median adjust cost was 1.34 (IQR: 0.99 to 1.96), the median quality was 0.89 (IQR: 0.79 to 0.91) and the median value of the efficiency index was 0.26 (IQR: 0.08 to 0.42).

The results of the efficiency index could be used in future investigations to determine its sensitivity to detect the impact of interventions on a practice such as training modules or practice restructuring.

JAMA Ophthalmol 2015;133:8:924-929.

Chen A, Kim EA, Aigner D, Afifi A, Caprioli J.

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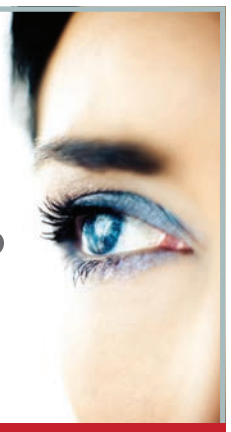

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A new lid bump prompts treatment for presumed dacryocystitis, but the patient then develops diplopia and seeks help at Wills Eye.

Alison Huggins, MD

Presentation

A 13-year-old Caucasian female presented with complaints of a new bump in her right lower lid for seven to 10 days. She denied vision changes, pain, history of trauma or recent illness, but had begun to experience diplopia in the 24 hours preceding her presentation. Systemic review of symptoms was negative for joint pains, shortness of breath, cough, abnormal bowel movements or urinary symptoms. She had first presented to her ophthalmologist one week prior, and treatment was initiated with warm compresses and cephalexin for presumed dacryocystitis. At that time she had had a questionable right hypertropia with a 5 x 10-mm fluctuant mass beneath her nasal right lower lid; her exam was otherwise unremarkable.

Medical History

The patient had a past medical history of scoliosis and ocular history of refractive error and soft contact lens use. She denied tobacco, alcohol and intravenous drug abuse. She was not on any medications and denied any known drug allergies.

Examination

At the time of presentation she was afebrile with stable vital signs. Her external examination demonstrated a firm, non-tender, 20-mm nodule nasally beneath the right lower lid. Hertel exophthalmometry revealed 6 mm of right-sided proptosis *(See Figure 1)*. On ocular examination, best corrected visual acuity was 20/40 OD and 20/25 OS. Pupillary exam showed no anisocoria or relative afferent pupillary defect. A 10 prism diopter right hypertropia was present in primary gaze, but extraocular motility was full bilaterally. Visual fields were full to confrontation, and Ishihara color plates were 10/10 in both eyes. Anterior slit-lamp examination and fundoscopic examination were normal; intraocular pressures were 16 mmHg OU by Goldmann tonometry.

Figure 1. External photography demonstrating right orbital mass lesion beneath right lower lid.

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

Diagnosis, Workup and Treatment

The differential diagnosis included both inflammatory/infectious lesions as well as malignant and benign mass lesions. The painless nature of her presentation made inflammatory lesions less likely, and the presence of a focal mass decreased the suspicion for infection. Given the rapidly progressive course of the child's orbital process, magnetic resonance imaging of the brain and orbits with intravenous contrast was obtained on an urgent basis to further characterize the lesion. Imaging revealed a right orbital mass located medially that showed diffuse enhancement with gadolinium *(See Figure 2)*.

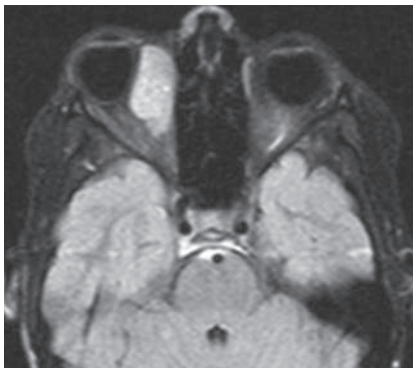

Figure 2. T1 MRI axial image post contrast demonstrating a right medial mildly lobulated orbital mass measuring 2.8 x 1.7 x 3.1 cm with diffuse enhancement post contrast.

Because of the high clinical suspicion for rhabdomyosarcoma and consistent appearance on imaging, the patient underwent urgent biopsy of the lesion. Incisional biopsy with debunking rather than excisional biopsy was pursued given the lesion's close proximity to the globe and optic nerve posteriorly. The biopsy revealed embryonal cell rhabdomyosarcoma, confirmed with immunohistochemistry *(See Figure 3)*.

The patient was diagnosed with rhabdomyosarcoma and referred to an oncologist for further staging and treatment. Plans were made for the patient to undergo four courses of combination chemotherapy with vincristine, actinomycin and cyclophosphamide followed by weekly treatments of vincristine alone to complete a six-month course. Additionally, she would undergo six weeks of proton beam radiation therapy for local control. On her first postoperative visit, following a single course of chemotherapy treatment, the right orbital mass was no longer clinically detectable. At six-month follow-up she had mild dry-eye syndrome, but was completely tumor-free.

