REVIEW® of Ophthalmology

November 2014

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Dry-Eye Issue

CATARACT SURGERY SO POWERFUL IT CAN EVEN HELP YOU SEE THE FUTURE

LENS EXTRACTION

CATALYS® PRECISION LASER SYSTEM & WHITESTAR SIGNATURE® SYSTEM

It's tough to make capital investments in the middle of a technology evolution. How do you choose the platform that prepares you for the future of cataract surgery? Consider this: the **CATALYS®** Precision Laser System offers precise incisions and complete cataract segmentation and softening.[1] The **WHITESTAR SIGNATURE®** Phacoemulsification System provides switch-on-the-fly transition between peristaltic and venturi pump modalities, for true low-energy lens extraction.[2] Let the future come; you'll be ready.

Plan your future in lens extraction at

ExtractTheFuture.com

IMPORTANT INDICATIONS AND SAFETY INFORMATION for the CATALYS® Precision Laser System and WHITESTAR SIGNATURE® System
Reference the labeling for a complete listing of Important Indications and Safety Information.
CAUTION: Federal law restricts these devices to sale by or on order of a physician.

CATALYS® Precision Laser System
INDICATIONS: The CATALYS® System is indicated for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, phacofragmentation, and the creation of single-plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure.

CONTRAINDICATIONS: Should not be used in patients with corneal ring and/or inlay implants, severe corneal opacities, corneal abnormalities, significant corneal edema or diminished aqueous clarity that obscures OCT imaging of the anterior lens capsule, patients younger than 22 years of age, descemetocele with impending corneal rupture, and any contraindications to cataract surgery. **ADVERSE EFFECTS:** Complications include mild Petechiae and subconjunctival hemorrhage due to vacuum pressure of the LIQUID OPTICS Interface suction ring. Potential complications and adverse events include those generally associated with the performance of capsulotomy and lens fragmentation, or creation of a partial-thickness or full-thickness cut or incision of the cornea. **CAUTION:** Should be used only by qualified physicians who have extensive knowledge of the use of this device and have been trained and certified by Abbott Medical Optics/OptiMedica.

WHITESTAR SIGNATURE® System
INDICATIONS: The WHITESTAR SIGNATURE® System incorporating FUSION® Fluidics is a modular ophthalmic microsurgical system that facilitates anterior segment (cataract) ophthalmic surgery. The modular design allows the users to configure the system to meet their surgical requirements. **WARNINGS:** Risks and complications of cataract surgery may include broken ocular capsule or corneal burn. This device is only to be used by a trained licensed physician.

1. Conrad-Hengerer et al. *J Cat Refract Surg.* 2012; Conrad-Hengerer et al, JCRS 2012; 38(11): 1888-94.
2. Fabian E et al. New Phaco Fluidics Control: Case to Prevent Surge. Presented at ESCRS, Sept 2006, London, U.K.

Abbott
A Promise for Life

REVIEW NEWS
Volume XXI • No. 11 • November 2014

Academy Announces Key Milestones for IRIS Database

In presentations at its annual meeting in October, the AAO revealed that close to one-third of the nation's eye physicians and surgeons are participating in the IRIS Registry, which is the first comprehensive database of eye diseases and conditions in the United States.

The IRIS (Intelligent Research In Sight) Registry is a centralized data repository and reporting tool that aggregates patient data from electronic health records to perform statistical analysis. It provides information that enables ophthalmologists to improve patient care, potentially reduce cost and enhance the speed of some large clinical trials, assist in monitoring resource utilization and comply with federal incentive programs. In less than a year after announcing a limited roll out during the AAO's 2013 annual meeting, the IRIS Registry is being utilized by more than 5,000 ophthalmologists across the country, with data related to more than 10 million patient visits.

"The IRIS Registry is proving to be a revolutionary tool that Academy member physicians are embracing as a catalyst for improving the quality of care we can provide to our patients," said David W. Parke II, MD, CEO of the AAO. "Ophthalmologists are now able to harness the power of many millions of pieces of clinical information in order to make evidence-based patient care analyses that were not previously possible."

The ophthalmology database provides the ability for clinical benchmarking at the practice, regional and national levels, enabling physicians to monitor patient care, track interventions and evaluate outcomes across different populations. It features subspecialty modules that can help analyze how different pre-existing conditions, risk factors, severity of disease and demographics affect outcomes for age-related macular degeneration, cataract surgery, diabetic retinopathy and retinal surgery.

Though the IRIS Registry is still in its infancy, it is already generating aggregate data that hint at the insights that will be available as more information enters the system. The following has been revealed about patients seen by ophthalmologists participating in the IRIS Registry thus far:

- 2 percent of patients without comorbidities require an additional procedure for complications within 30 days after cataract surgery (not including YAG laser);
- 80 percent of patients without comorbidities have a vision of 20/30 or better within 90 days after cataract surgery;
- 10 percent of patients have age-related macular degeneration;
- 46 percent of patients with age-related macular degeneration receive counseling about antioxidants when seen by an ophthalmologist;
- 11 percent of all patients have primary open-angle glaucoma; and
- 6 percent of all patients in the IRIS Registry have diabetic retinopathy.

"Within a very short amount of time, ophthalmology practices are already making meaningful improvements in patient care, based on information gleaned from IRIS Registry data," said William L. Rich III, MD, medical director of health policy for the AAO. "As the database continues to grow, our profession will have a wealth of statistically relevant data that will fill

FDA Approves Revised DME Indication for Allergan's Ozurdex

Last month, the Food and Drug Administration approved Allergan's Ozurdex (dexamethasone intravitreal implant) 0.7 mg, a sustained-release biodegradable steroid implant, for the treatment of diabetic macular edema. Ozurdex was originally approved in June as a treatment for DME in adult patients or who are pseudophakic or scheduled for cataract surgery. Based on ongoing review of clinical data demonstrating efficacy and safety, the FDA has now approved Ozurdex for use in the general DME patient population, estimated at 560,000 in the United States.

The FDA approval of Ozurdex is based on the MEAD (Macular Edema: Assessment of Implantable Dexamethasone in Diabetes) study where Ozurdex has demonstrated long-term efficacy in the treatment of DME without the need for monthly injections. MEAD includes two multicenter, three-year, sham-controlled, masked, randomized clinical studies assessing the proportion of patients with 15 or more letters improvement in best-corrected visual acuity from baseline. The most common adverse events in the studies included cataracts and elevated intraocular pressure. An increase in mean IOP was seen with each treatment cycle, and the mean IOP generally returned to baseline between treatment cycles.

many gaps in ophthalmic knowledge to improve the overall quality of patient care."

The IRIS Registry is available exclusively to all U.S.-based Academy members and their practices at no cost.

Study Ties MS and Uveitis Diagnoses

The results of the largest retrospective study of multiple sclerosis in uveitis patients has revealed that nearly 60 percent of patients with both diseases were diagnosed with each within a five-year span. While it has long been known that there is an association between the eye condition and MS, this is the first study to provide a detailed description of the relative onset of uveitis and MS and to calculate the likelihood of an MS diagnosis among uveitis patients.

Diagnosed in approximately 38,000 Americans a year, uveitis causes swelling and irritation of the middle layer of the eye and can lead to permanent vision loss if left untreated. It is well-established in the medical community that uveitis can be a sign of MS and it is estimated that 1 to 10 percent of MS patients have uveitis. The disease affects approximately 2.3 million people worldwide, causes irreversible nerve deterioration and is notoriously difficult to diagnose.

To achieve a better understanding of the association of the two diseases, researchers from Casey Eye Institute at the Oregon Health & Science University and the University of Heidelberg, Germany conducted a database search of approximately 3,000 patients with uveitis from the Casey Eye Institute and 5,319 patients from the University of Heidelberg between 1985 and 2013. Of these, 24 patients from the Casey Eye Institute and 89 patients from the University of Heidelberg fulfilled the inclusion criteria of diagnoses for both uveitis and MS and were included in the study.

Based on the prevalence of MS in American and European populations, the researchers found that MS is 18 times and 21 times more likely in an American and European population with uveitis, respectively, relative to the general population. The study found that MS was diagnosed before uveitis in 28 (29 percent) of patients, simultaneously in 15 (15 percent) of patients and after uveitis diagnosis in 54 (56 percent) of patients.

"With a population size four-times larger than any study to date on this topic, our study provides a wealth of clinical information to allow clinicians to make more accurate diagnoses while giving patients a better understanding of their prognosis," said Wyatt Messenger, MD, lead researcher from the Casey Eye Institute (now a research fellow at the University of Utah). "Knowing more about the onset may enable patients to seek treatment earlier, therefore slowing the progression of the disease and limiting the damage done to the nervous system."

Additionally, this is the first study to estimate the relative frequency of anatomical sub-types of uveitis in patients with MS. Traditionally, uveitis in patients with MS is said to present with intermediate uveitis (also referred to as pars planitis). While 80 percent of cases in this study had intermediate uveitis at the time of MS diagnosis, researchers found that nearly one in six of participants presented with anterior uveitis. The study also showed that visual acuity is generally stable in this population; the majority of patients improved during follow-up after treatment.

The researchers noted that a major limitation of the study is the lack of availability of brain magnetic resonance images on all of the patients or detailed neurological studies, which would have allowed correlation of the patients' uveitis with their neurological disease.

Smartphone Aids Diabetes Diagnosis

A smartphone-based tool may be an effective alternative to traditional ophthalmic imaging equipment in evaluating and grading severity of a diabetic eye disease, according to a study released at the American Academy of Ophthalmology meeting in Chicago last month. The results of the research indicate the lower-cost method could be useful for bringing the service to patients in isolated or underserved communities.

Researchers from the University of Brescia, University of Molise and "Federico II" University of Naples, Italy, developed a small optical adapter called D-Eye, which could attach magnetically to an iPhone 5, creating a smartphone ophthalmoscope. They then used the iPhone ophthalmoscope as well as a slit-lamp biomicroscope to perform dilated retinal digital imaging on 120 patients with diabetes who were scheduled to have a routine dilated eye exam. After comparing the results of the smartphone method to the traditional one, an exact agreement between the two methods was found in 85 percent of the eyes and an agreement within one step (or grade of disease progression) was found in 96.7 percent of the eyes. In most of the one- and two-step disagreements, the severity level was graded higher by biomicroscopy grading.

In the smartphone ophthalmoscopy results, nine eyes were not gradable due to small pupil or cataract. In the biomicroscopy results, the number of non-gradable images was four. Therefore, while biomicroscopy is still found to be the more accurate method for grading diabetic retinopathy, researchers believe smartphone ophthalmoscopy shows great potential for use in rural or remote communities who would

normally receive little to no testing at all.

"Using the iPhone method is thousands of dollars cheaper than using traditional equipment," said lead researcher Andrea Russo, MD. "The affordability of this option could make it much easier to bring eye care to non-hospital remote or rural settings, which often lack ophthalmic medical personnel."

Stem Cells Derived From Limbus

Scientists at the University of Southampton in England have discovered that the corneal limbus harbors special stem cells that could treat blinding eye conditions. The research, published in *PLOS ONE*, showed that stem cells can be cultured from the corneal limbus *in vitro*. Under the correct culture conditions, these cells could be directed to behave like photoreceptor cells.

The loss of photoreceptors cells causes irreversible blindness, and researchers hope this discovery could lead to new treatments for conditions such as age-related macular degeneration. Professor Andrew Lotery, of the University of Southampton and a consultant ophthalmologist at Southampton General Hospital, led the study. He comments: "These cells are readily accessible, and they have surprising plasticity, which makes them an attractive cell resource for future therapies. This would help avoid complications with rejection or contamination because the cells taken from the eye would be returned to the same patient. More research is now needed to develop this approach before these cells are used in patients." Furthermore, these stem cells also exist in aged human eyes, and can be cultured even from the corneal limbus of 97-year-olds. Therefore this discovery opens up the possibility of new treatments for the older generations, researchers believe. REVIEW

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The LENSAR® Laser System can help you make all the right moves in femtosecond laser cataract surgery. That's because LENSAR was thoughtfully designed from the ground up to meet the needs of cataract surgeons, with unique features that increase workflow and procedural efficiencies, reduce CDE up to 100%,[1] and create a safe patient experience. And now with pending capabilities to connect with pre- and post-op diagnostics, LENSAR can help you further refine outcomes for increased accuracy and greater patient satisfaction.

Learn more about LENSAR's winning combination of features at www.LENSAR.com.

LENSAR®
CATARACT LASER WITH AUGMENTED REALITY

Reference:
1. Data on file. LENSAR, Inc.

The LENSAR Laser System – fs 3D (LLS-fs 3D) is intended for use in patients undergoing cataract surgery for removal of the crystalline lens. Intended uses in cataract surgery include anterior capsulotomy, laser phacofragmentation, and the creation of full and partial thickness single-plane and multi-plane arc cuts/incisions in the cornea, each of which may be performed either individually or consecutively during the same procedure. Laser Capsulotomy, laser phacofragmentation and/or corneal incisions surgery is contraindicated in patients: who are of pediatric age, whose pupils will not dilate or remain dilated to a diameter greater than that of the intended treatment and for capsulotomies and/or laser phacofragmentation with intended diameters of less than 4 mm or greater than 7 mm, who have existing corneal implants, who have previous corneal incisions that might provide a potential space into which the gas produced by the procedure can escape, who have conditions that would cause inadequate clearance between the intended capsulotomy cut and the corneal endothelium, such as: hypotony, uncontrolled glaucoma, who have corneal disease or pathology that precludes transmission of light at the laser wavelength or causes distortion of laser light, such as: corneal opacities, residual, recurrent, active ocular or uncontrolled eyelid disease or any corneal abnormalities (including endothelial dystrophy, guttata, recurrent corneal erosion, etc.) in the eye to be treated, ophthalmoscopic signs of keratoconus (or keratoconus suspect) in the eye to be treated, a history of severe dry eye that has not responded to therapy, a history of herpes zoster or herpes simplex keratitis.

Potential contraindications are not limited to those included in the list.

WARNING: The safety and effectiveness of this laser have NOT been established in patients with diabetic retinopathy, a history of treated glaucoma, or prior intraocular surgery.

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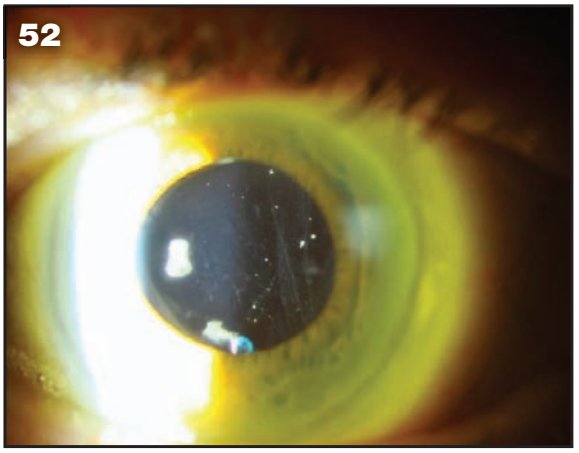

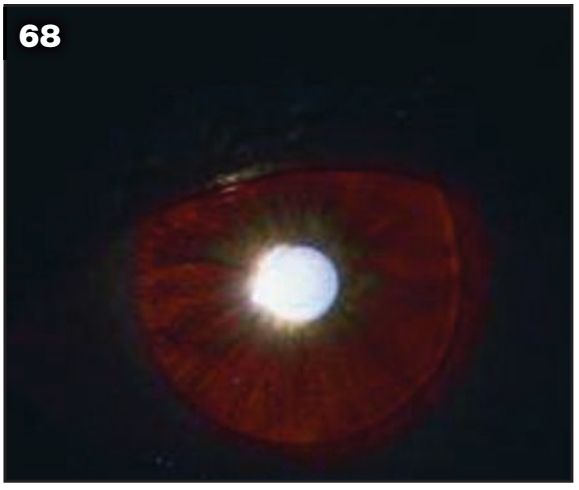

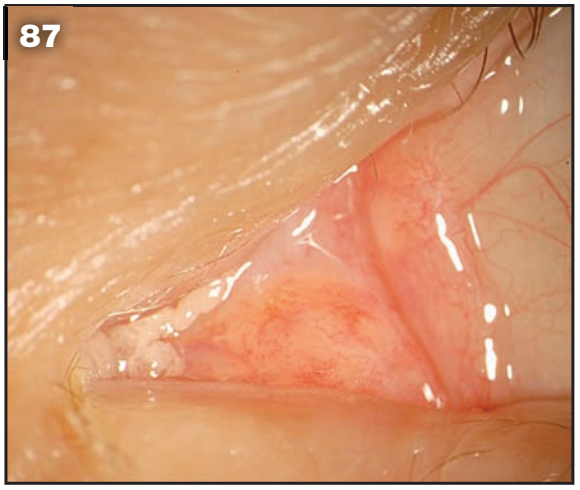

Classic beta blocker adjunctive therapy for the right patient at the right time[3]

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

Indications and Usage

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

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

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

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

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

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

Preservative-Free

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

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

Istalol®
(timolol maleate ophthalmic solution) 0.5%

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

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US/TOP/14/0017(1)

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

in OCUDOSE® (DISPENSER)

INDICATIONS AND USAGE

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

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

CONTRAINDICATIONS

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

WARNINGS

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

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

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

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

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

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

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

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

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

PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

OVERDOSAGE

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

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

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

DOSAGE AND ADMINISTRATION

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

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

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

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

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

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

Istalol® (timolol maleate ophthalmic solution) 0.5%

Initial U.S. Approval: 1978

STERILE

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

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

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

6.2 Postmarketing Experience

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

DRUG INTERACTIONS

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

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

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

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

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

OVERDOSAGE

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

NONCLINICAL TOXICOLOGY

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

PATIENT COUNSELING INFORMATION

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

Rx Only

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

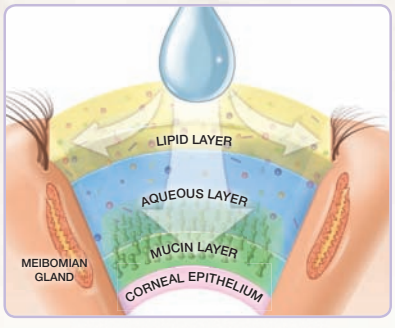
Based on 9401500 US/IST/14/0007 Issued 06/2013

For the 75% of dry eye patients worldwide with evaporative dry eye (MGD) symptoms[1]...

DRY EYE CAN BE RELENTLESS

CALM THE STORM WITH LASTING RELIEF

SYSTANE® BALANCE Lubricant Eye Drops:
Protecting the Ocular Surface by Increasing Lipid Layer Thickness (LLT)



SYSTANE® BALANCE Lubricant Eye Drops forms a protective matrix that is designed to replenish the lipid layer for long-lasting relief from the symptoms associated with evaporative dry eye (MGD). This unique formulation is designed to work on all 3 layers of the tear film, specifically increasing LLT. This helps create a protective environment for the ocular surface.[2]

SYSTANE® Brand products are formulated for the temporary relief of burning and irritation due to dryness of the eye.

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.

Your recommendation counts.

Make sure your patients get the lasting symptom relief they need by offering them SYSTANE® BALANCE Lubricant Eye Drops.[2]

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REVIEW® of Ophthalmology

REVIEW Editor's Page

Christopher Glenn, Editor in Chief

Compliance Faces New Economic Challenges

From dropless cataract surgery, to microincisional devices in glaucoma that reduce the need for drops, to sustained-release drug delivery devices and even simply cutting eye-drop administration to once a day, a common theme and holy grail in ophthalmology is simplifying and reducing the number of times a patient must self-administer treatment. The rationale has long been understood: The least effective drug in the world is the one that isn't taken. Equally well-studied is the reliability (or lack thereof) of patients as managers of their drug regimens.

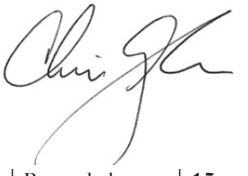
As if that weren't enough, compounding the compliance challenge are a couple recent trends that are negatively impacting patients, especially of Medicare age.

A *New York Times* report last month listed a host of repeated errors in Medicare Advantage plans, including improper claims denials and arbitrary and improper limits on coverage of prescription drugs. The data was based on dozens of federal audits of the plans, which are estimated to include about 16 million patients; another 23 million are in Medicare prescription drug plans. The study cited CMS findings including:

- In more than half of all audits, "beneficiaries and providers did not receive an adequate or accurate rationale for the denial" of coverage when insurers refused to provide or pay for care.
- When making decisions, insurers often failed to consider clinical information provided by doctors and failed to inform patients of their appeal rights.
- In 61 percent of audits, insurers "inappropriately rejected claims" for prescription drugs. Insurers enforced "unapproved quantity limits" and required patients to get permission before filling prescriptions when such "prior authorization" was not allowed.

A second trend that may affect all patients, insured or not, is the runaway increase in the price of many generic drugs, a mainstay of treatment for many elderly and lower income patients. The increase has drawn the attention of Congress, which is investigating charges that the price of some generics has increased by more than 1,000 percent in the past year alone.

While ophthalmic products have not been singled out, several generics whose use is common in patients of Medicare age have. If your patients are choosing between a glaucoma drop or a post-cataract NSAID among the mix of other medications they're prescribed, it's not a stretch to imagine the eye drop losing out. Nor is it a stretch to see the price gouging trend extend to other generics. Why? As one observer said when asked why generic manufacturers would raise prices so dramatically: "Because they can. Who is to stop them? It's unregulated."



Donna McCune, CCS-P, COE, CPMA

Compliance Programs: What Are They?

Optional for now, compliance programs are a part of the ACA. Here are steps to develop a program before they're mandatory.

Q What is the Office of Inspector General compliance program for physician practices, and are all physician practices required to have a formal compliance program?

A The OIG previously developed a voluntary compliance program focused on several other areas and aspects of the health-care industry. The OIG believes that development of a compliance program for individual and small-group physician practices will assist providers in preventing submissions of erroneous claims or engaging in unlawful conduct involving federal health-care programs.

Although a deadline for mandatory implementation has yet to be established, the Patient Protection and Affordable Care Act states, in Section 6401, that "...a provider of medical or other items or services or supplier within a particular industry, sector or category shall, as a condition of enrollment in the program under this Title ... establish a compliance program." This means that physician ability to enroll in federally funded programs, e.g., Medicare and Medicaid, will rely on the practice's having a formal compliance program.

Q Who will establish the mandatory guidelines and set the implementation date?

A The Secretary of Health and Human Services, with assistance from the OIG, will establish the core elements of a program and the required implementation date. In a recent Center for Medicare & Medicaid Services webinar discussing compliance programs, listeners were encouraged to consider developing a program, even though no official deadline has been established.

Q What is involved in developing a compliance program?

A The program is actually a two-step process, and there is no one-size-fits-all plan. The first step is developing a written plan. Plan templates to get practices started are available from a variety of sources; these are customized to create a unique plan for the practice. Depending on the size and structure of the practice, legal counsel and/or outside consultants may be required to assist in analyzing contracts, performing a chart review and conducting necessary training. The second step is putting the program in motion by taking the written document and turning it into an activity. The activities are not one-time occurrences; therefore, the practice needs to commit to the program for the long term.

Q Do guidelines exist to assist with developing a program?

A In the fall of 2000, the OIG published *Compliance Program Guidance for Individual and Small Group Physician Practices*. Many speculate that this guidance will be utilized when formulating the core elements as directed by the ACA. The October 2000 document can be found on the OIG website at: http://oig.hhs.gov/authorities/docs/physician.pdf.

Q What are the core elements in the OIG guidance document?

A There are seven core elements described in the OIG plan. They are:

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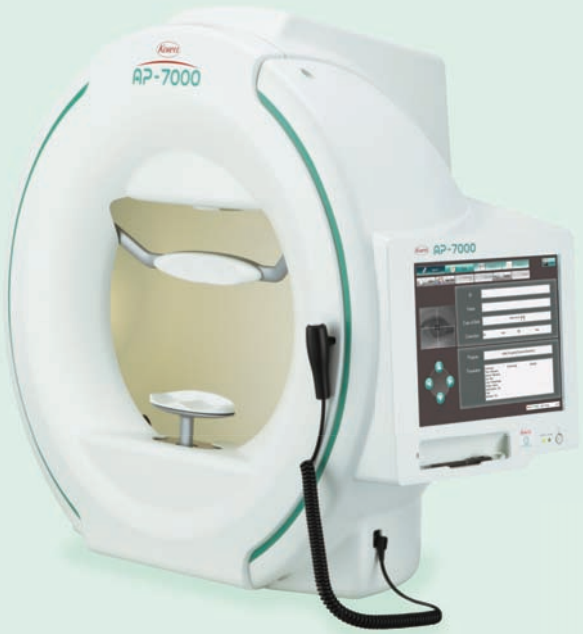

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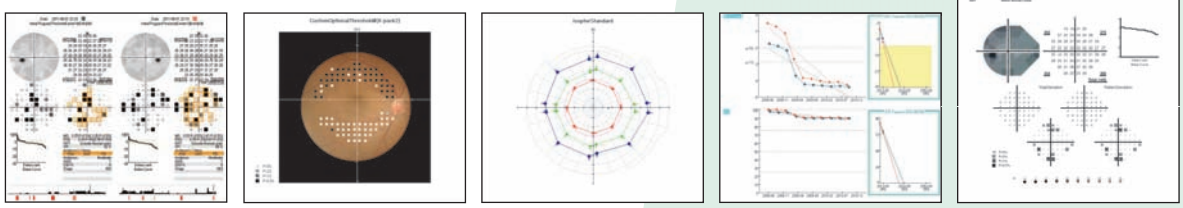

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1. conducting internal monitoring and auditing;
2. implementing compliance and practice standards;
3. designating a compliance officer or contact;
4. conducting appropriate training and education;
5. responding appropriately to detected offenses and developing corrective action;
6. developing open lines of communication; and
7. enforcing disciplinary standards through well-publicized guidelines.

Q What is involved in auditing, and how extensive does the audit need to be?

A Auditing involves a review of practice standards and procedures associated with patient care, as well as submission of claims for payment. An audit of patient medical records and claims will assess whether the claims are accurately coded and whether the documentation is complete, and ensure that services provided are reasonable and necessary.

The OIG guidance recommends a random sample of five to 10 charts per physician with a focus on federally funded programs. A comprehensive baseline audit is recommended as a starting point, assessing a small sample of everything. This is typically about 1 percent of all claims.

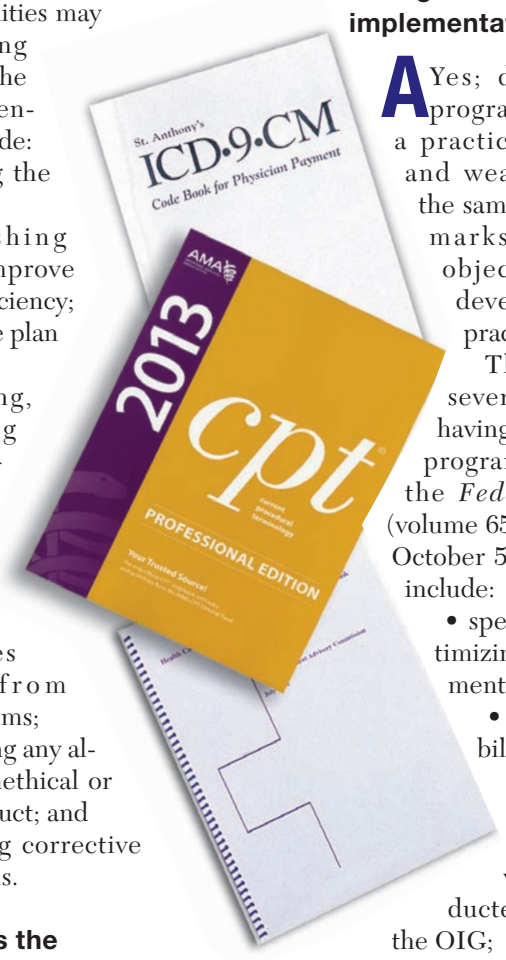
Q Who should do these internal audits?

A Audits can be performed by an independent party (e.g., attorney, consultant or accountant) or by practice staff. Internal auditors may include physicians, billing staff, medical assistants, a compliance officer or a committee of individuals.

Q What is the role and responsibility of a compliance officer?

A The compliance officer should be someone of moderate authority, because while the role(s) and responsibilities may vary depending on the size of the practice, in general, they include:

- overseeing the program;
- establishing methods to improve quality and efficiency;
- revising the plan as needed;
- developing, coordinating and participating in training programs;
- checking the OIG's list of Parties Debarred from Federal Programs;
- investigating any allegations of unethical or improper conduct; and
- monitoring corrective action programs.



Q How does the compliance officer check the OIG's list of Parties Debarred from Federal Programs?

A The OIG has made this quite simple: there is a link on its home page for the list. It can be found at: http://oig.hhs.gov/ and is a large button that says, "Exclusions Database." Searches may be performed for a single name or a list of names. The OIG spokesperson participating in the recent CMS webinar indicated that not checking the exclusion database is a common compliance error practices make.

Q Are there any benefits to having a voluntary compliance program while waiting for mandatory implementation?

A Yes; developing a program will reveal a practice's strengths and weaknesses. At the same time, benchmarks, goals and objectives will be developed for the practice.

There are also several benefits to having a compliance program, as cited in the *Federal Register* (volume 65; number 194; October 5, 2000). They include:

- speeding and optimizing proper payment of claims;
- minimizing billing mistakes;
- reducing the chances that an audit will be conducted by CMS or the OIG;
- avoiding conflicts with the self-referral and anti-kickback statutes;
- demonstrating good faith effort to comply with laws and regulations; and
- indicating that staff have an affirmative, ethical duty to report billing errors or fraudulent conduct so it may be corrected. REVIEW

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

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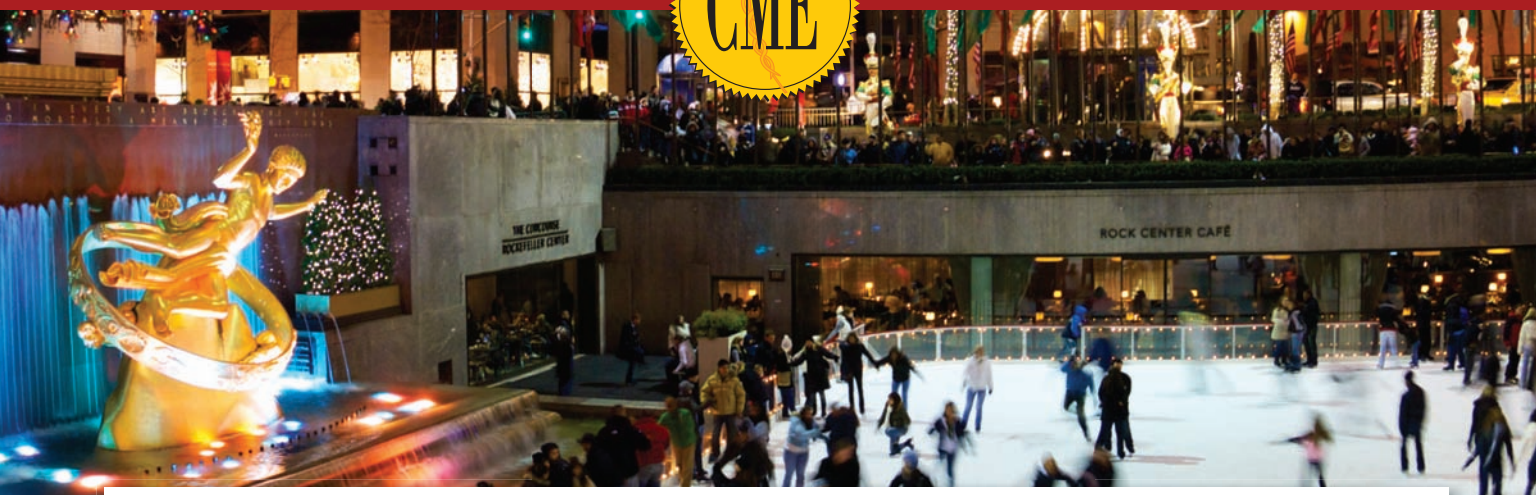

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Smartphone Camera Adapters Get Simpler

Devices that help smartphones take high-quality pictures of the eye are getting more portable, less expensive and easier to use.

Christopher Kent, Senior Editor

With the proliferation of smartphones and the increasing quality of their built-in cameras, many companies and individuals are working on ways to make this technology usable by ophthalmologists and technicians. Here, two MDs on different continents describe the devices they're developing, designed to make smartphone eye photography easy, inexpensive and as accurate as possible.

Photos Without a Slit Lamp

A team at Stanford University in California—Robert Chang, MD, Alexandre Jais, MS, and David Myung, MD, PhD—is developing a new inexpensive adapter dubbed "EyeGo," which is designed to allow ophthalmologists and health-care providers to capture clear images of the eye using a smartphone and existing ophthalmic lenses. "Everyone is talking about adapters that hook your smartphone onto the slit lamp," notes Dr. Chang, assistant professor of ophthalmology at Stanford University's Byers Eye Institute. "We tried those, but they were cumbersome and took too long to set up. We wanted something you could just pull out of your pocket to capture an image of the eye instantly.

Robert Chang, MD

The EyeGo smartphone adapter, developed at Stanford University, will allow accurate photography of the anterior segment, as well as dilated-eye photos of the retina. The adapter is designed to be simple and inexpensive, and it will fit into a coat pocket.

"Smartphone cameras have become more powerful, and ophthalmic lenses are very high quality, so we felt we could obtain an image of the retina by performing indirect ophthalmoscopy just using the phone and a 20-diopter lens," he continues. "However, it was not easy to obtain a clear image of the eye just holding the two in midair. So we started experimenting with the simplest adapter possible to aid in aligning the phone and lens in the correct positions. We also knew portability was key."

Dr. Chang says they've been using 3-D printers to create different adapter designs. "We're constantly

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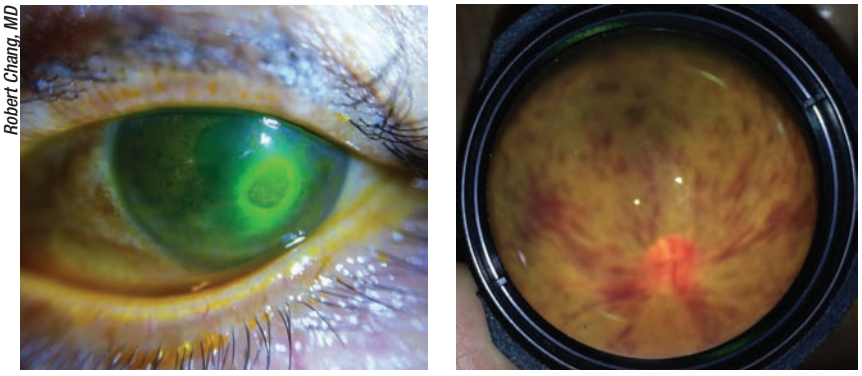

Robert Chang, MD

Sample pictures taken using the EyeGo smartphone adapter. Left: corneal ulcer. Right: central retinal vein occlusion.

improving on the prototypes, and the 3-D printing component has helped us evolve faster," he explains. "We're trying to print every component."

Initially, the team focused on an adapter for photographing the anterior segment. "You don't need to dilate the eye, so the barrier is much lower," Dr. Chang says. "It simply involves using a macro lens with proper LED lighting, optimized to provide a clear picture of the cornea and anterior chamber. Other smartphone attachments such as the Olloclip already facilitate macro photography. We customized ours for the cornea, and we intend to combine it with our posterior segment adapter.

"Capturing photos of the back of the eye came next, which is a much more challenging goal—especially undilated images," he continues. "We played around with the optics and lighting to achieve a dilated image of the retina, but we're still working on undilated eyes."

Working in the Field

After reaching this point, Dr. Chang says they began a couple of research studies. "The first was a proof of concept study—demonstrating that residents could take high-quality, useful photos in the emergency department or at the patient's bedside in the hospital," he explains. "In the clinic, we incorporated it into diabetic screening day, where we showed that the images were highly correlated with the indirect exam in determining which individuals needed a retina referral due to severe diabetic retinopathy." Dr. Chang says more studies will be forthcoming.

The team also realized early on that they needed a secure and HIPAA-compliant way to label and organize the resulting photos. "We envisioned a telemedicine-type service for storage and interpretation," he says. "This kind of service already exists for dermatology patients who can use a camera app to have a skin rash evaluated remotely. To accomplish this, we're partnering with DigiSight Technologies in Portola Valley, Calif., another start-up with an app and secure cloud platform that helps providers share images and store and retrieve medical information."

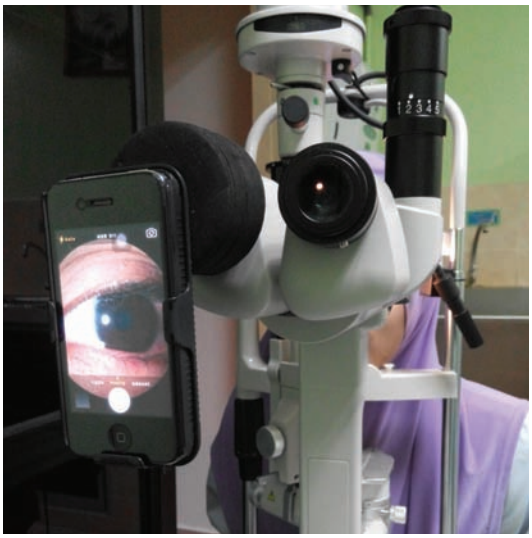
Dr. Chang emphasizes that the EyeGo images are not meant to diagnose disease or replace existing office-based cameras. "Obviously we have better diagnostic equipment than this," he says. "The EyeGo adapter may be best utilized for triaging when no other alternative is available. For example, primary-care doctors at Stanford Urgent Care sometimes send us photos taken with our adapters when they're not sure about an eye problem. That's better than having them try to describe the finding without a picture.

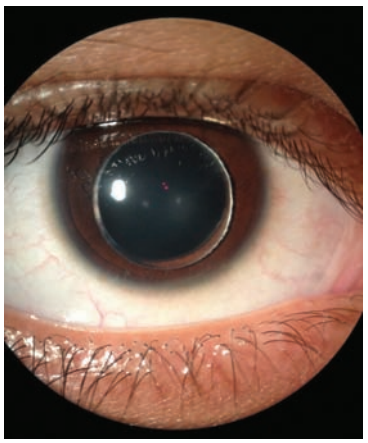
"Ultimately, it would be great if patients were able to take their own anterior photos using the EyeGo," he adds. "Patients already send us smartphone selfie pictures of their eyes, but without an adapter the photo quality is usually not very good. Imagine every postop cataract patient being sent home with an adapter in case they experience a problem. The treating physician could better distinguish something routine from something serious. Of course, if people are concerned about their eye and they have access to a doctor, they'll probably just go see the doctor. But someone in a rural area without easy access might be happy to have this alternative."

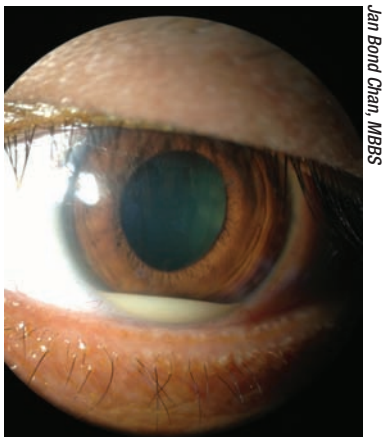
Dr. Chang says they'd like to make the EyeGo adapters available as soon as possible, emphasizing that low price is a priority. "We're currently working on the regulatory and liability issues, which hopefully will be solved in the coming months," he says. "We want this to be available to everyone. We believe that's how we can help the world the most. There are already a lot of smartphones out there, and if you could turn one into a medical triaging device capable of being used by anyone, that would be a remarkable breakthrough."

A Low-cost Slit Lamp Adapter

Another way to use smartphone photo technology, of course, is to capture the high-quality images produced by a slit lamp. In order to do that, several companies have created adapters designed to allow the surgeon to attach a smartphone directly to the oculars. However, most of these adapters range in price from $75 to more than $500. That inspired Jan Bond Chan, MBBS, who practices at Hospital Selayang and Hospital Universiti Sains in Malaysia, to create a simple alternative that can be easily assembled from inexpensive parts. (The total cost of creating his adapter







Jan Bond Chan, MBBS

This slit-lamp adapter, designed by a surgeon in Malaysia, can be assembled in a few minutes from parts costing about $15. It slides onto the slit lamp eye piece (left) allowing a tech or surgeon to capture images like those above.

is in the range of $15.)

"We tried using smartphones to take pictures directly through the eye piece of the slit lamp without an adapter, but getting a perfect picture was very difficult," he explains. "Doing so usually required three people. The first person would hold the patient in place at the slit lamp and get him to keep his eye open. The second person would use both hands to stabilize the smartphone camera, and the third person would manage the zoom function and press the button to take the picture." Dr. Chan realized an adapter was practical, but he wanted to create a simpler, less expensive alternative to those on the market.

Dr. Chan's adapter is constructed from four hard, cylindrical sponges that are about 1 cm thick, with a diameter at least 20 mm wider than the diameter of the slit lamp's eyepiece, in conjunction with an inexpensive, removable smartphone case. (One online source for the 1-cm thick cylindrical hard sponges can be found at: daisojapan.com/p-20209-eva-cushion-d315-in-4-pcs-12pks.aspx.) Using the slit lamp's eyepiece as a guide, circular holes are cut in three of the four sponges, which are stacked and glued together, forming a sponge tube that will slide over the eyepiece. A smaller hole is then cut in the fourth sponge; that hole will be centered over the smartphone camera lens. The fourth sponge is then added to the stack. The exact length of the resulting tube should match the focal length of your cameraphone.

To complete the assembly, the sponge tube is slid onto on the functioning eyepiece. With the smartphone inside the case, the camera is carefully aligned to allow a clear, centered view through the adapter; the adapter is then glued to the smartphone case. A detailed description of the device and its assembly has already been published,[1] and a YouTube video showing how the adapter is assembled can be seen at: youtube.com/watch?v=jwq7nDwgxa0&feature=youtu.be. (A picture of the adapter in use, and sample pictures taken using the adapter, can be seen above.)

"Initially I created the adapter for my own personal use," says Dr. Chan. "However, my colleagues saw my invention and encouraged me to continue working on the design to improve it. I eventually entered a local innovation competition in Malaysia and won first prize for the design."

Dr. Chan says one obvious disadvantage of his invention is that it may have to be recreated when a different phone is purchased. "The quality of picture you get also depends on the smartphone that you use," he adds. "I do notice that the speed of the camera that captures the picture makes a big difference. The iPhones I've used will take a picture within half a second after I push the button. Some competing phones take as long as one second to capture the image. This makes a huge difference, as patients tend to move their eyes. Also, exposure and focus are very important to getting a great picture, so the built-in camera may need help from additional apps to get the best shot. For example, separating the focus area and the light exposure has required purchasing an additional app."

Dr. Chan says he's been using the adapter for about three years and has improved the design several times. "I use it about once a week," he says. "Meanwhile, the first version of it is still being used and has yet to fall apart. I've introduced the adapter to four hospitals so far, and everyone is very happy with it." REVIEW

The intellectual property for the EyeGo adapters is owned by the Stanford University Office of Technology and Licensing. For more information about EyeGo, please contact eyegotech@gmail.com.

1. Chan JB, Ho HC, Ngah NF, Hussein E. DIY Smartphone Slit Lamp Adapter. J Mobile Tech Med 2014;1:16-22.

Putting Dry Eye To the Test

Walter Bethke, Managing Editor

Experts describe the best ways to incorporate the latest point-of-care dry-eye tests into your ocular surface disease workup.

Ophthalmologists say the multifactorial nature of ocular surface disease can be maddening; there are patients with any of the following: no symptoms but significant signs; significant symptoms but test results that don't seem so bad; and surface disease due to dysfunction of the meibomian glands, aqueous insufficiency or both. Because of this, experts say it can be helpful to have an objective method to help steer clinicians in the right direction with therapy. It's important, though, to know how to work these objective tests into your patient evaluation and how much weight to give to them. Here, ocular surface experts familiar with these objective tests share their advice on how to work with them.

(For an in-depth look at the latest point-of-care test, Sjö, see "Dry Eye: More Than a Symptomatic Disease" on p. 50.)

Inflammadry

The Inflammadry test from Rapid Pathogen Screening tests the tears for the enzyme known as matrix metalloproteinase-9. The company says MMP-9 on the ocular surface is a sign of inflammation, and that its presence means that a dry-eye patient may respond to anti-inflammatory therapy.

The Inflammadry test has been likened to a pregnancy test in that it doesn't provide a quantitative result, just basically a yes or a no. To administer the test, the tech or physician collects a tear sample, then activates it with a buffer solution. In 10 minutes, the test will be ready, and will either show a solitary blue line, indicating a negative result, or a blue line accompanied by a red line, which is positive. The test uses 40 µg/ml of MMP-9 as a cutoff point; anything above that will yield the red line, anything below will register as negative. In a study partially sponsored by RPS, researchers analyzed 46 dysfunctional tear syndrome patients and 18 controls. They found significantly higher mean MMP-9 activity in the test groups (as high as 381.24 µg/ml for one group) than in the controls, which registered a mean of 8.39 µg/ml. The researchers say that the MMP-9 levels showed significant correlation with symptom severity scores, decreased low-contrast visual acuity, fluorescein tear breakup time, corneal and conjunctival fluorescein staining, topographic surface regularity and the percentage area of abnormal superficial corneal epithelia.[1]

Wills Eye Hospital Attending Surgeon Sadeer Hannush uses the Inflammadry test, in addition to tear osmolarity, and says it can help support

his clinical exam and direct treatment. "Tear osmolarity is usually elevated in all types of dry eye, irrespective of etiology, while the Inflammadry test homes in on whether the cause of the dryness is inflammatory," he says. "Between listening to the patient's symptoms, performing vital-dye staining and looking at the tear-film breakup time, the height of the tear lake, lids and lid margins, I can pretty much piece everything together. Clinical exam alone, however, may not reveal the etiology of the dry eye."

Physicians say, though, that the test shows there's ocular inflammation but you have to rely on other diagnostic information to drill down to the cause, if desired. "With the MMP-9 test, if it's positive, I know there's inflammation," says Mina Massaro-Giordano, MD, co-director of the Penn Dry Eye and Ocular Surface Center at the University of Pennsylvania's Scheie Eye Institute. "So the next question is: What's causing it? Is it dry eye? If it is, what type of dry eye is it? Is there another reason for the abnormal ocular surface? It might not even be dry eye at all. For example, conjunctival chalasis can cause higher MMP-9 levels as that loose skin rubs up and down with blinking. But if you remove it, hopefully the inflammation will get better."