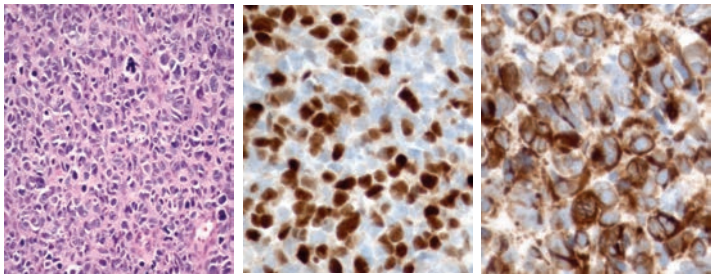

Figure 3. Right orbital mass biopsy. Histopathology section demonstrating embryonal cell rhabdomyosarcoma on hematoxylin and eosin staining (left). Immunohistochemistry demonstrating positivity with antibodies to Desmin (center) and Myogenin (right).

Discussion

Rhabdomyosarcoma arises from pleuripotent mesenchymal cells. It accounts for 5 percent of all childhood cancers and 20 percent of all malignant soft tissue tumors.[1] Ocular rhabdomyosarcoma typically arises from the orbital soft tissues and can manifest with a variety of clinical features including proptosis; globe displacement; blepharoptosis; conjunctival and eyelid swelling; a palpable mass; as well as with pain.[1] Orbital rhabdomyosarcoma accounts for nearly 25 to 35 percent of head and neck rhabdomyosarcomas.[1]

This case demonstrates the diagnostic dilemma that may be present in cases of orbital rhabdomyosarcoma, because rhabdomyosarcoma may masquerade as a more benign process before the patient begins to manifest orbital signs. It is important to always consider rhabdomyosarcoma in the scenario of a rapidly growing orbital lesion in children and teenagers. Infections can also progress rapidly, but typically cause generalized inflammation rather than a focal mass lesion, with the exception of a concomitant abscess. Making the diagnosis depends primarily on imaging.[1] Therefore, clinical suspicion must remain high so that imaging is pursued in an expedited manner. In a child, care should be taken to limit radiation exposure, making MRI a more attractive modality. However, availability of MRI can be limited, in which case a computed tomography scan may be preferable. The appearance of rhabdomyosarcoma on MRI is certainly not diagnostic but typically manifests as a well-circumscribed homogenous round mass that is isointense to the extraocular muscles on T1 and hyperintense on T2.[1] The most common orbital location is superonasal, but as seen in this case, it may be anywhere.[1] Diffusion-weighted images may be helpful in distinguishing malignant orbital tumors from benign lesions.[2] The mean apparent diffusion coefficient has been shown to be lower in malignant masses.[2] This property is thought to relate to the reduced ex-

tracellular matrix and diffusion space in malignant tumors due to their enlarged nuclei and hypercellularity relative to benign tissues.[2]

In order to confirm the diagnosis, a biopsy must be performed. There has been some debate in the literature regarding the surgical approach in patients with orbital rhabdomyosarcoma.[1] While some believe that an attempt should be made to remove the mass in its entirety,[1] often there is the consideration of the surrounding critical structures that can make complete excision challenging. Malignant cells lack cohesiveness and are easily detached and freed to start a new malignant colony in normal tissue if the primary tumor is disrupted.[3] This property has been demonstrated in the literature, with tumor seeding in breast malignancy following fine-needle aspiration biopsy.[3] Increased risk of seeding has likewise been seen when cutting into a mass for incisional biopsy.[3] Therefore, for malignancies in general, excisional biopsy is preferred when the tumor can be removed in total with wide margins.[3] However, in children with rhabdomyosarcoma, total resection should not be pursued if there is a high risk of functional or cosmetic consequence.[4]

Advancements in radiation therapy have helped to optimize local control while limiting adverse effects in these young patients. Children are now treated with proton beam radiation therapy, which utilizes the proton properties to target the tissue of interest with lessened impact on the surrounding critical structures.[5] In fact, PBRT can decrease the doses applied to normal tissues by a factor of two to three.[5] One study evaluated the dose exposure to adjacent structures in the treatment of rhabdomyosarcoma.[5] In cases of orbital rhabdomyosarcoma, the authors found that use of PBRT resulted in a reduction in radiation to the ipsilateral and contralateral temporal lobes and lacrimal glands as well as the hypothalamus, the pituitary and the maxilla. Additionally, these patients had a reduction in dose exposure to the contralateral lens and retina.[5] Therefore, with these advancements in local therapy, incisional biopsy may become increasingly preferred to limit damage to adjacent critical structures in delicate spaces like the orbit.