Dr. Hannush says knowing there's inflammation present is often helpful enough. "There's only so much testing and examination you can do at each patient visit," he says. "Often, the ophthalmologist has to decide what single additional diagnostic test would help direct the patient's treatment. For most of us who do this type of work, it's trial-and-error. If you perform one test and it's revealing, you may not wish to further pursue the etiology of the dry eye, but instead recommend a treatment. So, if I do Inflammadry and find inflammation, I'm going to treat it and not keep looking for another problem. But there's no doubt that there may be more than one cause for the dry eye. One of the benefits of a negative Inflammadry test is that it directs you away from inflammation as a cause of the dryness. This is helpful because then there's no reason to spend the time and money on anti-inflammatories such as corticosteroids or cyclosporine A. Instead, you can concentrate on tear supplementation and/or occlusion of the puncta."

Dr. Hannush says another group of patients who might benefit from dry-eye diagnostic testing is individuals coming in for a surgical procedure. "This would include laser vision correction and cataract extraction with premium intraocular lens implants, specifically multifocal lenses," he says. "If you don't diagnose a corneal surface problem accurately it can lead to suboptimal results in these patients. For their part, toric and accommodative IOLs may not have their performance compromised as significantly by the ocular surface as multifocal implants. Of course patients who are spending $1,000 or $2,000 out-of-pocket on any premium lens implant have very high expectations. Also, if a patient has a dense cataract, you may not be able to tell what his or her visual potential is until after removal of the cataract, so it would be helpful to eliminate the ocular surface problems ahead of time."

Interpretation of Lactoferrin and IgE Testing

Tear Chemistry	Indicates	Possible Cause of Symptoms
Normal lactoferrin and IgE	1. Normal lacrimal function 2. No ocular allergy present	Evaporative dry eye
Normal lactoferrin and high IgE	1. Normal lacrimal function 2. Ocular allergy present	Ocular allergy and possibly evaporative dry eye
Low lactoferrin and normal IgE	1. Suppressed lacrimal function 2. No ocular allergy present	Aqueous-deficient dry eye
Low lactoferrin and high IgE	1. Suppressed lacrimal function 2. Ocular allergy present	Aqueous-deficient dry eye and ocular allergy

Lactoferrin Testing

The Advanced Tear Diagnostics' Tearscan system is designed to detect the levels of the protein lactoferrin, which is produced in the acinar cells of the lacrimal glands. The idea behind tracking this protein is that it reflects aqueous tear production. The company also makes a test kit for immunoglobulin E levels in order to detect allergic conjunctivitis.

Ken Greenberg, MD, a practicing ophthalmologist and ATD's chief medical officer, says the test takes three to five minutes. "The lactoferrin test process involves taking a sample of tears and then putting the sample in a diluent," he explains. "The mixture is then placed on a test strip. In terms of which patients undergo the test, if someone has symptoms such as foreign body sensation, burning, intermittent blurry vision or a scratchy sensation, we'd start to consider using the test. We sometimes use the Ocular Surface Disease Index, a validated questionnaire, to help decide who should undergo the test, as well. We also test patients who are contact lens intolerant.

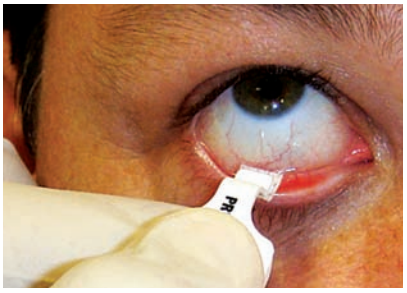
"Lactoferrin is an interesting protein," Dr. Greenberg continues. "It has anti-microbial and anti-inflammatory properties. So, by having an idea of the lactoferrin level in the tear film, we can assess what the tear production in the lacrimal glands is. This allows us to determine the underlying cause of the dry eye—whether it's aqueous deficiency or evaporation—since the lactoferrin levels are reduced in patients with aqueous-deficient dry eye. The test has a sensitivity of 83 percent and

a specificity of 98 percent." A study of human tears found the average lactoferrin level to be 1.5 mg/ml (range: 0.9 to 2 mg/ml),[2] so ophthalmologists who use the Tearscan test classify any result below 0.9 mg/ml as aqueous-deficient.

In an effort to determine lactoferrin's correlation to patients with dry eye, researchers in Japan prospectively divided 103 dry-eye patients into three groups: Sjögren's syndrome (n: 23); dry eye not associated with Sjögren's (n: 71); and Stevens-Johnson syndrome (n: 9). Sixteen normal patients also had their tears tested. All patients had their concentrations of lactoferrin, epidermal growth factor and aquaporin 5 measured by enzyme-linked immunosorbent assay. The investigators found that the concentration of lactoferrin was significantly decreased in tears of non-Sjögren's (p=0.0001), Sjögren's (p=0.00005) and Stevens-Johnson syndrome compared to control patients. The study's researchers say that the tear components in dry-eye patients apparently differ from those in normal patients both quantifiably and qualitatively.[3]

Dr. Greenberg says periodic checking of lactoferrin levels while a patient is undergoing therapy can be helpful, and is similar to other tests with which patients are already familiar. "We'll initiate treatment, then bring them back in a month to three months," he explains. "We do start to see the lactoferrin levels rise, though this hasn't been officially studied and is just my clinical impression. I think it can be helpful for patients to have a quantitative test, because they're used to undergoing lab tests and then hearing whether their cholesterol or anemia is better or worse since their last visit."

There may be potential synergies in testing both lactoferrin and IgE at the same visit in patients whose symptoms seem to combine both the hallmarks of dry eye and allergy. "The signs and symptoms of dry eye and allergy sometimes overlap," says Dr. Greenberg. "So, you may very well administer it at the same time. The classic case is the contact lens patient where the signs and symptoms of the two conditions can overlap quite a bit. The IgE test just adds another piece of information for the clinician."



LipiView (above) can help tell if dry eye is from an evaporative cause, while Inflammadry (right) ferrets out inflammation.

LipiView

The TearScience LipiView system is the diagnostic arm of a pair of products, the other of which is the LipiFlow treatment device. LipiView combines digital interferometry imaging of the lipid layer of a patient's eye with a quantitative measurement in an effort to suss out evaporative dry eye. If the lipid layer shows a certain amount of thinning, TearScience says, this indicates a problem.

Surgeons say the short, 19-second video that LipiView uses for its measurement can also clue them into patients who may have telltale blinking problems indicative of dry eye. "You can often look at the ocular surface and tell that the oil glands are clogged or see foamy tear film that says you're dealing with abnormal lipid levels," explains Dr. Massaro-Giordano. "Where LipiView does help is it helps measure partial blinks, a task that's sometimes difficult to do when you're talking to a patient. We'll watch the video and measure incomplete or partial blinks. I'll look at that number and talk to patients about how to improve blinks, because improving that can improve the quality of the oil coming out of their meibomian glands. This is an example of how I use bits from different tests during the discussion of patients' dry eyes." Dr. Massaro-Giordano says the LipiView can

For the treatment of elevated IOP

UNLOCK TREATMENT POSSIBILITIES

SIMBRINZA® Suspension delivered 21-35% mean IOP reduction at Month 3[1-3]

- 1-3 mm Hg greater than either component[4]
- Efficacy proven in two pivotal Phase 3 randomized, multicenter, double-masked, parallel-group, 3-month, 3-arm, contribution-of-elements studies. Primary objective of studies was to compare IOP-lowering efficacy of SIMBRINZA® Suspension, brinzolamide, 1%, and brimonidine, 0.2%. IOP was measured at 8am, 10am, 3pm, and 5pm[1,2]
- The most frequently reported adverse reactions in a 6-month clinical trial in patients treated with SIMBRINZA® Suspension occurring in approximately 3-7% of patients were eye irritation, eye allergy, conjunctivitis, blurred vision, dysgeusia (bad taste, conjunctivitis allergic, eye pruritus, and dry mouth[5]
- Only available beta-blocker-free fixed combination[2,3]

INDICATIONS AND USAGE

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

Dosage and Administration

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

IMPORTANT SAFETY INFORMATION

Contraindications

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

Warnings and Precautions

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

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

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

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

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

Adverse Reactions

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

Drug Interactions—Consider the following when prescribing SIMBRINZA® Suspension:

Concomitant administration with oral carbonic anhydrase inhibitors is not recommended due to the potential additive effect. Use with high-dose salicylate may result in acid-base and electrolyte alterations. Use with CNS depressants may result in an additive or potentiating effect. Use with antihypertensives/cardiac glycosides may result in additive or potentiating effect on lowering blood pressure. Use with tricyclic antidepressants may blunt the hypotensive effect of systemic clonidine and it is unknown if use with this class of drugs interferes with IOP lowering. Use with monoamine oxidase inhibitors may result in increased hypotension.

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

Learn more at myalcon.com/simbrinza

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

ONE BOTTLE. MANY POSSIBILITIES.

References: 1. Katz G, DuBiner H, Samples J, et al. Three-month randomized trial of fixed-combination brinzolamide, 1%, and brimonidine, 0.2% [published online ahead of print April 11, 2013]. *JAMA Ophthalmol.* doi:10.1001/jamaophthalmol.2013.188. **2.** Nguyen QH, McMenemy MG, Realini T, et al. Phase 3 randomized 3-month trial with an ongoing 3-month safety extension of fixed-combination brinzolamide 1%/brimonidine 0.2%. *J Ocul Pharmacol Ther.* 2013;29(3): 290-297. **3.** Data on file, 2013. **4.** SIMBRINZA® Suspension Package Insert. **5.** Whitson JT, Realini T, Nguyen QH, McMenemy MG, Goode SM. Six-month results from a Phase III randomized trial of fixed-combination brinzolamide 1% + brimonidine 0.2% versus brinzolamide or brimonidine monotherapy in glaucoma or ocular hypertension. *Clin Ophthalmol.* 2013;7:1053-1060.

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

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

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

DOSAGE FORMS AND STRENGTHS

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

CONTRAINDICATIONS

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

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

WARNINGS AND PRECAUTIONS

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

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

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

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

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

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

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

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

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

ADVERSE REACTIONS

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

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

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

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

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

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

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

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

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

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

DRUG INTERACTIONS

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

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

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

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

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

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

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

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

OVERDOSAGE

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

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

PATIENT COUNSELING INFORMATION

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

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

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

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

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

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

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

U.S. Patent No:
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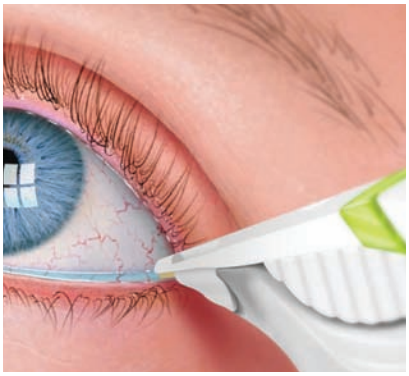
sometimes aid in following patients who are on therapy. "It might help me see that their oil layer seems to be healthier over the course of several visits," she says. "If their blinks are getting better, and I can see they're showing some improvement in lipid, that might be a guide for my therapy. My ocular exam is always number one, though."

Duke cornea specialist Alan Carlson says that, by the end of 2014, ophthalmologists will have access to the LipiView II, a new device with additional ways to analyze a patient's lids. "It actually gives you three different analyses of photos of the meibomian glands in the lower lid," Dr. Carlson says. "The first one is an infrared photo. The next is a transillumination image. The third is a merged image of the first two methods. So, you'll actually see if the glands are normal, dilated, if there are areas of dropout and even if there is some infection present."

Dr. Carlson says LipiView can help him avoid undertreatment, and is useful for documentation. "Not everyone in my practice gets a LipiView exam," he says. "Meibomian gland dysfunction is more frequently on my radar, though. Even Ed Holland and Donald Korb wrote an article on 'non-obvious MGD,' and if they can miss it, others certainly can as well. We still undertreat, but I'm becoming more sensitive in picking it up. It's common for me to get several LipiView analyses on patients, but even that doesn't always guide my decision making. Also, if patients are symptomatic and I see gland obstruction, I'm going to treat them, but I'll also get documentation with LipiView. Now, with LipiView II, documenting the status of the lid morphology is going to be an added benefit." Dr. Carlson adds that, as a refractive surgeon, he's acutely aware of the issues posed by an inadequate ocular surface postop. "If you have a busy surgical practice, by definition you're seeing dry-eye patients and have the potential to make them worse," he says. "If he's a nonsymptomatic dry-eye patient to begin with and even has small-incision cataract surgery, he will be getting drops afterward that can irritate the eye. This can tip the patient over to symptomatic dry-eye while he's recovering from surgery. So, I have a pretty low threshold for performing LipiView and LipiFlow on the patient preop."



A special pen and test card extracts a tear sample for osmolarity testing.

TearLab Osmolarity Testing

The TearLab test measures how concentrated the electrolytes in the tears are, with higher levels signifying that the aqueous component of the tears is low. To administer the test, the physician or technician takes a 50-µl sample of a patient's tears from each eye using a special pen and sample card. The TearLab device analyzes the card and provides a readout of the osmolarity level in the sample. Experts say a reading of 307 mOsms/L or below is normal. Anything above that in one of the eyes is a sign of dry eye, the severity of which increases with increasing osmolarity. A difference between the eyes, where one is high and the other normal, is a red flag as well. The test takes about two minutes.

Experts say that, like the other dry-eye tests that have come online in recent years, osmolarity testing should be just a part of a clinician's overall exam. Rhode Island ophthalmologist Michael Lemp, who helped develop the osmolarity test, says a questionnaire can be useful for identifying potential test candidates ahead of time. "To make sure you're not overtreating but, at the same time, not missing anyone, as well as to not slow down the patient flow in your practice, we've recommended practices develop a questionnaire for patients," Dr. Lemp says. "We recommend that it be one page, and that it contain a series of questions that will lead you to identify people who have a greater chance of having an abnormal osmolarity result. The questions can begin with, 'Have you ever been diagnosed with dry eye?' followed by a series of symptoms the patient can identify with, including symptoms that we now know are more common in relation to dry eye than we thought before, such as blurred vision during reading."

Dr. Lemp says such questions can help identify sufferers because they deal with issues most patients don't associate with dry eye. "One of the more common issues patients have when you ask them about it is eye fatigue," he says. "Most people just ascribe eye fatigue to getting older, but don't actually make the connection that there's a disease causing it. After the patient completes the questionnaire, the doctor can decide to perform the TearLab test if a certain number of responses are positive. The questionnaire results will be in the patient's chart when the doctor sees him."

Dr. Lemp says, logistically, physicians have learned it's probably best to place the testing unit in a small room or area of its own, rather than in an exam lane. "We've found one of the worst things to do is put one of these in an exam lane," he says. "If you decide a patient needs this test, the room the test is in will almost always be occupied, and the patient will have to wait for the room to be open."

(continued on page 83)

Is It Dry Eye, Allergy Or Infection?

Christopher Kent, Senior Editor

Although these conditions are usually easy to identify, they can sometimes mimic one another.

The modern world seems to have a knack for making some bad things worse. Cleanliness and relative isolation in childhood appear to be causing an increase in allergy problems; overuse of antibiotics is creating resistant bacteria; and air pollution, indoor heating and cooling and even some topical eye medications are helping to increase the prevalence of dry-eye syndrome.

Usually, when an ophthalmologist encounters these conditions, the signs and symptoms are sufficiently different to make identification straightforward. However, that's not always the case. Here, three experienced ophthalmologists share their advice for identifying and managing these problems when the nature of what you're dealing with isn't obvious.

Ask the Right Questions

"It's not often a clinician encounters a patient that's truly tough to diagnose," says Stephen C. Pflugfelder, MD, a professor and director of the Ocular Surface Center at Baylor College of Medicine's Cullen Eye Institute in Houston. "When faced with a patient who has dry eye, allergy or infection, most of the time the clinical features speak for themselves. But there can be occasional cases where it's hard to distinguish."

"Determining the nature of the problem starts with a good history and physical," says Bruce Koffler, MD, director of the Koffler Vision Group in Lexington, Ky., and associate clinical professor of ophthalmology at the University of Kentucky Medical Center. "It's important to ask the right questions. What is the chief ocular complaint? How long has this been going on? What are the signs and symptoms? Is anyone else in the family having similar problems? Does the patient have any systemic medical problems or indications that might play a role—for example, an immune disorder such as rheumatoid arthritis, lupus or vascular disease? Does the patient have a severe allergic condition, or any dermatologic problems relating to that such as psoriasis? The latter would suggest that the patient might have an unusual tendency towards allergy.

"It's also important to ask about any medications the patient may be using," he continues. "Is the patient taking an anticholinergic, antihistamines or one of the neurontin type of medications that people take for neurological pain? Some of those have significant drying effects. If it turns out that a systemic medication is contributing to the patient's problem, you

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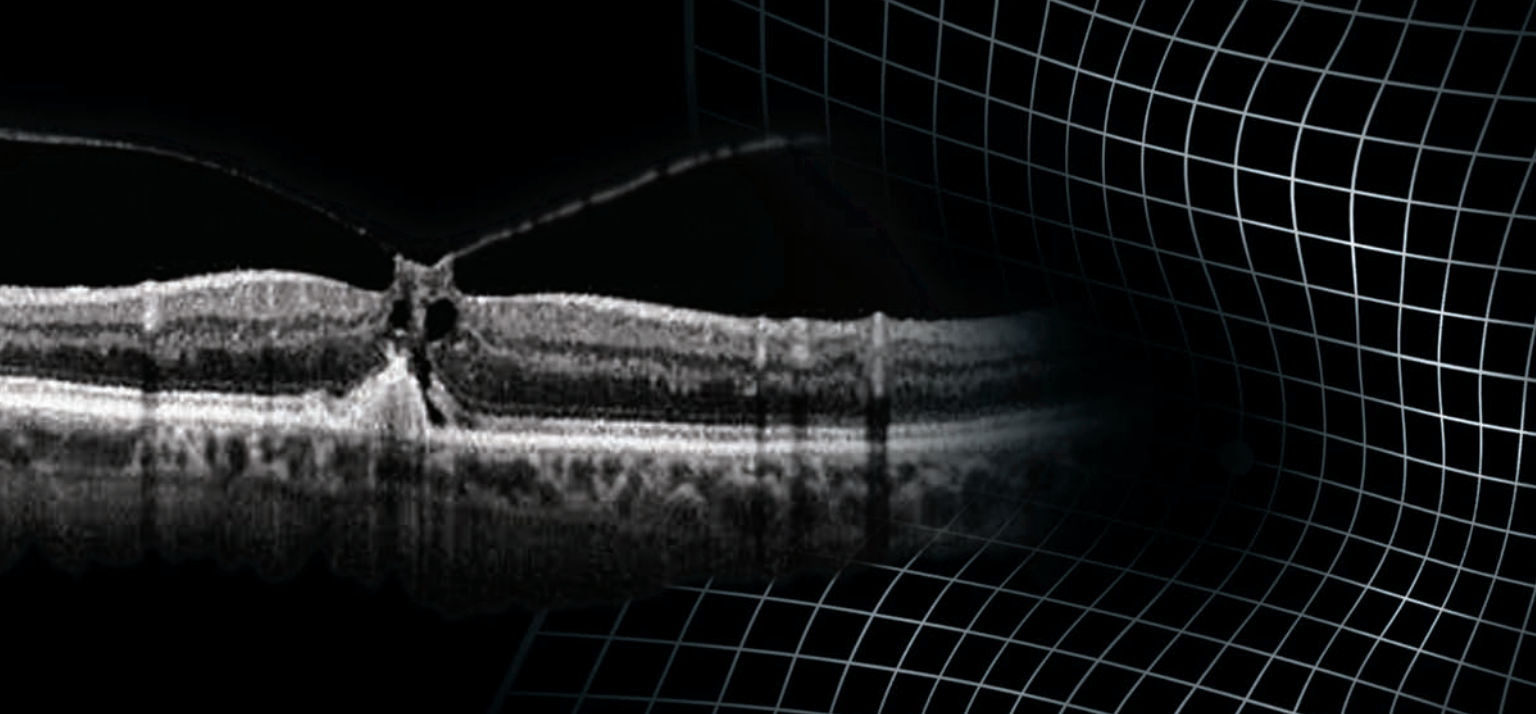

SYMPTOMATIC VITREOMACULAR ADHESION (VMA)

SYMPTOMATIC VMA MAY LEAD TO VISUAL IMPAIRMENT FOR YOUR PATIENTS[1-3]

IDENTIFY | Recognize metamorphopsia as a key sign of symptomatic VMA and utilize OCT scans to confirm vitreomacular traction.

REFER | Because symptomatic VMA is a progressive condition that may lead to a loss of vision, your partnering retina specialist can determine if treatment is necessary.[1-3]

THE STEPS YOU TAKE TODAY MAY MAKE A DIFFERENCE FOR YOUR PATIENTS TOMORROW

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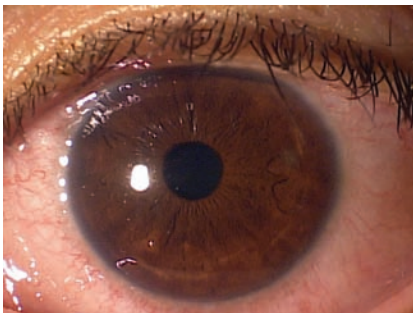
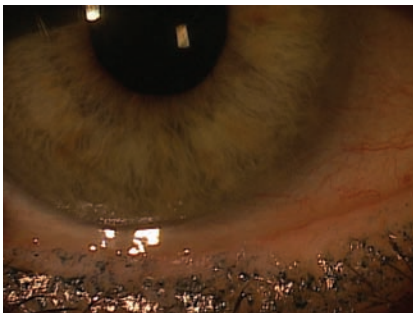
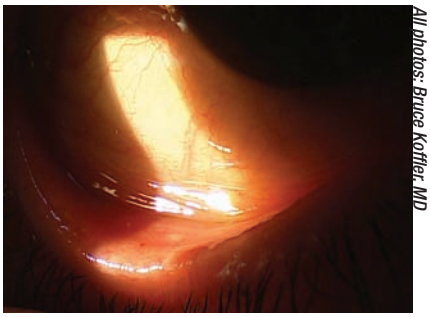
References: 1. Sonmez K, Capone A, Trese M, et al. Vitreomacular traction syndrome: impact of anatomical configuration on anatomical and visual outcomes. *Retina*. 2008;28:1207-1214. **2.** Hikichi T, Yoshida A, Trempe CL. Course of vitreomacular traction syndrome. *Am J Ophthalmol*. 1995;119(1):55-56. **3.** Stalmans P, Lescrauwaet B, Blot K. A retrospective cohort study in patients with diseases of the vitreomacular interface (ReCoVit). Poster presented at: The Association for Research in Vision and Ophthalmology (ARVO) 2014 Annual Meeting; May 4-8, 2014; Orlando, Florida.

All photos: Bruce Koffler, MD

When it's difficult to determine whether the problem is dry eye or allergy, symptoms may be a tip-off. Dry eye typically produces burning, scratching or foreign body sensation and possibly light sensitivity; allergy is typically associated with tearing and itching and may occur in concert with a seasonal or environmental allergen. Above left: An acute case of allergic conjunctivitis. Center: Allergic conjunctivitis secondary to eye makeup, which was not immediately obvious on examination. Right: Allergic conjunctivitis with a swollen contunctiva.

can ask the patient's internist to switch medications to something that doesn't dry the eye so much, or reduce the dosage, or stop the medication for a short period of time. But unless you're actively looking for this, you're not going to ask the right questions."

Dr. Koffler notes that failing to ask the right questions is often simply the result of being pressed for time. "In our busy days, with new factors such as electronic records to manage, digging deep looking for clues can get bumped down the priority list, especially for a non-specialist. We're busy running from room to room, and sometimes these probing questions take extra time to ask. Of course, if you're a cornea and external disease specialist, you're more likely to see cases that have not been diagnosed. In that situation you have to take the time to consider every possible factor that might be contributing to the problem."

Steven E. Wilson, MD, professor of ophthalmology and director of corneal research at the Cole Eye Institute of the Cleveland Clinic, agrees that in most cases, telling infection from allergy or dry eye isn't hard to do. "Usually a careful history and exam will enable a trained ophthalmologist to determine which condition is present," he says. "Most of the time they appear separately and present differently. However, sometimes it's hard to be sure whether you're seeing dry eye or allergy, or both, because one can exacerbate the other and there can be some overlap in the symptoms. It's even possible for a patient to have dry eye, allergy and an infection all at the same time; a patient could have blepharitis with chronic dry eye and get allergic symptoms once a year, too."

Allergy vs. Dry Eye

Dr. Pflugfelder says that in situations in which it's difficult to determine whether the problem is dry eye or allergy, the patient's symptoms are a partial tip-off. "If the problem is dry eye, the patient typically has burning or scratching or foreign body sensation, and possibly light sensitivity," he says. "The problem is often relieved with artificial tears. If the problem is allergy, the patient typically has tearing and itching and may report seasonal worsening, or worsening when he's challenged by an allergen such as a cat or certain weeds or flowers."

"If the patient has a red eye, boggy conjunctiva, watery discharge and itching, that's certainly allergic conjunctivitis," says Dr. Wilson. "On the other hand, if the symptoms are more subtle, where the eye isn't very red but appears irritated, that's the kind of patient that might make you wonder whether the problem is allergy or dry eye. Again, a detailed history is crucial. What symptoms does the patient have? Is itching a part of the symptom complex? That will make you lean more toward allergy. Is there a seasonal nature to it? Do the eyes get a very red conjunctiva periodically? Usually dry eye is not as much associated with that. Seasonal allergies tend to be more obvious to the clinician, based on the history and exam, especially when it's the right time of year for this patient and itching is the dominant symptom. That's not likely to be a dry-eye problem."

Dr. Wilson notes that while there is underlying inflammation in dry eye, it's a pathological diagnosis. "You don't necessarily see redness when looking at the whites of the patient's eyes, but you see it when you do a conjunctival biopsy or lacrimal gland biopsy," he points out. "In contrast, allergy patients often do have injection as a part of their signs. Itching and injection of the conjunctiva may not be constant, but they do recur. Another key question is whether the patient has other allergies, such as allergies to grass or certain foods, or has other conditions associated with allergy such as dermatitis or asthma. You can elicit that in the history."

Dr. Wilson adds that sometimes a patient doesn't believe he's having an allergic reaction simply because it's new to him. "I often see a patient who is 30 years old and having terrible itching, watering of the eyes and redness who tells me he's never had this before," he says. "My response is, 'Well, at some point everybody has it for the

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In addition to signs and symptoms, diagnostic dyes can help distinguish between dry eye and allergy; allergic conjunctivitis rarely produces staining on the surface of the eye. Above left: Classic inferior staining in dry eye. Center and right: Surface exposure in dry eye.

first time. This just happens to be your time.' "

Beyond the Exam and History

If the signs and symptoms are subtle, and you remain unsure whether the patient has dry eye or allergy (or both) after taking the history and conducting your exam, two more options remain: you can run tests, and/or you can see whether or not the patient responds to a given treatment.

Dr. Pflugfelder says that testing with diagnostic dyes like fluorescein and lissamine green can help differentiate dry eye and allergy when the presentation is ambiguous. "In allergic conjunctivitis there's very rarely staining on the surface of the eye, but in dry eye the cornea and conjunctiva may stain," he explains. "Tear breakup time can also help clarify the nature of the patient's problem. Breakup time will be rapid in dry eye, less than 8 seconds, whereas in most cases of allergy there's excess tearing and breakup time is not affected. It's true that there are a few chronic allergy conditions in which this might not be the case, but in an acute seasonal allergy attack, tear breakup time would unaffected."

Dr. Wilson agrees. "If you're still unsure, you can do lissamine green staining and examine the ocular surface and under the eyelids," he says. "Other tests such as Schirmer's might be helpful, although dry eye doesn't always have low tear production.

"If you examine the patient and you still can't decide whether you're dealing with allergy or dry eye, a common way to proceed is to decide on an initial therapy and see if the patient benefits from it or not," he continues. "Often the least expensive option is to prescribe one of the topical antihistamine medications and see if that relieves the symptoms. If the symptoms are very severe and I believe the problem is most likely allergy, I'll give the patient both a corticosteroid and an antihistamine. If the patient responds dramatically to that, I'm fairly certain the primary problem is allergy."

Dr. Pflugfelder says that if he really isn't sure, he might take a conservative approach and have the patient just lubricate the problematic eye. "There'd be no harm in also using topical antihistamine drops, or a combination antihistamine and mast cell stabilizer like Pataday or Elestat," he says. "Neither of those would cause any harm. However, I'd be reluctant to start corticosteroids if I really wasn't sure what the problem was."

Uncovering Infection

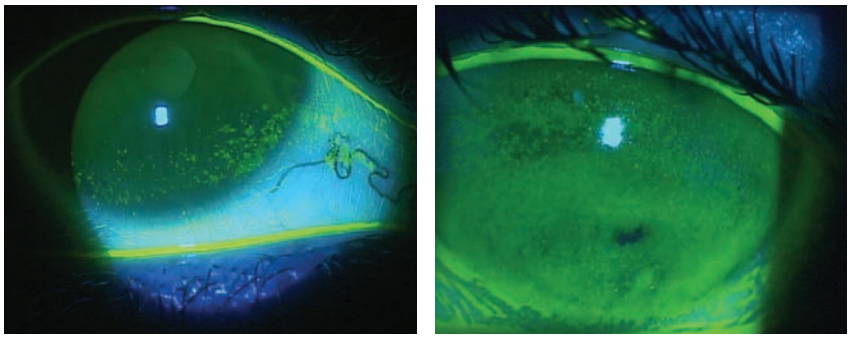
Making sure that any infection is diagnosed is key, both because of the potential for damage to the eye and the possibility of the infection being contagious. A common infectious finding is viral conjunctivitis.

"A classic situation in which you might have a little bit of uncertainty as to whether you're dealing with infection would be an early viral conjunctivitis," says Dr. Wilson. "The patient is just starting to get symptoms and has a little bit of injection. In most cases you probably wouldn't be thinking that the problem is dry eye, given that presentation, but you might be debating whether the patient has allergy or early viral conjunctivitis."

"If the patient has early viral conjunctivitis, the signs can be somewhat nonspecific," agrees Dr. Pflugfelder. "You might only see a red eye and tearing, which could be similar to allergy. On the other hand, in the classic, more full-blown cases the signs are very distinctive, potentially including prominent follicular reaction of the conjunctiva. In some cases membranes on the conjunctiva may need to be peeled off. Punctate erosions or infiltrates may be seen in the corneal epithelium, and after 10 to 14 days you may find small subepithelial infiltrates.

"If I suspect it might be a viral infection, I may use AdenoPlus, which is a rapid, in-office diagnostic test that confirms the presence of adenoviral antigens in the tears or on the conjunctiva," he continues. "If that's positive, that would solidify the diagnosis of viral conjunctivitis. The only other viral conjunctivitis would be herpes, which is rare, and might also produce corneal involvement such as dendrites in the epithelium."

"Usually, viral conjunctivitis will run its course in seven to 10 days," says



Above left: Inferior staining in a dry eye patient. Right: A dry eye showing diffuse staining.

Dr. Wilson. "In the winter and early spring here in Ohio we see hundreds of viral conjunctivitis patients. I tell them that I expect it to run its course in seven to 10 days, and only rarely will a patient come back. Actually, timing can also be an important part of telling viral infection and allergy apart. If the patient has established that this is a persistent problem, and it involves a lot of itching, the odds are very good that this is an allergy problem rather than a chronic infection. And, if you've treated what was really viral conjunctivitis with antihistamines and discover that this doesn't improve the patient's problem, the viral conjunctivitis will likely run its course in a few days. If it doesn't, and the patient is still having symptoms at that point, I'd do more testing and possibly initiate a different course of treatment."

He notes that the history may give you a strong indication that the problem is viral conjunctivitis. "The patient may report being exposed to someone who has pink-eye at work, school or home," he says. "During an epidemic of viral conjunctivitis 30 to 50 percent of people are aware that they were exposed to someone with pink eye. That makes identifying the problem easy."

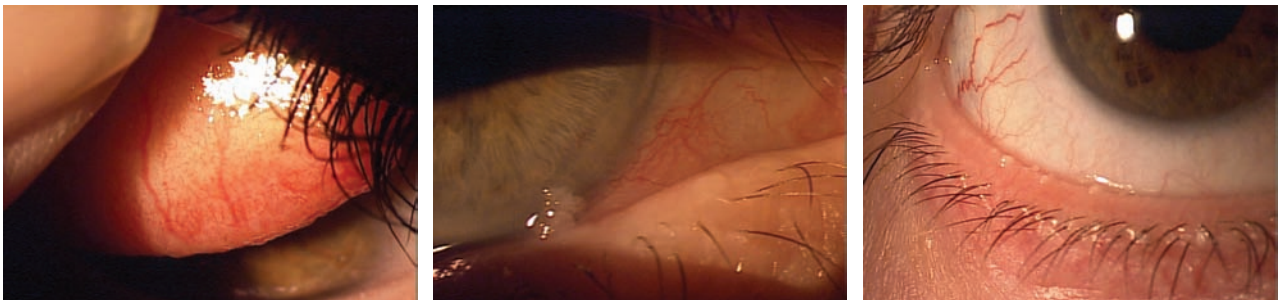
"If the patient has herpes, there are good antivirals you can prescribe, but for adenovirus there's no specific treatment," adds Dr. Pflugfelder. "About all you can do is inform the patient that he or she has it and warn the patient to be careful to not contaminate the other eye if it's not yet involved, as well as to avoid contaminating other people. It's usually advisable for the patient to stay home from work or school. Sometimes these patients have already infected other people, but at least you can prevent further exposure by having them stay home for a while."

Viral vs. Bacterial

Although less common, bacterial conjunctivitis is always a concern. "When it comes to confusing dry eye or allergy with infection, it depends on what type of infection you're talking about," says Dr. Wilson. "Keratitis usually isn't confused with allergy, but there are some situations in which patients with allergic conjunctivitis can have sufficient corneal involvement that they get infiltrates. Then you could find yourself wondering whether the patient simply has an allergy or if he's developed a secondary bacterial infection. If the uncertainty cannot be resolved, the clinician may find it necessary to perform cultures and treat for infection, and then monitor the response to the treatment."

Dr. Koffler notes that the presence of a discharge can reveal a lot about the nature of the problem. "This can help differentiate allergy from infection," he points out. "If it's a purulent discharge with a lot of mucus, we tend to be more oriented toward infection. If it's a clear, watery type of discharge accompanied by a lot of itching, we're more apt to look for allergy."

Dr. Pflugfelder says he'd only con-



Bacterial infection often presents with a purulent discharge. Above left: Papillary conjunctivitis with bacterial infection. The lid has a lumpy, bumpy appearance. Center: Bacterial conjunctivitis with a mucous discharge. Right: Plugged glands in bacterial blepharoconjunctivitis.

sider using antibiotics if he found a purulent discharge. "Severe dry eye can sometimes be accompanied by discharge," he notes. "In fact, these patients are probably a little bit predisposed to develop bacterial conjunctivitis. So if the problem was dry eye and the eye had a lot of pus, I would treat with topical antibiotics, just as I would if the problem was bacterial conjunctivitis. Otherwise, I'd avoid antibiotics; they might not cause any harm, but they're expensive and you could enhance resistance."

"If you have a patient who is a diagnostic dilemma and you need to rule out some form of infection, getting a good culture can be very helpful," says Dr. Koffler. "If a patient has been suffering for a long time, I don't hesitate to do this. In fact, the chronicity of the disease is an important consideration when deciding whether a culture is appropriate. If the patient comes in with a 24-hour or 48-hour history, we don't usually get a culture. But if the patient has been suffering for three months, then we're looking for something different. Most patients in this situation have seen a lot of different doctors, and no one has come up with the answer. So I would definitely consider getting a culture in that situation."

Dr. Wilson notes that some forms of bacterial conjunctivitis can be persistent and chronic. "Chlamydia conjunctivitis can persist until it's treated, and it often does," he says. "We sometimes encounter patients who have been seen by two or three other doctors and treated for dry eye or allergic conjunctivitis—despite the fact that the signs and symptoms of chlamydia are somewhat different from those of allergic conjunctivitis. The presence of a persistent follicular conjunctivitis should always raise the possibility of chlamydia in the doctor's mind. Cultures and immunofluorescent testing for chlamydia can be performed. If these are not available, clinicians often treat the patient presumptively for chlamydia—for example, with doxycycline 100 mg b.i.d. for four to six weeks.

"If a patient has already been treated before coming to us, we have the advantage of knowing that the previous treatments were ineffective," he adds. "If the patient is a sexually active adult, we always consider chlamydia as a possible cause. We may even consider this possibility when the patient is a child if there's any indication of abuse. We can culture for chlamydia to get confirmation; however, the results are not always positive even when chlamydia is present. So if we're suspicious this is the problem, we may go ahead and treat the patient with a course of doxycycline."

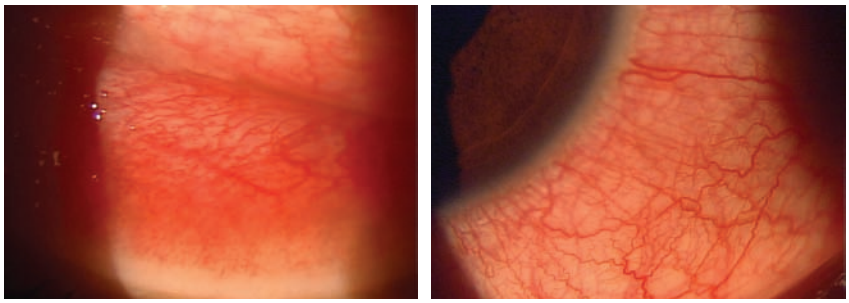
The Newer In-office Tests

In recent years a number of new in-office tests for factors associated with dry eye and other conditions have become available, but doctors have mixed feelings about how helpful they might be in this situation.

Like Dr. Pflugfelder, Dr. Koffler says he sometimes uses the AdenoPlus test, among others, to confirm a diagnosis. "Viruses are difficult to culture, but we now have immunoassays such as the AdenoPlus that can help confirm the presence of adenovirus," he says. "There are also herpetic assays that can also be helpful in difficult cases. I find it useful to have these handy in the office. If everything points me towards an adenovirus infection, and I get a positive AdenoPlus diagnostic test, I'm feeling pretty good that that might be my diagnosis. This is important, since patients with active adenovirus are encouraged to not go to work and to take infection-control measures at home."

Dr. Pflugfelder believes the usefulness of some other tests, as an aid to distinguishing between dry eye, allergy and infection, remains to be seen. "If tear osmolarity is elevated and is accompanied by other findings such as rapid tear breakup time or some staining on the eye, then I think it would be a meaningful supplemental diagnostic test," he says. "But even in this situation, it would only be valuable if it were definitely high. That's the problem with using it; the results might be equivocal and therapy would still be based on clinical findings.

"The same thing could be true of testing for matrix metalloproteinase 9," he adds. "If the level is high, I think it would supplement the clinical diagnosis. On the other hand, there might be enough of an increase in MMP-9 in allergy or viral conjunctivitis to make



Above left: Bacterial conjunctivitis produces a lower lid cul-de-sac reaction with discharge. Right: A marked blood vessel conjunctival reaction in bacterial conjunctivitis.

the test positive as well. I don't think this question has been resolved, so the specificity of these tests remains to be determined."

Dr. Wilson agrees. "The biggest problem with a test like the MMP-9 test is that it's non-specific," he says. "It can give a positive result in dry eye, in infection or in any inflammatory condition affecting the eye. Basically, all it tells me is that there's inflammation, which I often already know from my examination. Osmolarity testing is also problematic in this situation. People are using osmolarity to try to be more specific when diagnosing dry eye; the problem is, there's so much variability in the test. Even if you take a group of completely normal patients with no signs or symptoms of dry eye, the test could be positive. So in my mind, the jury's still out on these adjuvant tests. I think this kind of test can be useful, but I don't think it's a panacea for making a diagnosis that eliminates the need for a good history and examination.

"I think it would be really wonderful if we had much more specific molecular markers that could be tested," he adds. "That might allow us to say, 'This is definitely dry eye,' or 'This is definitely allergy.' I think the potential for this exists because the molecular pathways are different, but at this point we don't have tests that can do that."

Using Steroids

Corticosteroids can be helpful in many situations, but there are a host of caveats. "With a bacterial infection, I like to have 24 to 48 hours of antibiotic drops on the eye before I think about steroids," says Dr. Koffler. "Even when I believe the problem might be a *Staphylococcus* hypersensitivity reaction, I'll still often use plain antibiotics and add a steroid 48 hours later, after I feel that I have a better handle on the situation. Within 24 hours I'll be getting back information from the cultures, and that will give me a better idea as to whether antibiotics are the right approach. The main point is, don't rush with steroids. You can add them later. If you don't really know what the problem is, stick with an antibiotic first."

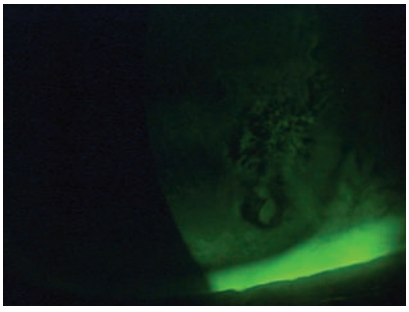
"Corticosteroids work well in dry eye or if the problem is allergy and the patient is pretty symptomatic," says Dr. Pflugfelder. "Corticosteroids also can do a good job of suppressing inflammation caused by viral conjunctivitis, but there's a debate about how advisable that is. Some people feel that you might prolong the viral infection by using steroids. So steroids generally improve dry eye and allergy, and improvement will be seen in viral conjunctivitis, but they are generally reserved for severe membranes or subepithelial infiltrates. On the other hand, treating bacterial conjunctivitis with steroids would not be advisable. Fortunately, bacterial conjunctivitis is pretty rare. It's usually only seen in sick or elderly people, and sometimes in children who have pharyngitis or otitis media."

Dr. Wilson notes that if you're not certain whether the patient has allergy or early viral conjunctivitis, caution is warranted. "If this patient actually has early viral conjunctivitis and you mistake it for allergy and treat with a corticosteroid, you might make the patient worse by inhibiting the patient's immune response," he says. "The outcome might not be too bad if the problem is actually adenoviral conjunctivitis; but if the problem is primary herpes simplex, and you give the patient corticosteroids thinking it's allergy, you could potentially have a very serious problem on your hands. For this reason, you have to be as sure as possible about the diagnosis before you give the patient corticosteroids." Dr. Wilson adds that you also have to be careful about steroid side effects, such as the possibility of a spike in intraocular pressure.

"The other problem that sometimes arises is that the relief may be so thorough and quick that the patient wants to know why he can't use the steroid drops all the time," he adds. "You have to be careful to explain to the patient right up front: 'This is something you can maybe use a couple of times a year, for a period of time, but you can't use this chronically because it can cause cataracts, glaucoma, increased risk of infection and so forth.' "

Managing Multiple Problems

"Sometimes one condition can lead to another," notes Dr. Koffler. "For example, allergy might end up plugging the meibomian glands, which then have *Staphylococcus* captured in them, potentially causing sties and chronic infectious blepharitis and conjunctivitis. Contact lens wear with chronic touching of the eye, along with the use of different disinfection agents, can go on to cause blepharitis, both infectious and noninfectious. And dry eye is associated with meibomianitis 50 percent of the time.



Primary herpes simplex. It's important to distinguish between an allergic reaction and early viral conjunctivitis. If the problem is herpes simplex and you mistakenly treat with corticosteroids, it could result in a worsening of the problem.

So, one problem can definitely lead to another.

"I think you should always go after the infection first, unless you're very sure that it's something different," he continues. "If you don't immediately treat allergy or dry eye, you're not going to hurt anything. But if you let an infection go on, you may get further scarring; it may even go on to ulceration. So if you're faced with multiple problems, work on the infection; maybe start some lid hygiene to quiet down the lids. Later on, after you feel things are under control, you might want to come in with a steroid or a specific antibiotic that's better at handling the inflammatory component of meibomianitis. The use of nighttime ointments can also be helpful for allowing the patient to get a good dose of antibiotic at nighttime."

Dr. Wilson points out that allergic conjunctivitis can sometimes lead to dry eye. "Patients with year-round allergies tend to be more problematic, especially if they're severe," he notes. "They may have ongoing atopic changes in the conjunctiva with a lot of irritation and itching, although sometimes that component isn't as prominent. You look at these patients and your exam tells you they most likely have allergic conjunctivitis—but a patient in this situation can also develop dry eye. So sometimes you have to treat both."

Dr. Pflugfelder says that in the rare instance where he encounters someone with all three problems, he focuses on the most symptomatic concern. "If I was sure that the patient had acute viral conjunctivitis, I probably wouldn't use corticosteroids," he says. "I'd just treat with lubricants, and treat the itching with an antihistamine drop. Once the viral conjunctivitis resolved, I might use other things such as corticosteroids or Restasis."

Going Down the Right Path

These pearls can help ensure that your diagnosis is correct and treatment goes according to plan:

- ***When taking the history, ask about workplace and home environments***. "Nowadays, many of us sit at a desk for long periods of time," notes Dr. Koffler. "Ask whether the patient is aware of air blowing on him during working hours. This could cause dry eye, or an allergic reaction if the vent is spreading some kind of allergen. The air at home could be a problem as well. Are there dust mites or other allergens in the house? Does the patient need a humidifier? The reality is, if you're not sure about the nature of the problem, you really have to search deeply."
- ***Don't forget to ask about eye drops and systemic medications the patient may be using.*** "These may explain dryness or irritation and help you avoid making an incorrect diagnosis," says Dr. Koffler. "Topical eye drops of different kinds can cause toxicity and irritation that presents in any one of a number of ways, from chronic dry-eye symptoms to meibomian gland disease to chronic red eyes. Often I'll just stop the chronic glaucoma drop a patient has been using, and her red eyes start to get better."
- ***Remember that a reaction to an eye drop may not happen for the first few months of use.*** "Eye

drops can cause delayed sensitivity, which means that initially the patient may appear to be doing fine," notes Dr. Koffler. "Then after six months or a year all of a sudden the patient starts to have an allergic reaction to the drop or to the preservative in the drop. The fact that the reaction just appeared doesn't mean you should eliminate the eye drops as a possible cause."

• ***Warn your staff to be careful around red-eye patients.*** "This is something many clinicians are not careful enough about," says Dr. Koffler. "Until you're sure what you're dealing with, avoid physical contact with this kind of patient. If the red eye is caused by an infection, it can easily be transmitted. I've seen a couple of ophthalmologists get nasty adenovirus infections—most likely from their patients—that put them out of work for a significant amount of time.

"I make every attempt to not touch the infected patient physically," he continues. "I like to shake hands with most patients, but I don't shake hands with red-eye patients. I also never touch the patient's eyelids with my hands; I always use cotton applicator sticks to hold the lids when doing the examination. Of course, you also have to instruct your staff to do the same, because they'll see the patient first. I tell my staff that when a patient has red eyes, don't be in a hurry to take pressures. A glaucoma attack could present as a red eye, but until I see the patient and get the feeling that glaucoma is the problem, I don't want them to touch the patient or use my instruments on the patient. Also, I have to assume that by the time I get into the room, the patient has touched several tables or my slit lamp. So when we're finished in a room that I think is infected, I quarantine the room. My team comes in with gloves and alcohol and completely wipes down all the surfaces—and they don't spare the alcohol.