Fortunately, the outcome of patients with orbital rhabdomyosarcoma is quite good.[6] The staging of rhabdomyosarcoma is determined by location in addition to tumor size, nodal involvement and metastases. Tumors present in the orbit and elsewhere in the head and neck are all classified as stage one regardless of tumor size or node status. Pathologic subtype of these tumors is another important consideration for patient risk stratification.[6] In children, the embryonal and alveolar subtypes are most common. The alveolar subtype is fortunately relatively rare, as it portends a worse prognosis, and these patients are automatically stratified as intermediate or high-risk.[6] Distinguishing the morphologic features on histology to determine the rhabdomyosarcoma subtype is not without its challenges. In fact, having any amount of alveolar morphology present in a specimen previously characterized the tumor as alveolar even if it was not the predominant finding.[7]

Tumor genetics is now reshaping the way rhabdomyosarcoma is histologically classified. Testing for the PAX/FOXO1 fusion gene by molecular methods has become increasingly important for determining prognosis.[7] The presence of this fusion gene in patients with the alveolar subtype of rhabdomyosarcoma imparts a worse prognosis, while gene-negative patients have clinical outcomes similar to patients with the embryonal subtype of rhabdomyosarcoma.[7] In a retrospective study of 210 cases, fusion gene-negative alveolar cell rhabdomyosarcoma had a similar period of tumor-free survival and frequency of metastasis when compared to embryonal cell rhabdomyosarcoma, whereas patients with fusion gene positive alveolar cell rhabdomyosarcoma had statistically significantly worse outcomes.[7]

This case highlights the importance of considering rhabdomyosarcoma in young teens; although more common among young children, it can still manifest in older age groups. It is vital to check for orbital signs when these patients present, because as seen in this case, the early manifestations of rhabdomyosarcoma may masquerade as more benign entities. In a disease process where tumor size impacts prognosis,[6] and growth in locations such as the orbit may jeopardize the surrounding critical structures, it is vital to expedite diagnosis and intervention to maximize functional outcomes and survival. REVIEW

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REVIEW

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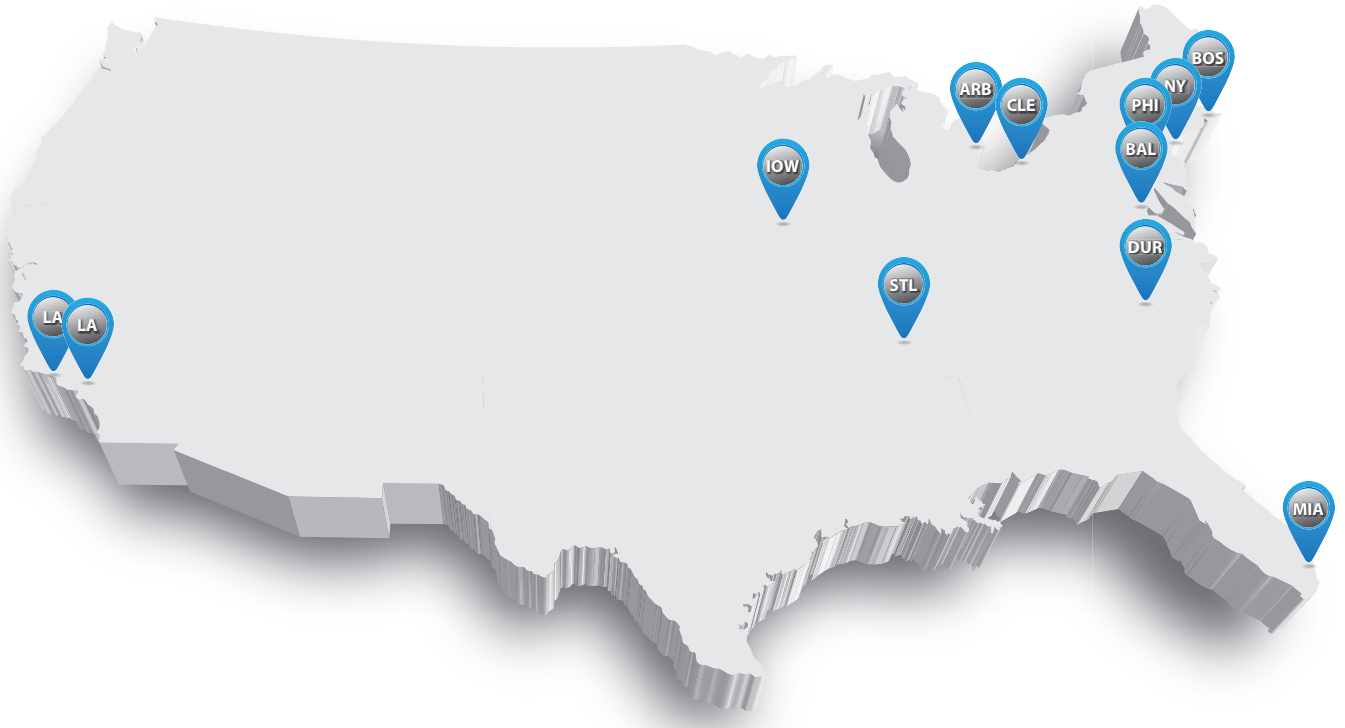

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