"Of course, if I think the problem is not infectious—viral or bacterial—then I'm not going to worry about this," he adds. "But sometimes you're not sure. That's why you really should back away from contact with a red-eye patient until you know what the problem is. We don't think about this enough, and we can suffer the consequences."

• ***Check for swelling in the preauricular lymph node.*** "A swollen lymph node in front of the ear is a classic sign of viral conjunctivitis," Dr. Pflugfelder points out. "Chlamydia can also cause that. So, that's one of the first things I check when I see someone with pink eye. If that node is swollen and other signs are present, it's almost diagnostic."

• ***Ask whether the patient is self-treating.*** "You have to be careful that the patient isn't mixing up something of his own and putting it on or in the eye," notes Dr. Koffler. "People may hear or read on the Internet about a do-it-yourself remedy using herbal medications, or putting a tea compress on the eye, thinking it will treat pink eye. It's important to know what they've been doing on their own."

• ***If allergy might be the explanation, consider getting smears when culturing for eosinophils.*** "If you take a culture, you can set aside some of the specimen on a slide and ask pathology to look at the cells," notes Dr. Koffler. "Increased eosinophil cells are a typical sign of allergy. You could also have an eosinophil blood count done, to see if the number is elevated, which would indicate a significant allergic reaction."

• ***In case of infection, look carefully at both the conjunctiva and cornea.*** "Bacterial infection usually causes a papillary conjunctivitis, and the corneal lesions tend to be round, whitish infiltrates," notes Dr. Koffler.

"Viruses like herpes simplex or adenovirus tend to cause more of a follicle reaction on the conjunctiva. On the cornea, adenovirus tends to produce classical stellate lesions, while herpetic disease tends to produce dendritic lesions. These signs can be very helpful to us in differentiating whether the infection is bacterial or viral."

• ***Consider topical cyclosporine A when treating both allergic conjunctivitis and dry eye.*** "If a problematic seasonal or year-round allergy patient is not controlled by antihistamine products or is in danger of steroid overuse, sometimes topical cyclosporine A will be very beneficial and keep the condition under control," says Dr. Wilson. "And if the patient also has dry eye, you're treating that, too. Cyclosporine A treats inflammation, which is a component in the pathophysiology of most dry eye, and there's an inflammatory component to allergic conjunctivitis as well. The inflammation in dry eye vs. allergy is mediated by different cell types, but cyclosporine A seems to address both types well."

"There's no harm in using Restasis in the presence of allergy," agrees Dr. Pflugfelder. "In fact, Restasis would probably help with severe allergic conditions, such as vernal conjunctivitis or atopic keratoconjunctivitis. I don't know that anyone has proven that it's good for seasonal allergic conjunctivitis, but again, it wouldn't hurt."

• ***Remember that you don't always need to treat.*** Dr. Pflugfelder notes that viral conjunctivitis is self-limiting. "Viral conjunctivitis will get better on its own, in most cases," he says. "There's really no specific treatment for viral conjunctivitis anyway. All we have are palliative treatments like using artificial tears and cold compresses. If the viral conjunctivitis produces corneal problems such as subepithelial infiltrates, then steroids or Restasis will help. In any case, there's really nothing you can do to prevent that from occurring; whether or not corneal problems occur depends on the particular virus you're dealing with, and they would occur subacutely after 10 days or two weeks.

"For viral pink eye, there's no harm in deferring treatment and reassessing in a week or so," he continues. "In fact, even mild, non-severe bacterial conjunctivitis is usually self-limited, even without antibacterial treatment, so there'd probably be no harm in waiting a week or two and then reassessing the patient in mild bacterial cases. In either situation, once the conjunctivitis has resolved you can deal with any remaining condition such as dry eye."

• ***Know when it's time to let someone else investigate.*** "Don't keep trying endlessly to treat a non-responsive problem," says Dr. Koffler. "If you need a cornea-external disease specialist for a given patient, go ahead and send the patient on to that individual. If the problem is systemic, consider getting help from an allergist. The latter is something we don't often think of, but in some cases it could be useful. A specialist in that area can delve into things even further and get allergy testing done."

The Diligent Detective

Ultimately, getting to the bottom of a mystery largely depends of the thoroughness of your exam and history, and being willing to stay on the case. "Doctors should get in the habit of doing a careful slit-lamp examination, checking for a preauricular lymph node, using diagnostic dyes and supplementing with tests for adenoviral antigens, MMP-9 or high osmolarity, if appropriate based on the clinical findings," says Dr. Pflugfelder. "And of course, take a good history. If the patient mentions that two people in the office had pink eye last week, that pretty much tells you what you're dealing with."

"Look at the situation systematically," advises Dr. Koffler. "Get a good history and physical. Examine the conjunctiva—are there papules or follicles? If appropriate, get a culture or smear. Have some diagnostic tests available, such as rapid immune tests for herpes simplex or adenovirus. And be very careful to safeguard yourself, your staff and other patients from individuals who may have contagious conditions."

Dr. Wilson admits that it's always possible to be fooled. "All of us who practice medicine are faced from time to time with a situation where we think we're dealing with one thing, and then it becomes clear that we're actually dealing with something else," he says. "For example, herpes can be like that. It's known as the great masquerader, because you think you're dealing with one thing and then the patient gets worse because you didn't treat him with an antiviral. The patient may go on to develop corneal epithelial lesions with or without infiltrates that are characteristic of herpes simplex, and you realize that you were fooled.

"Medicine really is a mix of art and science," he adds. "Sometimes a patient is a bit of a mystery case, where you have to explore and do multiple tests and try more than one treatment until you discover what the problem really is. The best approach is to take a thorough history and do a careful examination, looking at all the signs and symptoms. If necessary, you can run appropriate tests. However, be careful not to rely too much on tests. It's the history and exam that usually will lead you to the correct diagnosis." REVIEW

Dr. Wilson is a consultant for Allergan. Drs. Koffler and Pflugfelder have no financial ties to any product mentioned.

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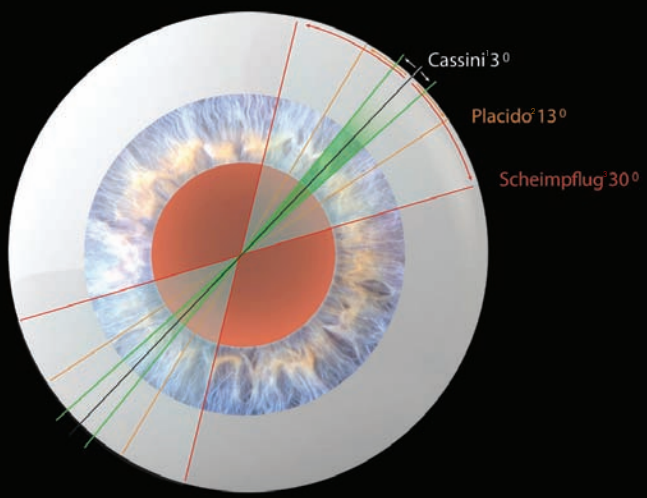

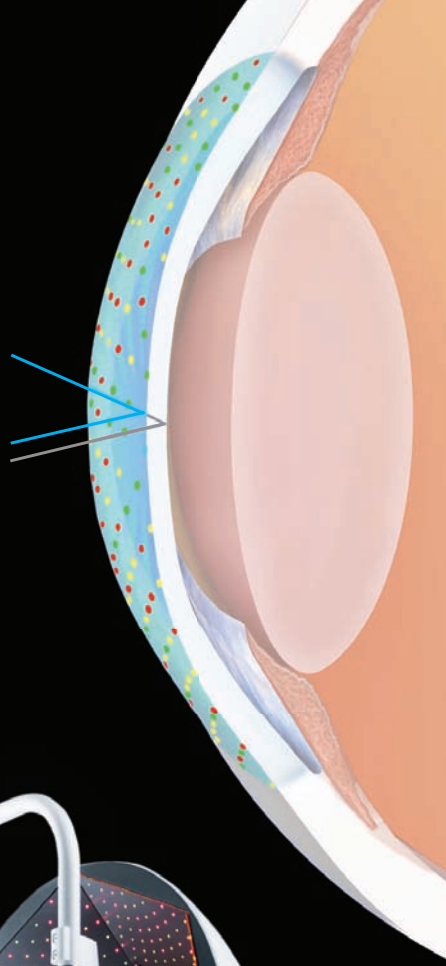

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[1] A. John Kanellopoulos, MD. Clinical Professor Of Ophthalmology New York University Medical School
[2] Karabatsas et al. EJO 2005, [3] McAlinden et al. IOVS 2011

i-optics

In the Dry-Eye Pipeline: Slow Progress

Michelle Stephenson, Contributing Editor

New agents are promising, but approvals are likely several years away.

Dry eye affects an estimated 25 million Americans, with estimates worldwide as high as 60 million people. Patients with dry eye can experience poor vision and chronic pain. Fortunately, there are new drugs in the pipeline that look promising for the treatment of dry eye.

"Between 10 and 15 percent of ophthalmic pharmaceuticals are dry-eye medications, and that percentage is growing. It is projected to double in the next 10 years, so it is a growing niche," says Leonard Bielory, MD, from Rutgers University and Robert Wood Johnson University Hospital, New Brunswick, NJ.

Lifitegrast

Lifitegrast (Shire) is a small-molecule integrin antagonist that inhibits T-cell inflammation by blocking the binding of two key cellular surface proteins (LFA-1 and ICAM-1). It is currently in Phase III clinical trials.

OPUS-2 was a multicenter, randomized, double-masked, placebo-controlled, parallel-arm study comparing lifitegrast (5.0% ophthalmic solution) to placebo administered twice daily for 84 days (12 weeks) in dry-eye patients with a history of active artificial tear use within 30 days prior to screening. The study included 718 patients at 31 U.S. sites and consisted of five visits over 98 days.[1]

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

None of the patients in this study experienced serious treatment-emergent adverse events. The most commonly reported treatment-emergent adverse events associated with lifitegrast were dysgeusia (16.2 percent vs. 0.3 percent for placebo), instillation site reaction (7.0 percent vs. 1.1 percent for placebo), and reduced visual acuity (5 percent vs. 6.4 percent for placebo).

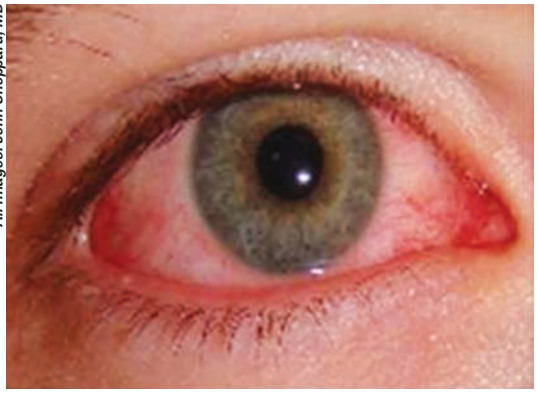
Additionally, top-line results from SONATA, a prospective, randomized, double-masked, placebo-controlled study, indicated no ocular or drug-related serious adverse events.[1] At day 360 of the study, the ocular adverse events that occurred in 5 percent or more of study participants included instillation site irritation (15 percent vs. 4.5 percent with placebo); instillation site reaction (13.2 per-

cent vs. 1.8 percent for placebo), reduced visual acuity (11.4 percent vs. 6.3 percent for placebo), and dry eye (1.8 percent vs. 5.4 percent for placebo). The most commonly reported non-ocular adverse event associated with lifitegrast was dysgeusia (16.4 percent vs. 1.8 percent for placebo).

According to John Sheppard, MD, professor of ophthalmology, microbiology and molecular biology at Eastern Virginia Medical School and president of Virginia Eye Consultants in Norfolk, this agent is the leader of the pack. "It treats via a very different inflammatory pathway and offers the potential for less mechanistic and medication-based toxicity," he says. "We all know that Restasis can be slow to act and stings some of our patients. As a result, the engineers at Sarcode actually designed this drug from the bottom up to create the ideal ocular surface medication. The molecule was designed first to have a very high and irreversible affinity for a key binding site. The drug then acts as a molecular decoy to prevent the actual signaling that occurs with ICAM-mediated inflammation."

According to Dr. Sheppard, additional advantages of lifitegrast are that it has a pH of 7.0, which is consistent with or most prevalent in the tear film. It is also fully aqueous-soluble, so it can be delivered in saline. "Finally, it is stable at room temperature for long periods of time, giving it an excellent pharmaceutical shelf life," he adds.

Data has been submitted to the Food and Drug Administration and under review. "I think that this will be a blockbuster drug for the ocular surface to complement Restasis in the marketplace," says Dr. Sheppard.



All images: John Sheppard, MD

Figure 1. Exposure area conjunctival injection, lid margin erythema and meibomitis, and decreased tear meniscus in a 45-year-old otherwise healthy woman with moderate dry eye.

MIM-D3

MIM-D3 from Mimetogen Pharmaceuticals is currently undergoing Phase III trials. The company has released top-line data from its second clinical study with MIM-D3,[2] and the trial demonstrated significant improvements in signs and symptoms with 1% MIM-D3 versus placebo, along with excellent safety, comfort and tolerability profiles.

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

Study participants reported that MIM-D3 was comfortable and well-tolerated, and there were no unexpected or serious ocular adverse events. The most commonly reported ocular adverse events were reduced visual acuity (3 percent vs. 3 percent for placebo), instillation site pain (1 percent vs. 1.5 percent for placebo), and eye irritation (0 percent vs. 1.5 percent for placebo). All adverse ocular events were mild and transient.

"MIM-D3 is a secretogogue for mucin. Mimetogen has affiliated closely with Bausch + Lomb and is carrying out Phase III trials," Dr. Sheppard says. "We strongly believe that this new mechanism of action, which is unique in the pipeline space, will be highly complementary to other dry eye drugs in the pipeline because of the difference in their targets."

RU-101

RU-101 by R-Tech Ueno is an ophthalmic solution containing recombinant human serum albumin. Stage 1 of the Phase I/II clinical trial has been completed, and enrollment for stage 2 has begun.

In stage 1, the safety of RU-101 was evaluated using placebo as the control to understand what dose can be used in patients with severe dry eye. Stage 2 will also use placebo as the control and will evaluate the efficacy and safety of RU-101 by administering it at the maximum dose for which safety has been established in stage 1 for 12 weeks.[3]

"This product uses human serum albumin, which is an entirely new mechanism of action," says Dr. Sheppard. "They have taken recombinant serum albumin and turned it into a medication. We all know that human serum tears, which are almost always autologous, produce a profound effect on severe dry-eye patients, although cytokines and growth factors may also play a part. Nevertheless, human serum tears are cumbersome, expensive, difficult to access in all

but the most experienced facilities, and potentially dangerous due to the risk of infection. The biorecombinant product is in Phase II, and I believe the results could be very promising. Certainly, the side effect profile should be minimal. Human albumin protein by itself has a lot of anti-inflammatory effect and beneficial activities in terms of wound healing that we hope will translate into the repair of ocular surface disease caused by dry eye."

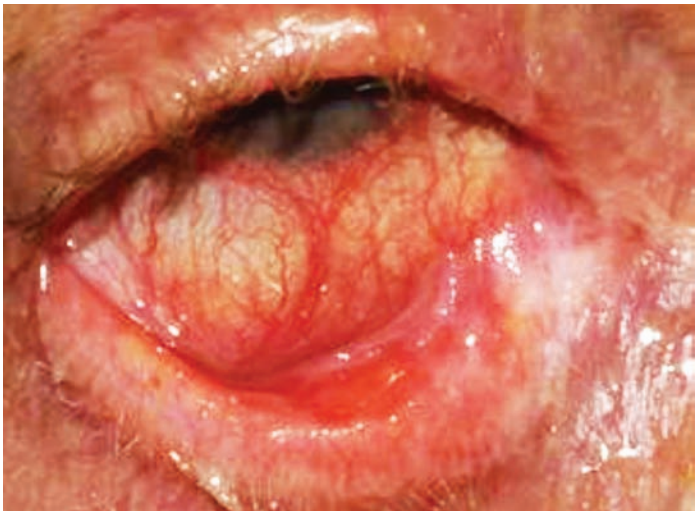


Figure 2. Severe dry eye seen in ocular cicatricial pemphigoid, with diffuse erythema, inferior symblepharon, chronic secondary infectious conjunctivitis and severe inferior confluent staining.

KPI-121

KP-121 by Kala is a loteprednol etabonate mucus-penetrating particle (MPP) drug product that is currently in Phase II trials. In the trial, investigators will study the safety and efficacy of 0.25% LE-MPP compared to vehicle dosed four times daily in patients with meibomian gland disease.[4] Kala plans to enroll approximately 150 patients in up to 10 centers in the United States.

"This is a unique vehicle formulated to deliver very high doses in stable form to the ocular surface and the deeper layers of the tear film," says Dr. Sheppard. "This particular technology is also capable of delivering many other drugs. It is also being looked at with loteprednol for other indications like allergy and blepharitis. Bausch + Lomb scientists, apparently prior to the Valeant acquisition, have also successfully reformulated a lower concentration of loteprednol in a nanoparticle-based vehicle, which should also prove to be an exciting prospect for clinical investigation in dry eye. We are really excited about new technologies for delivery with familiar, old, efficacious, safe anti-inflammatory molecules like loteprednol, as well as a host of entirely new mechanisms."

EGP-437

EGP-437 from EyeGate Pharmaceuticals is a corticosteroid formulation that is currently in a Phase III trial for anterior uveitis.[5] According to Dr. Sheppard, EGP-437 is dexamethasone delivered with iontophoresis, which is a way of delivering charged particles to the eye.

"Eyegate Pharmaceuticals has a major portfolio of iontophoresis intellectual property used to deliver any drug or entity that has a charge to it. You can deliver positively or negatively charged drugs to the eye with iontophoresis. It's currently available for research as a simple cylindrical device that looks like a thimble and acts like a contact lens with a drug-laden sponge on it. A secondary electrode on the forehead drives that charge through the eye. It's a pain-free and brief procedure," he explains.

Dr. Sheppard notes that the Phase II trials of iontophoresis for treating dry eye were unsuccessful. "However, this bold new venture into human iontophoresis technology shows promise with further refinements in the delivery, schedule, patient selection, molecules, dosage, and indications," he says. "The iontophoresis delivery of dexamethasone has been proven with a Phase III trial to statistically significantly improve acute anterior uveitis when compared to prednisolone. We know this drug works, and, remarkably, dexamethasone by iontophoresis doesn't raise the intraocular pressure."

Robert Latkany, MD, says that there is no question that many ophthalmologists are turning to steroid use for alleviating some of the symptoms of ocular surface disease. "I think it's almost the norm across the board. Steroids do relieve a lot of these symptoms. The concern with any steroid is pressure elevation and cataract formation. These patients are never cured by the short-term application of steroids. It is going to require long-term usage, and the concern of the long-term use of steroids in the eye is still there and always will be there," explains Dr. Latkany, who is founder of New York Eye and Ear Infirmary's Dry Eye Clinic.

EBI 005

EBI 005 by Eleven Biotherapeutics is a bioengineered drug, with IL-1 as the target. "The team at Eleven has strategically culled data and advice from the most successful aspects of innumerable previous clinical trials," says Dr. Sheppard. "It is well into Phase III now, with a successful Phase II.[6] Based upon previously submitted data, the drug likely will be efficacious as well."

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Rebamipide

Rebamipide ophthalmic suspension (OPC-12759, Otsuka Pharmaceuticals) met the threshold of noninferiority and superiority to sodium hyaluronate in corneal and conjunctival staining tests and was judged by patients to be significantly better at relieving foreign-body sensation and eye pain in a multicenter randomized clinical trial that included 188 patients with dry eye.

According to Rutgers' Dr. Bielory, rebamipide was designed to stimulate increased mucus in the conjunctiva and cornea. It is approved in Japan for protection of gastric mucosa and for treatment of dry eye. It has been shown in human and animal studies to enhance secretion of mucin to support tear film adhesion and slow tear-film breakup time.

In Phase II studies, 2% rebamipide suspension was shown to be superior to placebo at improving objective measures of dry eye, including fluorescein corneal staining score and lissamine green conjunctival staining.[7] Additionally, patients reported significantly more relief from photophobia, dryness, foreign-body sensations, pain, and blurred vision than patients instilling placebo.

Rebamipide is currently in Phase III trials in this country.

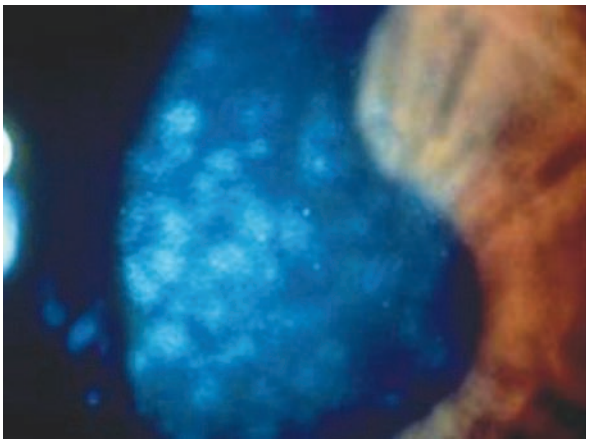

Figure 3. Diffuse nummular keratitis following acute adenovirus infection, which is universally followed with a significant diminution in tear production and accompanying ocular surface compromise.

OTX-DP

OTX-DP by Ocular Therapeutix is sustained-release dexamethasone that is administered as a one-time absorbable intracanalicular plug, designed with a four-week tapered release. The Phase II study included 60 patients. In this randomized, placebo-controlled, clinical trial, patients undergoing cataract surgery were administered OTX-DP or a proprietary placebo intracanalicular plug at the end of the cataract procedure. Primary endpoints included reduction of inflammation as determined by absence of anterior chamber cells and absence of pain.[8,9]

According to the study results, 34.5 percent of patients administered OTX-DP had an anterior chamber cell count of 0 on day 14, compared with 3.4 percent of patients in the control group. Additionally, the OTX-DP group was statistically superior to the control group for absence of pain at all time-points evaluated through day 30. All of the OTX-DP plugs were retained through day 14, and most (96.6 percent) of the plugs were retained through day 28. Results are comparable to commercially available ophthalmic corticosteroids. No increases in intraocular pressure related to OTX-DP were experienced.

Ocular Therapeutix has initiated a Phase III trial. "The wonderful aspect of using a punctal plug to deliver a medication is that it also provides a reservoir effect for tears by inhibiting outflow into the nasolacrimal system," says Dr. Sheppard. "This uses low steady doses, which seems very promising for a wide variety of clinical indications from dry eye to allergy, glaucoma, and cataract surgery."

The Future

None of these drugs is likely to be approved very soon. "It is frustrating because it is a very slow process to get anything approved," Dr. Latkany says. "I'm very excited about anything that could be available that I can try on my patients, but unfortunately, I don't see any of that happening in the next year or so. Lifitegrast and MIM-D3 are the two closest to any sort of approval."

Dr. Sheppard agrees. "In three years, there will probably be two to five new drugs in the marketplace with many others in early Phase II, and many small companies risking everything they've got with venture capital to come up with another way to produce beneficial results in human clinical trials for dry eye." he says. REVIEW

Dr. Bielory has no financial interest in any of the products mentioned. Dr. Sheppard is a consultant for EyeGate, Kala, R-Tech and Shire. Additionally, he participated in the clinical trials of lifitegrast, albumin and EBI 005. Dr. Latkany has no financial interest in any of the products mentioned. He participated in the lifitegrast clinical trial.

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Dry Eye: More Than a Symptomatic Disease

Jacqueline Dauhajre, MD, and Richard Teofilo Atallah, New York City

You can now determine whether Sjögren's syndrome is contributing to your patients' dry eyes.

There was a time when almost half of the dry-eye patients who presented to ophthalmic practices were treated with artificial tears. The other half continued to return for follow-up visits as their symptoms persisted. After considering the reason for this cycle, it is clear that the potential implications of dry eye need to be examined further, not only as a body of symptoms but also as a possible warning sign for systemic disease. Identifying systemic disease in patients who present with dry-eye symptoms not only allows you to approach the patient differently, but also acts as a form of managing expectations of treatment. Dry-eye patients who are diagnosed with a systemic disease are aware that their symptoms may not improve; however, they are also aware that targeted treatment based on an understanding of their true etiology can prevent their symptoms from progressing.

Systemic Disease and Dry Eye

There is a well-known association of several systemic diseases associated with dry-eye syndrome, among them Sjögren's syndrome, rheumatoid arthritis, scleroderma and systemic lupus erythematosus.[1] Sjögren's syndrome is a chronic autoimmune disease characterized by white blood cells attacking the patient's moisture-producing glands, including the lacrimal and salivary glands. Sjögren's syndrome is classified as either primary or secondary. Although both are systemic diseases, primary Sjögren's syndrome causes early and gradual decreased function of the lacrimal and salivary glands and can include many extraglandular conditions. Secondary Sjögren's syndrome occurs in people who have another autoimmune connective tissue disease, such as rheumatoid arthritis or systemic lupus erythematosus.

Sjögren's syndrome affects an estimated 4 million people in the United States, of which 3 million are undiagnosed, yet it is one of the three most common autoimmune diseases. Most importantly, aqueous-deficient dry eye is associated with decreased lacrimal secretion and is a common early symptom of Sjögren's syndrome and a hallmark of the condition.[1-3] Sjögren's syndrome can progress to the entire body in the form of systemic manifestations, such as kidney dysfunction, lung disease and increased risk of lymphoma. Lymphoma is a serious complication of Sjögren's disease that increases in risk as the disease progresses. According to the National Institutes of Health, one in 10 Sjögren's patients will develop lymphoma, and approximately 20 percent of deaths in primary Sjögren's

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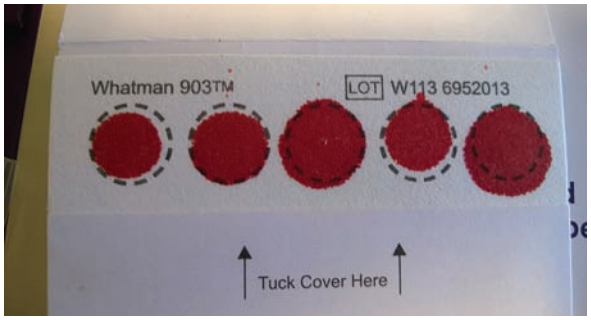

Figure 1. A Sjö blood collection card.

patients are attributed to lymphoma.[4,5] In a recent study, Sjögren's patients' risk of developing lymphoma was estimated to be 44 times higher than the general population's.[6]

Recent Clinical Findings

Sjögren's is thought to be caused by a combination of genetic, environmental and hormonal factors. The initiating factor may come from one or more events and is also likely to have a basis in genetic predisposition. Early and accurate diagnosis of Sjögren's syndrome is an important factor in limiting complications of the disease, yet there is currently an average delay of 4.7 years for patients to receive an accurate diagnosis.[1] Achieving an accurate diagnosis has historically proved challenging, requiring a number of diagnostic tests including serology. Traditional serological biomarkers associated with Sjögren's syndrome—Sjögren-specific antibody A (SS-A), Sjögren-specific antibody B (SS-B), rheumatoid factor (RF), and antinuclear antibody (ANA)—have some limitations, including a low clinical sensitivity (SS-A, SS-B), low specificity (ANA, RF), lack of detectability and manifestation late in disease progression; the result of systemic-based, rather than organ-specific, markers.[7]

A recently developed, advanced diagnostic panel for early identification of Sjögren's syndrome in dry-eye patients (Sjö, Nicox Inc.), tests patients for three new biomarkers—salivary gland protein-1 (SP-1), carbonic anhydrase-6 (CA-6) and parotid secretory protein (PSP)—that detect Sjögren's syndrome earlier and with a high specificity and sensitivity, in addition to traditional biomarkers *(See Figures 1 & 2)*. These new autoantibodies are gland-specific and detect Sjögren's syndrome with a high specificity and sensitivity.[4] SP-1 antibodies have the greatest specificity and sensitivity for early Sjögren's syndrome, and autoantibodies to CA-6 add additional sensitivity to the diagnosis of early Sjögren's syndrome along with PSP, SS-A and SS-B.

In an in-office study, we tested 90 patients who presented with dry-eye signs and symptoms using the new diagnostic panel to determine which patients were likely to have Sjögren's, early Sjögren's, secondary Sjögren's or unlikely to have Sjögren's at all. Seventy-eight were female and 12 were male. Even given our understanding of the disease's prevalence, the serology results were surprising: only 50 were negative for any markers of autoimmunity.

Thirty-three patients were found to have markers of Sjögren's syndrome, representing 36.7 percent of those patients tested. Thirteen of these patients were defined as early Sjögren's syndrome; 13 were defined as Sjögren's syndrome; and seven were defined as secondary Sjögren's syndrome. Of the 33 who tested positive for markers of Sjögren's syndrome, 28 were female (35.9 percent of females tested were positive for markers of Sjögren's syndrome) and five were male (41.7 percent of males tested were positive for markers of Sjögren's syndrome). Seven were positive for markers indicative of rheumatoid arthritis *(See Table 1)*. Surprisingly, a large percentage of patients who presented with only dry eye were found to have Sjögren's syndrome and were detected early.

Diagnosis Changes Management

A Sjögren's-syndrome diagnosis carries with it a significant effect on patients' expectations and a physician's strategy for follow-up care. With early detection and co-management with other medical specialists, (i.e., rheumatologists, dentists and general practitioners, etc.), identification and treatment of the manifestations of Sjögren's syndrome may lessen complications affecting the liver, lungs and thyroid. Potential Sjögren's therapies on the horizon could include biologics that block B cells, T cells and lymphotoxin. These patients should also be monitored more closely, in general.

In regards to ocular signs and symptoms, the specific treatment regimen for the Sjögren's-syndrome patient will depend on the severity and stage of the disease. Early treatment to try to normalize the tear film and break the cycle of inflammation may protect the ocular surface from subsequent complications (scleritis, keratitis and uveitis) and improve patients' quality of life. In my practice, initial treatment consists of using artificial tears every two hours followed by cyclosporine ophthalmic emulsion 0.05% (Restasis) and loteprednol etabonate, with follow-up visits scheduled every six months. However, if the patient tests positive for Sjögren's, then follow-up is every three months.

Some patients present with dry-eye complaints at their initial visits and are tested for Sjögren's syndrome. Others don't take the test until after multiple visits and repeated complaints of symptoms that don't improve. Once patients are aware of their diagnosis, their expectations change and their

(continued on page 56)


Safety of Intravitreal Anti-VEGF Agents

After nearly a decade of use, what the data says about the ocular and systemic safety of these increasingly used drugs.

By Andrew A. Moshfeghi, MD, MBA, Lexington, Ky.

Retinal specialists have been delivering intravitreal injections of vascular endothelial growth factor inhibitors for nearly a decade in their clinical practices. While neovascular age-related macular degeneration was the first, and is still the most common, indication for intravitreal anti-VEGF injections, additional approved indications include central and branch retinal vein occlusion-related macular edema as well diabetic macular edema. These agents are also used in an off-label fashion to diminish the effects of proliferative diabetic retinopathy, vitreous hemorrhage, neovascular glaucoma, retinopathy of prematurity and many other retinovascular diseases.

Pegaptanib, a selective inhibitor of the $VEGF_{165}$ isoform, was the first anti-VEGF agent approved for an ocular indication in 2004,[1] followed by non-selective VEGF inhibitors with a more robust efficacy profile: ranibizumab in 2006[2] and aflibercept in 2011.[3] Off-label intravitreal bevacizumab, also a non-selective VEGF inhibitor, has been in robust use since 2005[4] and retains predominant market share due to having similar efficacy to ranibizumab combined with a distinct pricing advantage.

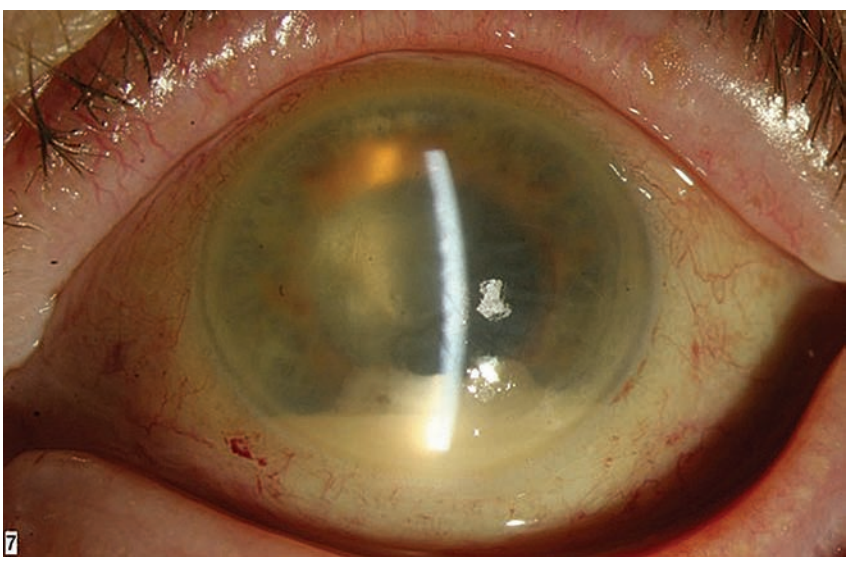

Figure 1. Slit-lamp photograph of a patient one day following intravitreal ranibizumab injection for neovascular age-related macular degeneration. The patient developed endophthalmitis due to *Streptococcus intermedius* infection.

The popularity of non-selective anti-VEGF agents has largely been driven by their apparent efficacy that is measurable both functionally and anatomically. Patients, too, appreciate the merits of these anti-VEGF agents for various indications, and they do so despite knowing the burden of needing intravitreal injections every one to three months in order to realize these anatomic and functional benefits over the long term.

A lot has been said about the ocular and systemic safety of anti-VEGF agents over the last 10 years. From the beginning of the anti-VEGF era in ophthalmology in 2004, retina specialists and clinical trialists were appro-

priately concerned about the potential ocular and systemic side effects of constitutively inhibiting VEGF, albeit in minute anti-VEGF doses delivered into the relatively isolated intraocular environment.

The original salient concern for ocular complications following intravitreal anti-VEGF injections was for endophthalmitis *(See Figure 1)*,[5] followed by raised awareness of non-infectious inflammation to the biologic anti-VEGF agents *(See Figure 2)*; retinal tears; retinal detachment; tears of the retinal pigment epithelium; elevated intraocular pressure; and cataract.

Our views on the systemic safety profile of these agents have likely been significantly prejudiced by the mechanism of action of these agents vis-à-vis what is known about the systemic side effects of similar drugs delivered intravenously in manifold higher doses for systemic management of disease.[6] These concerns have perhaps been mitigated by empiric data from clinical trials for ocular indications as well as from our own clinical experience with these agents. As we will see, however, subgroup analyses of the existing data can lead to persistently unanswered questions regarding the relative systemic safety of each of these agents. Additional concerns have been raised by recent pharmacokinetic studies for each of these agents.

Ocular Safety

It is clear from our clinical trial and everyday clinical experience that the aging eye tolerates multiple intravitreal injections of anti-VEGF agents very well. The most concerning risk is the development of endophthalmitis, which multiple large retrospective studies have demonstrated occurs roughly once out of every 5,000 injections (endophthalmitis rate equal to 0.02%).[7] Not all post-injection cases of endophthalmitis due to a bacterial source are irreversibly blinding, however, there is a relatively high proportion of culture-positive cases that have the virulent *Streptococcal* species as the causative organism. Many of these *Streptococcal* cases have dismal functional results, with visual acuity often dropping to hand motions or worse level and many cases leading to evisceration or enucleation.

While the exact source of the infectious nidus remains unknown, some evidence suggests it may be due to respiratory flora from the patient, the medical assistant or the injecting physician.[8,9] Therefore, most practitioners have a no-talking policy during the injection process. While some have advocated the use of face masks, this is not the prevailing standard of care.[10]

Severe eye pain, with or without decreased vision, in the first two days following the antecedent intravitreal anti-VEGF is the most common symptom.[7] Hypopyon, anterior chamber fibrin, cell and flare, along with vitreitis are the most common ocular signs. Because patients can have variably significant ocular irritation for the first 48 hours after a routine injection due to the povidone iodine 5% sterilizing solution applied to the ocular surface, it is important to emphasize that this pain tends to lessen over time while severe and deep eye pain that worsens over time is the most concerning sign for infectious cause of their symptoms. While the "per-injection" risk of endophthalmitis is quite low, clinical trial data has revealed the "per-patient" risk of endophthalmitis is closer to 1 percent.[3]

Initially it was felt to be important to provide pre- or post-injection antibiotic prophylaxis to reduce the risk of endophthalmitis.[5] We later learned that this practice not only did nothing to reduce the risk of infection, it also created more antibiotic-resistant bacteria for those cases that did develop despite the use of antibiotics.[11,12] As a result, the use of pre- or post-injection prophylactic antibiotics is not advocated.

Insofar as off-label intravitreal bevacizumab is only available through compounding pharmacies, there is a potential risk for contamination of bevacizumab during the aliquoting process, during transportation from the pharmacy to the physician's office or during storage of the drug.[13] It is important for physicians to become aware of their supplying pharmacy's procedures for the above and check in with them regularly to ensure appropriate compliance. Unfortunately, outbreaks of blinding cases of endophthalmitis have occurred when deviation from established protocols has led to widespread contamination of bevacizumab lots.[14]

While retinal tears, retinal detachment, vitreous hemorrhage and traumatic iatrogenic cataract are reported risks following retinal intravitreal anti-VEGF agents, these are not only quite uncommon,[5] but are also less permanently visually debilitating in general than endophthalmitis is.

Tears of the retinal pigment epithelium have been observed in cases of neovascular AMD without treatment, with thermal laser treatment, with photodynamic therapy and with each of the anti-VEGF agents *(See Figure 3)*.[15] While RPE tears can occur with natural history alone, the risk of RPE tears with anti-VEGF treatment can be higher in patients with unusually large (i.e., tall) pigment epithelial detachments, according to a poster presentation this August at the American Society of Retina Specialists Annual Meeting, San Diego, Calif. *(Carle MV, et al. Tears of the retinal pigment epithelium during aflibercept therapy: PED and treatment characteristics.)* Visual loss typically occurs when the atrophic aspect of the tear is subfoveal in location. Not infrequently, massive submacular hemorrhages are found to be associated with a new tear of the RPE. RPE tears tend to do well with subsequent anti-VEGF injections.

Geographic atrophy is a well-known consequence of AMD progression, but was also observed as the number one cause of decreased vision in patients undergoing ranibizumab therapy in the MARINA trial.[16]

It is well-known that ocular hypertension can occur transiently immediately following the bolus injection of 50 to 100 microliters of an anti-VEGF drug. What is more concerning is the potential for significant and sustained elevations in intraocular pressure elevation. This appears to occur in 3.5 percent to 11 percent of patients receiving chronic anti-VEGF agents.[17-19] It is unclear whether the etiology of this is mediated by the drugs' mechanisms of action on the trabecular meshwork, hydrostatic damage to the trabecular meshwork, outflow impairment, a combination of these, or due to some other unidentified mechanism. The key point here is to recognize the possibility of the risk (especially in patients with pre-existing risk factors for glaucoma), to monitor the IOP and optic nerve and to make the appropriate adjustments to the injection protocol when delivering subsequent anti-VEGF injections (e.g., lowering the volume of drug injection, using a larger-bore needle or increasing the injection interval).

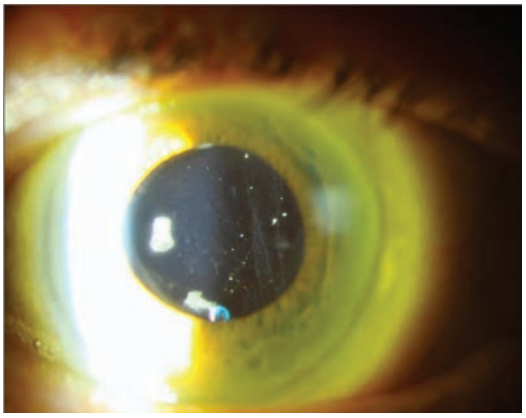

Figure 2. Slit-lamp photograph of a patient several days following his third injection of intravitreal aflibercept. Large vitreous aggregates were observed following the presentation of mild pain and decreased vision. These resolved after several weeks of topical anti-inflammatory therapy alone.

Systemic Safety

VEGF is a potent promoter of vascular hyperpermeability. Anti-VEGF agents significantly reduce vascular hyperpermeability, and when delivered systemically, can also raise systemic arterial blood pressure.[20,21] Systemic arterial hypertension is the single greatest risk factor the development of cerebrovascular accidents. Systemically delivered anti-VEGF agents are also widely known to promote the development of other thromboembolic events.[20,21] Arterial thrombotic events, or ATEs, are defined as nonfatal stroke, nonfatal myocardial infarction or vascular death (including deaths of unknown cause). However, these systemic events have been observed following systemic administration of anti-VEGF agents in much larger doses than what are being injected intravitreally. Do these same risks occur with such small doses that we inject into the eye routinely?

The short answer is that we do not definitively know yet. There have been no statistically significant signals derived from Level I evidence that directly point to a greater risk for the development of ATEs for patients in the anti-VEGF cohorts compared with those in the control groups in these studies. It must be understood, however, that these rigorous clinical trials were not statistically powered to answer this specific question. Additionally, it is unlikely that clinical trials designed to answer this question will be carried out, insofar as each arm of such a study would have to include more than 10,000 patients in order to be sufficiently powered to detect a meaningful difference for these rare events. That said, there is compelling clinical trial subgroup analysis and pharmacokinetic data pointing to the possibility of a risk of ATEs from intravitreal anti-VEGF drugs.

The CATT trial, for example, revealed that there was a greater risk for serious adverse events associated with bevacizumab compared with ranibizumab even though there was no significant difference between the two drugs with respect to the risk for ATEs.[22] Similarly, the IVAN study demonstrated that circulating serum VEGF levels were more significantly diminished in the bevacizumab group as compared with the ranibizumab group.[23]

Ranibizumab was approved for the treatment of diabetic macular edema after regulators evaluated data from the ranibizumab 0.5-mg and 0.3-mg cohorts as compared with a control group. Although each ranibizumab group had very similar efficacy data, there was an indication that the 0.5-mg group may have had a more concerning safety profile. In the pooled analysis of the RISE and RIDE ranibizumab for DME studies at three years, the ATE rate was 10.4 percent (26 of 249) with 0.5 mg ranibizumab and 10.8 percent (27 of 250) with 0.3 mg ranibizumab; the stroke rate was 4.8 percent (12 of 249) with 0.5 mg ranibizumab and 2.0 percent (five of 250) with 0.3 mg ranibizumab.[24] Additionally, over three years, fatalities occurred in 6.4 pecent (16 of 249) of patients treated with 0.5 mg ranibizumab and in 4.4 percent (11 of 250) of patients treated with 0.3 mg ranibizumab.[24] Although not statistically significant, these numerical differences were enough of a dose-dependent concern for both the sponsor and the regulator to agree to a 0.3-mg approved indication instead of the 0.5-mg dose that was previously approved for AMD and retinal vein occlusion.

The European Medicines Agency recently provided a Public Assessment Report (EPAR) on the use of aflibercept for neovascular AMD.[25]

In its analysis of the available pooled data, the agency observed that the number of cerebrovascular accidents was higher in the aflibercept group (n=35, 1.9 percent) compared with the ranibizumab group (n=2, 0.3 percent) and that the magnitude of this difference was especially noticeable when analyzing the oldest pool of patients. For those 85 years of age and older, the number of cerebrovascular accidents after one year of therapy was 20 (7.1 percent) in the aflibercept arm versus just one (1.1 percent) in the ranibizumab arm. After two years of therapy, the difference was 27 cases (9.5 percent) in the aflibercept arm compared with three cases (3.4 percent) in the ranibizumab arm.[25]

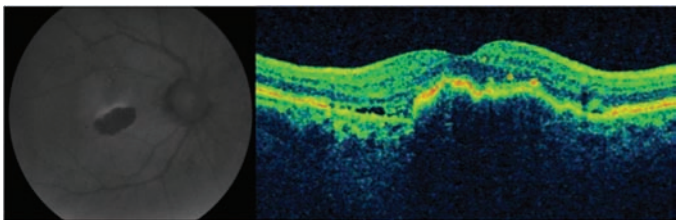

Figure 3. Fundus autofluorescence photograph of a neovascular AMD patient prior to initiation of anti-VEGF therapy. Depicted is a retinal pigment epithelial tear and corresponding vertical optical coherence tomography raster line scan through the tear.

One significant structural difference between ranibizumab[26] and both aflibercept[27] and bevacizumab[20] is that ranibizumab is an antibody fragment that lacks the Fc domain. Not only does ranibizumab have a much smaller molecular size than the other two, but it also exhibits lower systemic exposure following intravitreal injection by virtue of lacking the Fc domain. Robert Avery, MD, and colleagues recently demonstrated this in their pharmacokinetic study of ranibizumab, bevacizumab and aflibercept.[28] They observed that systemic exposure to aflibercept was five-, 37-, and ninefold higher than ranibizumab, whereas, bevacizumab was nine-, 310-, and 35-fold higher than ranibizumab. After three doses of each drug, both bevacizumab and aflibercept demonstrated systemic accumulation, while ranibizumab did not.[28] Furthermore, aflibercept substantially suppressed circulating plasma-free VEGF, with mean levels below the lower limit of quantitation as early as three hours after administration and lasting until ≥ seven days. Mean free VEGF levels with ranibizumab were largely unchanged. These data tend to support the notion that there may be pharmacokinetic variations amongst the non-specific VEGF inhibitors that could represent clinically meaningful differences in the context of the risk of ATEs.[28]

Barry Kuppermann, MD, nicely characterized the anti-VEGF patient populations at the highest risk for ATEs in an August 2014 interview. He enumerated four high-risk groups based upon available clinical trial data, clinical experience and theoretical factors. They are: diabetics; patients 85 years and older; patients with prior strokes; and premature infants. With respect to retinopathy of prematurity, although we have limited Level 1 data, there is considerable theoretical justification for concern for the use of anti-VEGF drugs in this very vulnerable patient population.[29,30]

Anti-VEGF agents for retinal disease are ubiquitous and very well-tolerated from an ocular perspective. While irreversible loss of vision following intravitreal anti-VEGF agents due to endophthalmitis is rare, it is a continuing risk that requires constant vigilance and attention to detail by the treating physician.

The superior efficacy of these agents over those treatments previously available is readily apparent, but clearly they remain suboptimal treatments. They are lacking not just in the fact that such frequent administration is required to achieve visual acuity and anatomic improvements, but also by their very mechanism of action that makes them so efficacious. Inhibiting systemic VEGF at such low levels opens the door to the potential for the development of ATEs. While clinical trial data have not definitively demonstrated that this risk is real, the data we do have is sufficiently concerning to warrant continued investigation and monitoring of this potential problem to determine if there are drug-specific safety characteristics that would favor one over the other.. REVIEW

Dr. Moshfeghi is an associate physician and surgeon at Retina Associates of Kentucky, in Lexington.

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(continued from page 51)

Table 1. An In-house Study of Sjö Among Dry-Eye Suspects

	Patients tested	Negative for any autoimmunity	RA	Early Sjögren's	Sjögren's	Secondary Sjögren's
Female	78	44	6	12	11	5
Male	12	6	1	1	2	2
Total	90	50	7	13	13	7

complaints diminish. They understand they are taking medications, not to improve, but to prevent progression of the disease.

The overlap between Sjögren's syndrome and dry eye means that eye-care professionals are in a unique and critical position to identify Sjögren's years ahead of the current standard. Not only can we make a difference in the lives of our patients by the early identification of a serious autoimmune disease, but knowing if there is an underlying cause of dry eye can also help us to better manage their ocular symptoms more effectively. Our findings support the need for increased diligence for eye-care professionals managing dry-eye patients and the recommendation that the potential presence of Sjögren's syndrome should be considered in all dry-eye patients, regardless of disease stage. REVIEW

Dr. Dauhajre is an ophthalmologist at Mount Sinai Hospital of Queens in New York. Mr. Teofilo Atallah is a premed student at New York University School of Medicine. *The authors report no financial interest in any product discussed, and they received no financial support for their in-house study.*

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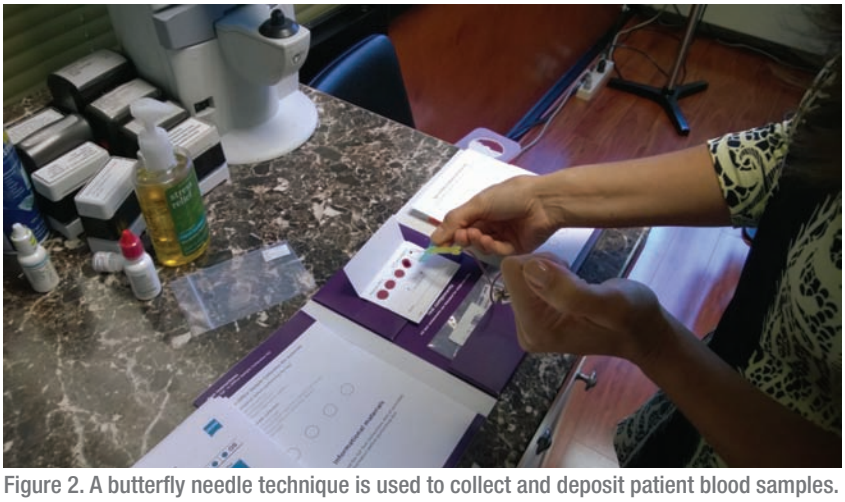
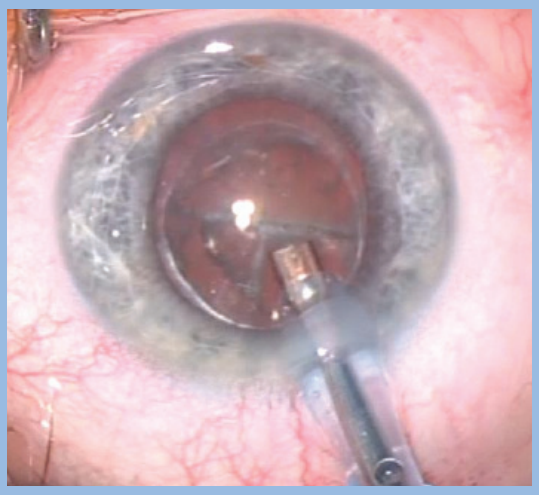


Figure 2. A butterfly needle technique is used to collect and deposit patient blood samples.



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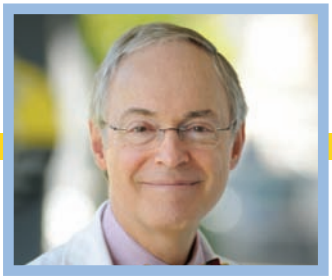

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The Other Side Of the Cornea

The endothelium can begin to falter from disease, but there are methods in development to help restore it.

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

Our efforts in this column are often devoted to the examination of new topics and treatments for ocular surface diseases. Allergy and dry eye are just two examples of disorders that impact the health of the conjunctival and corneal epithelium. There is, however, literally another side to corneal physiology and corneal disease. This month, we consider the biology of the endothelium that lines the posterior surface of the cornea, and discuss how its dysfunction can lead to corneal endothelium pathologies. We'll touch on current therapies, and then describe the status of nonsurgical approaches to the treatment of endothelial disorders.

The endothelial layer is often considered a one-trick pony; its job is to maintain stromal deturgescence by regulating—usually limiting—flow of fluid from the aqueous humor into the corneal stroma. Composed of a single layer of flat hexagonal cells lining Descemet's membrane, corneal endothelial cells form the interface between the cornea and the aqueous humor-filled anterior chamber. At just ~5 µm thick, the CE is the thinnest of the cellular corneal layers. The CE cells actively pump water from the stroma to the aqueous humor, maintaining a flow that balances the fluid leak through the extracellular space, and thus preserving the optical clarity of the cornea.

On average, the human cornea has an endothelial cell density in the range of 5,000 to 6,000 cells/mm^2 at birth; that number decreases by 40 to 50 percent by adulthood[2] at a cell loss of about 0.6 percent per year.[1] Stromal edema typically appears when cell density decreases to between 400 and 700 cells/mm^2. Why the cell loss? Under normal conditions, CE cells die at a rate comparable to other endothelial cells, however; they enter a state of apparent senescence early in life. The predominant compensatory response to cell loss is cell spreading and migration for maintenance of a uniform endothelial monolayer. If cell loss is accelerated, there comes a breaking point where the density of remaining cells cannot maintain stromal deturgescence and transparency.

Fuchs' corneal endothelial dystrophy, perhaps the most common pathology defined by loss of CE cells, can lead to corneal clouding, pain and eventual blindness.[3] Like other ocular disorders, most CE disease occurs in older individuals so, with an aging population, its incidence is likely to rise. Surgical approaches to CE failure such as corneal transplant have improved significantly in recent years, but this procedure is invasive, expensive and depends upon the availability of a healthy supply of donor corneal tissue. While this has not been a problem in the United States, worldwide shortages do exist and are likely to worsen.

To Divide or Not to Divide

Technically, it is not accurate to say that CE cells can't divide. They can, but they don't; a combination of cellular roadblocks freezes them in a well-differentiated state in the G1 phase of cell division. For many of the environmental and cellular regulators of cell division, signaling pathways converge on one or more of the kinases in the cyclin family. Cyclins function as gatekeepers in the transition between the phases of mitosis. For example, inhibition of cyclin E is thought to underlie the phenomenon of contact-mediated

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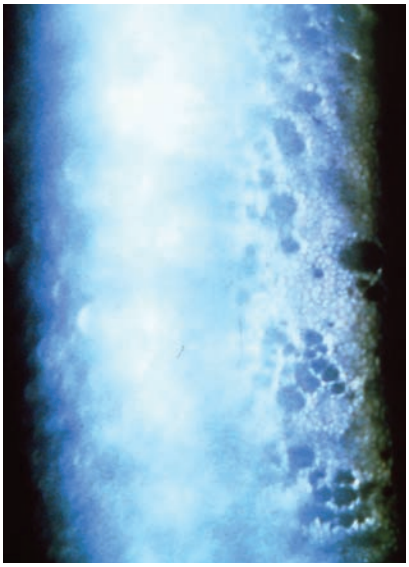
growth inhibition exhibited by many cells, including CE cells. Evidence from studies in both human CE and in animal models points to one cyclin inhibitor, a protein designated p27Kip1, in contact-mediated cell cycle arrest. Expression of p27Kip1 exhibits a twentyfold increase when cultured CE cells transition from subconfluent to confluent.[5,6] These same cultures can be induced to divide when cell-cell contacts are disrupted, and under these conditions p27Kip1 expression drops significantly.

Another factor that suppresses proliferation of CE cells is transforming growth factor beta 2, a cytokine found in relatively high levels in the aqueous humor; a number of studies have shown that TGF-β2 can suppress expression of key cyclins while also acting to maintain high levels of p27Kip1.[6] These and perhaps other inputs act to prevent CE proliferation under normal physiological conditions.

Contrary to the long-standing notion of CE senescence, many recent reports suggest that CE cell division and proliferation can occur under specific conditions.[7,8] For example, one group used a rat model of bullous keratopathy to show that peripheral CE cells divide and migrate toward the central endothelium, but cells in the central region do not.[7] Other studies aimed at releasing CE cells from mitotic arrest have met with modest success and have established that the age is an important criterion; CE cells from younger donors have a much greater proliferative capacity than those from older donors.[2,9]

Predicting Endothelial Failure

Endothelial disorders are relatively common; recent estimates suggest 5 percent of individuals over 40 will experience some degree of Fuchs' endothelial corneal dystrophy.[2] Perhaps more important, patients with FECD who undergo surgical procedures for cataracts or glaucoma face an increase in the potential for endothelial dysfunction resulting from surgical trauma. Recent efforts have explored approaches to minimize this risk. For example, a 2013 study comparing torsional and longitudinal phacoemulsification showed that when less ultrasonic energy is used, the risk of endothelial sequela is reduced.[10] But despite continuous refinement of surgical techniques, a modest perturbation of the CE can initiate an apoptotic cascade, accelerating the rate of cell death.



Corneal guttata leads to endothelial dysfunction and corneal edema in Fuchs' dystrophy.

Even with these refined protocols to reduce the potential for adverse post-surgical CE outcomes, a different strategy may be required for patients already diagnosed with FECD who are also in need of cataract surgery. These patients face a complicated treatment outlook that often includes both cataract removal and eventual corneal transplant. While there has been significant progress in techniques used for endothelial transplant (see the September 2014 issue of *Review* for several excellent discussions of various methods for corneal transplantation) it's clear that there is a need for non-surgical options to prevent or reverse CE cell loss.[11]

A significant advance came with the genome-wide association studies of FECD that identified several single risk alleles with unusually high odds ratios, confirming the strong genetic component of the disease.[12-14] The association between FECD and single-sequence variants in the transcription factor 4 gene yielded odds ratios of 5.5, and those with multiple risk alleles had odds ratios of 30. It's thought that TF4 may be involved in the differentiation of peripheral CE cell proliferation or in a limbal stem cell's transition to an endothelial progenitor cell. Either case means the potential for endothelial regeneration is lost or impaired in individuals that carry TF4 variants.

The GWA studies are significant for another reason; they present the potential for screening patients and identifying those at risk for FECD before they are symptomatic. With such a test, therapeutic strategies to promote CE health have the potential to reduce the need for corneal transplants and all the associated sequela. We can imagine a scenario where patients will be treated prior to surgical procedures to enhance CE proliferation or attenuate activation of apoptotic signals, providing a prophylaxis against subsequent endothelial cell loss. The search for such treatments is far from a conclusion, but it is well under way.

Future Endothelial Therapies

While there is a significant body of research on potential therapies for CE diseases, most of this work has focused on *in vitro* studies or trials using animal models. The ultimate goal of these efforts has been the targeted prevention of endothelial cell death following various surgical procedures. Using a number of different protocols

and experimental designs, comparisons of cell explants or cultured cells from FECD patients with control CE cells has yielded a general consensus that FECD cells are more sensitive to oxidative stress than control cells.[15-17] This means that patients with one or more of the predisposing genetic traits linked to FECD are more vulnerable to triggers that initiate generation of reactive oxygen species, such as trauma or inflammation. There are likely additional factors contributing to increases in CE cell death in those with FECD: Even without the provocation of peroxide or some other oxidative stressor, FECD explants exhibit an average of 10 times the rate of apoptosis seen in control cells.[17] Oxidative stress in FECD can also lead to apoptosis via effects on mitochondrial function, further supporting the idea that the molecular defect in FECD is an inability to respond appropriately to oxidative stress.[18]

As a proof of principle, a number of studies have demonstrated that classical anti-oxidants can mitigate CE cell loss under conditions of stress, even in cells from FECD subjects. A study published in 2013 followed this logic and examined the effects of sulforaphane, a naturally occurring isothiocyanate found in cruciferous vegetables that has been shown to activate endogenous anti-oxidative protective pathways.[19] Interestingly, sulforaphane acts on a specific pathway (the Nrf2) that is known to be downregulated in FECD. Treatment of *ex vivo* corneas from FECD subjects with sulforaphane prior to peroxide exposure normalized the response, suggesting that this or similar compounds may be a potential treatment for prevention of CE cell loss. One such compound, RTA-408,[20] (Reata Pharmaceuticals; Irving, Texas) is currently in a Phase II trial for prevention of endothelial cell loss following cataract surgery.[21]

A completely different therapeutic strategy is exemplified by a new study testing Rho-associated kinase inhibitors as stimulators of endothelial cell proliferation.[22] This approach is aimed at the endogenous pathways that limit CE cell growth; by altering cell adhesion, ROCK inhibitors attenuate cell-contact growth inhibition. This mechanism hasn't been clearly established, but what is clear is that endothelial wound healing is accelerated by treatments mediated, at least in part, by new cell growth rather than by prevention of cell death.

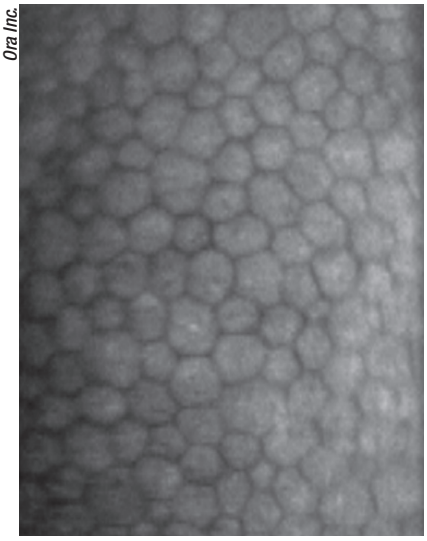

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Image of a healthy epithelial cell layer with characteristic hexagonal cell morphology. The task of monitoring corneal endothelial health requires determination of cell density using either a confocal microscopy method (shown here) or specular microscopy.

These examples demonstrate that there are at least two distinct approaches that we may adopt in our efforts to preserve corneal endothelial cell function. Whether it's by preventing cell death or, alternately, stimulating growth of new corneal endothelial cells, the overall function of the endothelial layer can be maintained. Ideally these efforts will lead to a reduction or elimination of the need for most corneal transplants. The benefits of these new therapies will be clear for all to see. REVIEW

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Optimizing Glaucoma Progression Analysis

Statistical analysis of progression can be misleading unless the doctor compensates for changes in the patient's condition.

Paul Harasymowycz, MD, MSc, Montreal

In order to make effective treatment decisions that will help us preserve our patients' visual function, we need to know whether a patient is getting worse. Until recently, we primarily used visual fields to determine that; however, we know that an eye can lose a significant portion of its ganglion cells and axons before that loss will be apparent on a visual field. For that reason, most of us now use imaging concurrently with visual fields to follow early, moderate and late glaucoma.

Imaging technology not only complements what we learn from visual fields, it may also allow us to diagnose glaucoma or follow progression when a visual field cannot. Optical coherence tomography, for example, not only can pick up very early damage, it also gives us a structural measure that we can follow over time, even into the late, advanced stages of glaucoma. Historically, when someone had a central island of vision, which we would try to follow with 10-2 visual fields, the optic nerve was so damaged that there wasn't much helpful information to elicit. But even in that situation there are still ganglion cells remaining, and OCT lets us measure and monitor them over time. (The Heidelberg Retina Tomograph is another popular tool, featuring a very robust progression analysis program.)

However, in recent years, all of the tools we use to help us make treatment decisions—including the imaging devices—have become more complex. This has led to increasing opportunities for errors and oversights. Here, I'd like to discuss some ways we can avoid diagnosis- and treatment-related problems that can occur as a result of the way these technologies analyze progression.

The Impact of Treatment

The reason for trying to determine whether our patients are stable or progressing—and if progressing, at what speed—is to enable us to predict the probable future of the patient's vision. Our measurements, made via visual fields and imaging devices, allow us to make this assessment, and that knowledge then allows us to intercede, if necessary, to change the probable future for the better. However, there are two inherent dangers in this process that many clinicians overlook: First, our treatment changes the conditions inside the eye, potentially altering the anatomy we are measuring. Second, the statistical software that helps us project the patient's future condition works by comparing current measurements to baseline measurements. That process can produce misleading results if we fail to change what the program is using as a baseline after changes have taken place inside the eye.

The first problem—our treatment affecting our measurements—usually relates to the change in intraocular pressure our treatments are designed to cause. For example, the HRT is quite sensitive to IOP changes. It is often used to measure the optic nerve in front of the lamina cribrosa, but if the pressure suddenly increases from 10 to 30 mmHg, in many patients the lamina will bow back and the nerve will sink in, altering the HRT scan significantly. Similarly, if a patient presents to you with a pressure of 30 mmHg, and you've scanned the back of her eye, as long as that nerve still has lots of fibers and vessels and the

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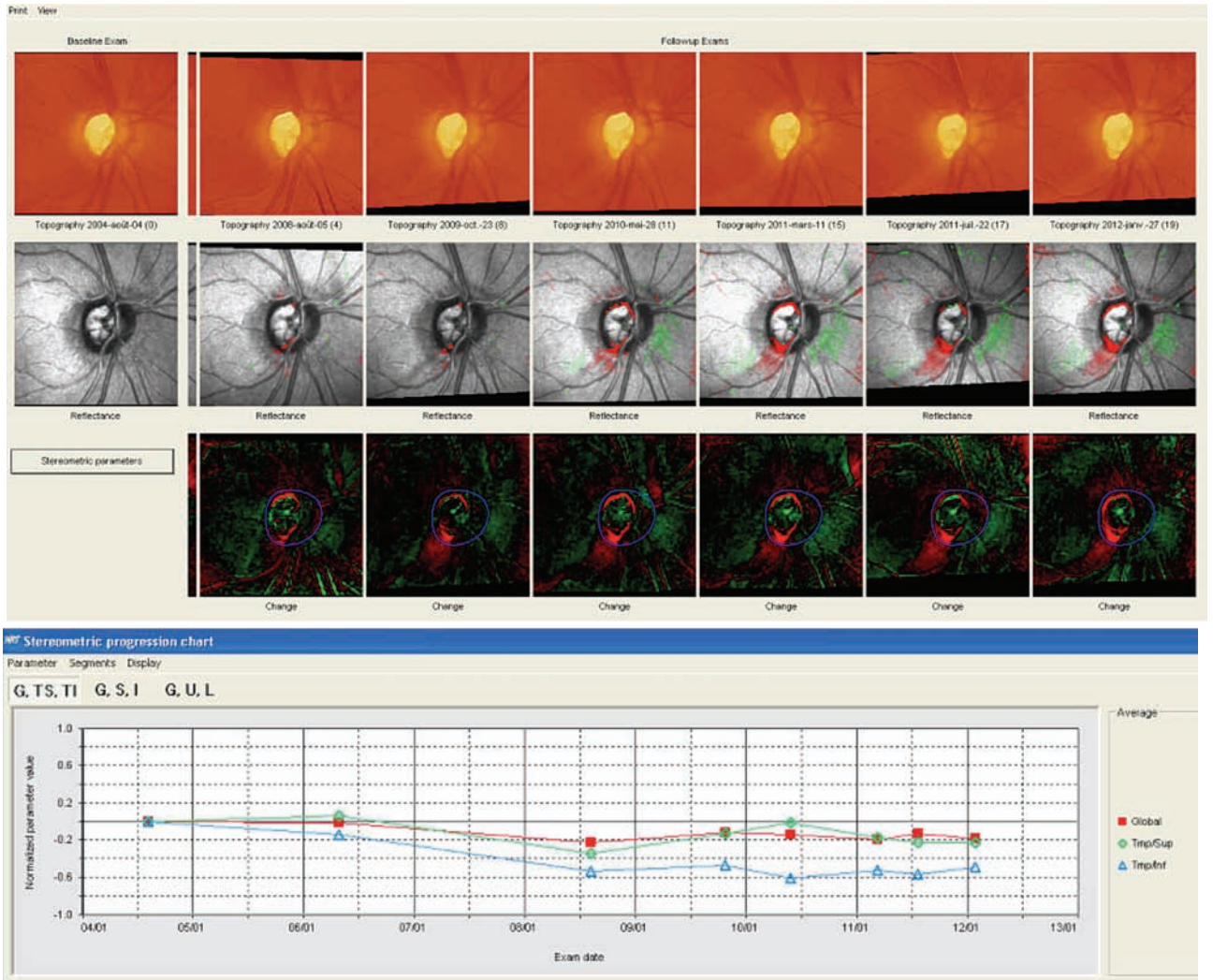
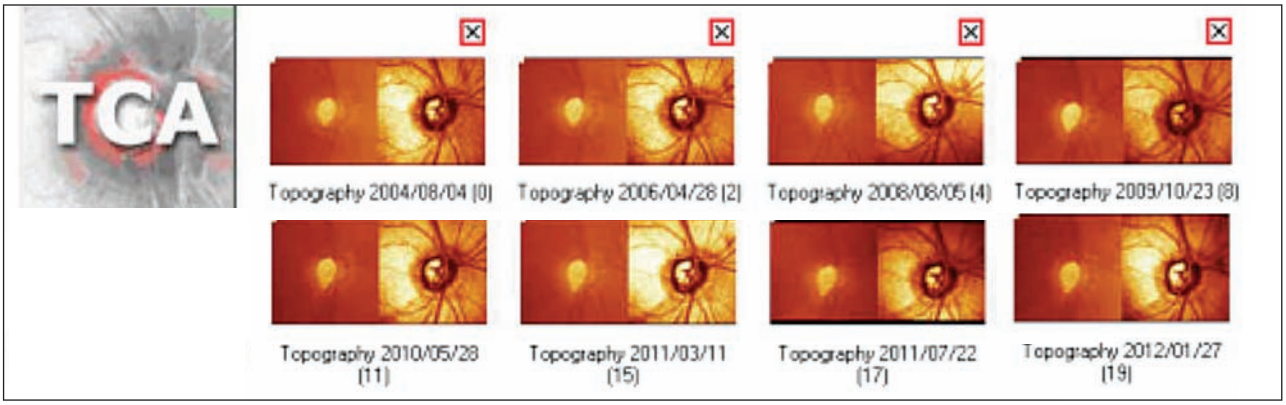


Top: A series of Heidelberg Retina Tomograph scans of a patient being followed for primary open-angle glaucoma. The Topographic Change Analysis shows increasing red pixelation on the inferior rim as well as deepening and widening of an infero-temporal retinal nerve fiber layer bundle defect, indicating a statistical progression on event-based analysis. Note that even at the last visit, the scan is statistically worse than the average of the first two HRTs. Bottom: Trend-based analysis also clearly demonstrates a downward slope. However, a plateau effect is visible midway along the timeline. At that point the patient had a combination agent added to his prostaglandin analogue, causing an additional 25 percent lowering of his IOP. Given that fact, the baseline needs to be reset in order to produce an accurate assessment of the patient's progression. (*Case continues on the following pages.*)

lamina is still moving and hasn't been crushed, once you lower her pressure 20 or 25 percent that nerve will pop back up towards you. Again, this will significantly alter the HRT scan.

What this means is that you can't really compare someone's HRT scan at a pressure of 30 mmHg to the same eye scanned with a pressure of 20 mmHg. If 20 mmHg will be the patient's new normal pressure, then you have to reset your baseline. (For this reason, it's important to note in the record what the patient's IOP was at the time the HRT scan was done.)

This concern also applies to OCT scans, although to a lesser extent. OCT technology scans a much thinner structure, which means there's not as much tissue to compress or expand when the IOP increases or decreases. However, in our practice we have seen artifacts of this change on some event-based analyses using the OCT. For example, we had a patient who had uneventful Cirrus OCT scans for quite some time. Then he suddenly showed signs of progression on event-based analysis. Indeed, the scans now looked very different from the earlier scans. It turned out that when the first five scans were taken, the patient's pressure was fluctuating between 4 and 6 mmHg. The patient didn't have great visual acuity; he was complaining of symptoms related to hypotony.



Here we're establishing a new baseline for this patient. The red x's indicate that we are excluding the four previous HRTs from our new analysis. (Note: Never delete earlier data unless it is clearly of extremely poor quality.) Now the first two visits after the lower IOP was achieved will be averaged and used as the new baseline. All future exams will now be compared to these two exams.

The later scans were taken after the patient was treated and had a revision of his glaucoma filtering procedure. This raised his pressure to between 10 and 12 mmHg; he was happier, and so were we. The OCT, however, said that he was getting worse.

This example shows that extreme variations in pressure, such as between hypotony and a more normal IOP, can affect measurements made using OCT.

Resetting the Baseline

The second often-overlooked aspect of these statistical analyses (trend- or event-based) is that you may need to change the exams you're using as your baseline after significant changes have occurred inside the eye. This is especially important given that glaucoma is a chronic disease, with many tests done over many years. Physicians often fail to make this adjustment, with the result that the statistical analyses may continue to say that the patient is getting worse when the patient is actually stable, leading to inappropriate and unnecessary treatment. Or, the analyses may indicate that the patient is stable when he's actually getting worse, leading to insufficient treatment.

Trend-based analysis takes a measurement, such as the mean deviation of the visual field, and plots it over time to determine whether there is a significant slope. The slope is drawn starting at the first two baselines—as you have chosen them—and ending at the most recent points measured. The problem arises when a change in the patient's status has occurred, and the new points on the graph are actually much closer to the recent measurements. The shallower slope between them indicates slower progression or even stabilization—but the instrument will still be drawing the line between your original baseline and the new points. The resulting slope might change somewhat, but the analysis will still report that the patient is worsening. In contrast, if you reset the system by creating a new baseline based on exams done after the patient's status has changed, the analysis might no longer find any significant slope at all.

For example, suppose you met your patient in 2004 and put her on a prostaglandin analogue. Her resulting pressure was running in the high teens, and over the next two or three years both imaging and visual fields indicated progression. At this point you decide to increase her therapy, so you add a combination agent, or perhaps perform selective laser trabeculoplasty. Her pressure will be lowered even further, and you'll continue to follow her with visual fields and imaging. However, if you perform a trend or event analysis, you'll still be comparing to your initial baseline, which may continue to indicate that the patient is getting worse.

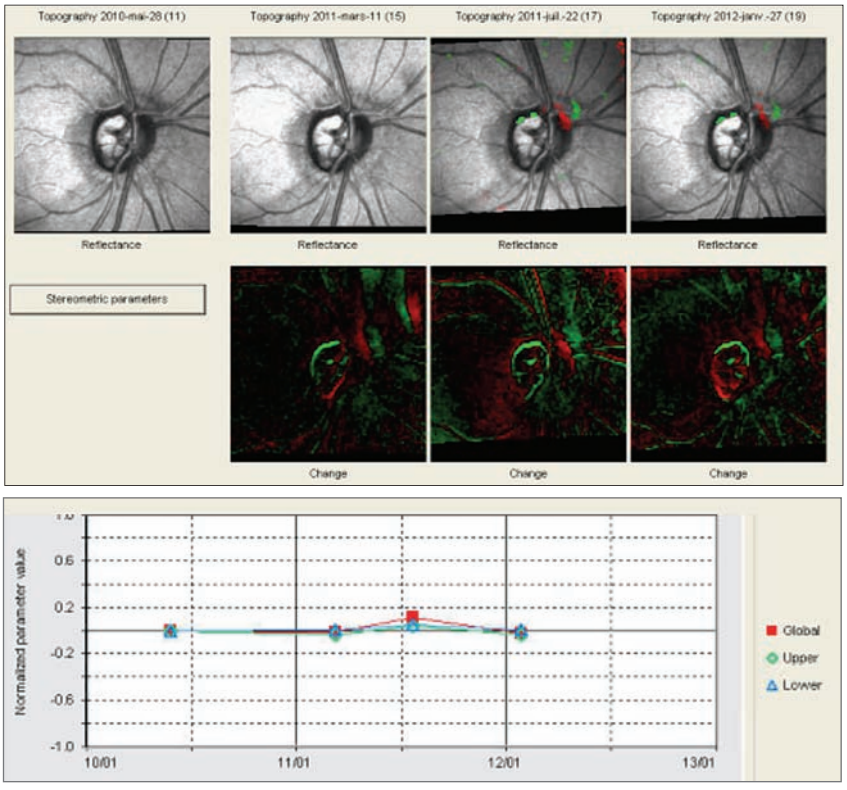
This can be particularly challenging with event-based analysis. After five exams, for example, the triangles indicating progression in Humphrey's GPA analysis may be completely black, and the blackness won't go away unless the patient has improvement in the visual field, which is an infrequent occurrence. Changing to a new baseline resets the measurement.

So, once the patient has progressed and you've altered her therapy, you have to establish a new baseline. Let's say I added a combination agent in 2006. The first visit after putting her on the new medication would be my new baseline exam one; she would have to come back six months later for baseline exam two. After that, any analysis will show whether the patient is getting worse on the current therapy.

Failing to do this can also backfire by leading the clinician to believe the patient is not progressing when she actually is. I recently encountered a patient whose physician had been following her with a series of HRTs that didn't seem to be changing much

on event-based analysis. But this analysis was based on a much earlier baseline. When we reset the baseline to a more recent set of exams, the analysis showed that over the past four years the patient had been getting worse. Needless to say, failing to reset your baseline could have significant consequences for your patient. (Note: On rare occasions, a patient's vision may actually improve after aggressive pressure-lowering; this might also call for a baseline reset.)

The need for a baseline reset can follow other kinds of changes as well. Certainly if your patient has a stroke that affects his visual field, that will affect all of your measurements. The same is true of a patient who has a retinal vein occlusion, or some other event or condition that affects the optic nerve or retinal nerve fiber layer. A patient who is diabetic may develop hemorrhages and macular edema, which may necessitate resetting the baseline, especially if the event leaves a scar. (Of course, some retinal pathologies can make the ganglion cells almost impossible to measure, regardless of other considerations.)



After establishing a new baseline, the analysis indicates that the patient is now stable, on both trend and event-based analysis.

Maximizing Our Tools

In addition to the issues mentioned above, these three basic principles will also help optimize your treatment decisions:

• ***Do more testing at the outset***. When you initially follow your glaucoma patients, test them more often so you can quickly determine which patients are progressing, and at what rate. If you only take one visual field a year, it could take three or four years for you to determine that a patient is losing 2 db per year. That patient is a rapid progressor, probably in need of more aggressive treatment. In contrast, if you do six or seven visual fields in the first two years, you'll detect that rapid progression much more quickly.

In addition, for statistical purposes when doing event-based analysis, it's important to have two baseline exams. That's true whether you're using HRT, OCT, GDx or visual fields. (Most of these instruments do both trend- and event-based analysis using their own software, such as the GPA analysis in the Humphrey visual field analyzer.) The instrument will average the two baseline exams and compare future exams to that average. For that reason, event-based analysis is impossible until you've performed at least three or four tests.

• ***Make sure you have good-quality exams.*** Both trend- and event-based analysis depend on good measurements. When doing visual fields, we want to make sure the results are reliable—that there are not too many false positives or false negatives. With the imaging instruments, the scan has to be well-centered; when using HRT it has to have a good standard deviation; and when using OCT each scan needs to have a good signal-to-noise ratio. Overall, you always want to get the best-quality image you can obtain from that patient. Furthermore, you want to make sure that the quality of the images is equally good over the series of exams, and make sure that the optic nerve looks similar from one exam to the next.

• ***Use both event and trend analysis***. Trend-based analysis tracks a given measurement over a series of exams to determine the rate of change, enabling us to project the likely future status of that measurement (if the eye were left in its current condition). In contrast, event-based analysis looks at a specific area of interest and compares it to a baseline measurement to see whether or not a given change has occurred. Both types of measurement can be done with visual fields and imaging,

and both give us useful information. In addition, they can act as a reality check on one another.

Ideally, we want to see agreement between the two types of measurement. If both event and trend analysis indicate that a patient is getting worse, we can feel more confident in our treatment choices. It's even better if the event and trend-based analyses agree on both imaging and visual fields; that's the equivalent of a home run. But when only one of them says there's a problem, and nothing else seems to be changing, we have to wonder: Is that measurement accurate? Did something happen to the reliability of the visual fields? Did something affect the quality of the acquired images? A disagreement can thus alert us to a potential problem with our measurements, and spare the patient a treatment decision based on faulty information.

Undoubtedly, the worst outcome of overlooking these issues would be to miss progression.

Staying on Track

Although these concerns were valid even when we relied almost entirely on visual fields to monitor progression, the current use of imaging technology has made them even more important to address. Undoubtedly, the worst outcome of overlooking these issues would be to miss progression, either because we didn't ensure that our imaging scans were of good quality, or because we failed to change to newer baseline exams. I have personally encountered several examples of missed progression resulting from this, so it's not merely a hypothetical possibility.

To avoid an undesirable patient outcome, make sure to check the quality of your imaging and visual fields; do both event- and trend-based analyses; make sure you do enough tests, especially when first working with a patient; and be sure to reset what you consider to be the baseline when the patient's clinical status, therapy status or IOP have undergone a significant change. REVIEW

Dr. Harasymowycz is chief of glaucoma at the University of Montreal and director of the Montreal Glaucoma Institute. He has no financial ties to any product mentioned.

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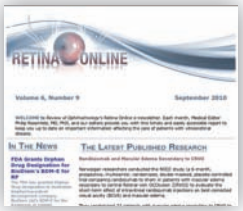

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Albinism: What You Can Do for Your Patients

Young patients with oculocutaneous albinism can benefit from traditional ophthalmological care and new low-vision devices.

K. Camille DiMiceli, MD, Brooklyn, N.Y.

Oculocutaneous albinism describes a heterogenous and phenotypically variable group of genetic disorders. OCA patients have varying degrees of hypopigmentation of the eyes, skin and hair with associated underdevelopment of the retina and visual pathways.[1] In some patients, only the eyes are affected, and this is referred to as ocular albinism. Individuals who have only skin, hair and iris hypopigmentation, but have normal vision and no other ocular involvement are described as "albinoid." While the image of white hair and translucent skin may first come to mind when thinking about albinism, the hallmark of the disorder is actually the visual pathway underdevelopment that occurs secondary to abnormal melanin production.

Diagnosis and Presentation

OCA is most often clinically diagnosed based on the features of ocular hypopigmentation (iris and retina), skin and hair, in conjunction with decreased visual acuity. Additional ocular signs include nystagmus; iris transillumination defects; foveal hypoplasia; anomalous retinal vasculature; anomalous optic nerves; and an abnormal optic chiasm. One or two of these features may be absent, but decreased visual acuity is almost always a feature of this condition. It is important to remember that not all children with OCA will have the snow white hair and translucent irises that may first come to mind; there is a range of light blonde to brown hair and eye color can be blue, brown or hazel *(See Figure 1)*. Therefore, albinism should be considered in the differential of any child who presents with chronic nystagmus and a fair complexion.

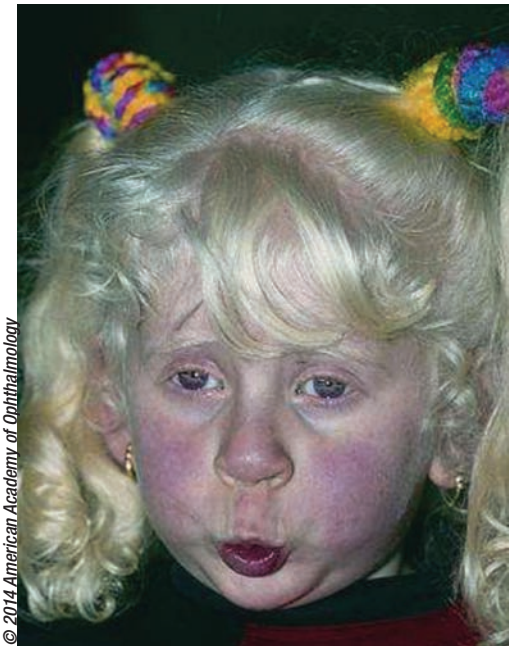

Figure 1. Young girl with oculocutaneous albinism.

Nystagmus is almost always present,[3] and is often the most bothersome and noticeable feature to the parents of children with OCA. The nystagmus typically develops over several weeks after birth. It starts as a large-amplitude, low-frequency pendular nystagmus, which parents sometimes interpret as an inability to fixate on objects.[3] The nystagmus often dampens over time and may even disappear later in childhood.[1] Stress, fatigue, illness and monocular occlusion all worsen nystagmus. Children may adopt head nodding and anomalous head positions in an effort to find a null point where the nystagmus is diminished. Visual acuity directly improves with decreased

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nystagmus. Clinicians should always make note of the patient's binocular visual acuity (with preferred head position), as this will likely be significantly better than monocular acuity and reflects more accurately the patient's visual function.

Iris transillumination defects (TIDs) are another common sign of OCA and may help make the initial diagnosis. Evaluation of TIDs is most effective at the slit lamp with a short beam projected directly through the undilated pupil. If the child is uncooperative, using a direct ophthalmoscope in a dark room while the parents hold the child works well also.

Macular hypoplasia is the most significant cause of decreased visual acuity in albinism. This is often evident on the fundus exam *(See Figure 2)*. Spectral-domain optical coherence tomography is much faster than time-domain OCT, and can demonstrate the foveal hypoplasia and absence of the foveal pit, or "fovea plana," which is characteristic of OCA, even in the presence of nystagmus.[5] Other details demonstrated by SD-OCT include persistence of an abnormal, reflective nerve fiber layer band; persistence of multiple inner retinal layers; loss of the normal thickened photoreceptor nerve layer; and increased reflectivity of the choroid due to decreased pigmentation.[6] RPE hypopigmentation has been shown to correlate with macular hypoplasia.[3,10]

In cases of significant foveal hypoplasia, the vasculature of the posterior pole becomes more anomalous, and vessels may be seen coursing near or through the area where the fovea should be. Besides foveal hypopigmentation and hypoplasia, there are also reduced numbers of photoreceptors—fewer rods in the macula and fewer cones in the foveal region.

Continuing posteriorly in the visual pathway, OCA patients also have anomalous optic nerves and optic chi-asm abnormalities, and the primary visual cortex shows disruption of binocular-driven neurons.

Best corrected visual acuity varies greatly among individuals with OCA. Most studies report a range of 20/30 to 20/400 with an average of 20/80.[6] BCVA depends largely on the genotype and phenotype of the individual, as well as the vision care the patient receives throughout his or her life. The patient's retinal image quality is degraded by refractive error (albinism patients are very rarely emmetropic), light scatter from the TIDs, and nystagmus, while the resolving power of the retina is limited by foveal hypoplasia.[1] Children with OCA face significant ocular and optical hurdles while their visual pathways are still developing, and thus often develop amblyopia. Orthotropia is uncommon in albinism—they are often esotropic or exotropic, and their anomalous visual pathway anatomy precludes the development of high-grade stereoacuity.[3]

Pathophysiology

The mechanism of disease is deficient melanin production. This can be due to defective melanosome (the organelle in melanocytes which produces melanin) maturation, an abnormality of melanosome enzyme function, or a decrease in the number or distribution of melanocytes in the tissue.[1] In the past albinism was characterized as tyrosinase-negative or tyrosinase-positive; however tyrosine production can be only partially affected, and there are other enzymes in the pathway that may be affected.

Genetics

The genetics of pigmentation is complex. More than 100 genes are involved in the pigmentation of the hair, skin and eyes. These genes are not expressed as simple Mendelian traits, but rather multiple genes are inherited and interact with each other, and this complex interaction generates a large range and variety of phenotypic expression. The albinism phenotype results from a defect in one or more of 13 genes that determine melanocyte function. These genes are inherited most often in an autosomal recessive fashion such as the tyrosinase gene on chromosome 11, protein P gene on chromosome 15, tyrosine-related protein gene (TRP1) on chromosome 11, and membrane-assosciated transport protein gene (MATP). But the most common form, accounting for 10 percent of albinism cases, is the X-linked GPR143 gene.[3] All genotypes result in misrouting of the optic nerve fibers during embryogenesis and underdevelopment of the neurosensory retina, along with varying pigmentation of the hair, skin and irises. All races and sexes are affected.

Associated Syndromes

Hermansky-Pudlak Syndrome (HPS) is a rare condition globally, but occurs much more frequently in the northwestern and central regions of Puerto Rico, with an incidence of 1:1,800. It also occurs more frequently in the Swiss.[3] It is important to be aware of this condition, which is associated with a potentially life-threatening bleeding diathesis caused by platelet storage pool deficiency. In addition to platelet aggregation defects, certain genotypes of HPS are also predisposed to interstitial lung disease, granulomatous colitis, and/or neutropenia. Patients with HPS often have visual acuities less than 20/200.[2]

All patients with the OCA phenotype who report any Puerto Rican or Swiss ancestry should be formally evaluated for HPS by their primary-care physician or hematologist. Testing for bleeding times and platelet aggregation is thought to be unre-

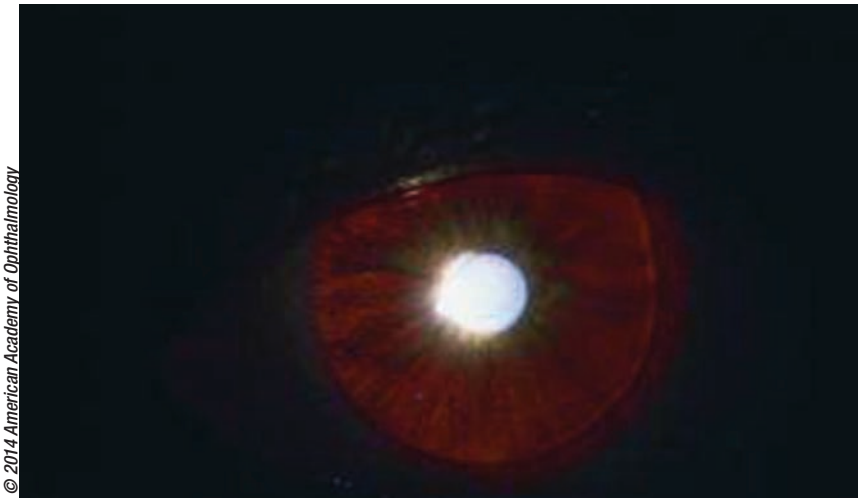

Figure 2. Iris transillumination defects seen with retroillumination in albinism.

liable, and there are few commercially available genetic tests.[2] On skin biopsy, abnormally large melanosomes, called macromelanosomes, are observed.[3] HPS is suspected in baby boys with the OCA pheynotype who have bleeding complications after circumcision or in toddlers with excessive bruising.[2] There are nine genotypic variants of HPS that have distinct phenotypes. Currently, commercial lab tests are available only for the HPS-1 and HPS-3 genotypes.

Chediak-Higashi syndrome (CHS) is a condition of OCA phenotype with associated neutropenia, natural killer cell dysfunction and frequent bacterial infections.[2] CHS can also be associated with retinal dystrophy.[1] The diagnosis of CHS in made by the presence of giant granules in neutrophils and other leukocytes. Griscelli syndrome is phenotypically similar to CHS, but lacks the giant granules.

Deafness may also be associated with albinism because of the affected pigmentation in the development of the stria vasculosa of the ear.[3]

Management

There is currently no cure for oculocutaneous albinism, but there are a number of measures that can be taken to improve your patient's visual function and to educate him on the importance of protection from sun damage.

First and foremost, clinicians must aim to maximize correction of any refractive error. This can be difficult with the associated nystagmus, but it is important to do careful retinoscopy in young patients. Full correction of any myopia and astigmatism as well as any hyperopia greater than 2 diopters is recommended. Using tinted lenses to alleviate photophobia is helpful in some patients. Color filters have not been shown to objectively improve reading performance; however, there is significant subjective improvement reported. This improvement may be a placebo effect, but could also be due to the color filters improving asthenopia and photosensitivity through reduced chromatic aberration and contrast.[7]

Monitoring for strabismus and anomalous head positioning is important. The Kestenbaum-Anderson procedure can be utilized if a significant head-turn exists. This procedure involves large recessions and resections of all horizontal muscles, and parents should be cautioned about potential consecutive head turns and strabismus after surgery. Richard W. Hertle, MD, and colleagues found horizontal muscle tenotomy to be effective in dampening nystagmus and improving visual acuity.[5] They have further shown patient quality of life surveys reflect this improvement; however, the power of their study was quite low (n=5 for patients with albinism).[4] Parents should also be cautioned that the visual improvement will likely be limited by the degree of retinal hypoplasia.[3]

As previously mentioned, children with albinism have an increased incidence of amblyopia and strabismus, and they should be monitored closely for these conditions. Screening is recommended every six months for the first year of life and annually.[3] Clinicians should initiate early treatment of any amblyopia with patching or atropine penalization (depending on the refractive error).

Skin and eye protection is of the utmost importance. Hypopigmented individuals are at increased risk of sunburn, photoaging and solar keratoses, as well as cutaneous malignancies: squamous cell carcinoma; basal cell carcinoma; and melanoma.[2] Parents are advised to avoid sun exposure during peak hours; to wear wide-brimmed hats and UVA/UVB protective sunglasses; and to apply sunscreen with at least 30 SPF to all sun exposed skin, at all times. Vitamin D levels should be monitored because deficiency can result secondary to the necessary sun avoidance.

Children with albinism do not have cognitive delay and generally have normal to above-normal intelligence. They are often high achievers in school. As for infant and toddler motor skill development, they are typically within normal range or a couple of months behind their normally sighted counterparts. They do, however, have difficulty with fixation when reading.[8] Relationships may be difficult during development because they may look very different from their

schoolmates, and their visual impairment may lead them to get too close to people, which can be perceived as an invasion of personal space.[1]

As mandated by the Americans with Disabilities Act, an Individual Education Plan should be developed for each school-aged child with OCA and reevaluated annually.[1] In addition, clinicians should consider a low vision referral to evaluate the need for magnifiers (near vision), handheld telescopes (distance vision), writing guides, closed circuit TVs and other devices such as bioptics. Bioptics are glasses with telescopes permanently mounted in them and may be used by some low-vision patients for driving.[1]

Genetic Testing/Gene Therapy

Genetic testing can help parents understand the basis and the risk of recurrence of OCA in future children. These tests can be quite costly and should be explained by a genetic counselor or ocular geneticist who is well-equipped to interpret the results, while taking into account false negatives and false positives.[4]

Gene therapy has been successful in mouse models. Adult mice that lack tyrosinase activity have associated retinal functional abnormalities and photoreceptor loss. Intraocular administration of an adeno-associated, virus-based vector encoding the human tyrosine gene has resulted in reversal of the retina anomalies. This may be a preview of very exciting and promising future treatments. For now, we must aim to support our patients and their families with traditional ophthalmologic care and new low-vision devices. REVIEW

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IOIS Remains a Diagnosis in Transition

In spite of a growing understanding of its molecular basis, idiopathic orbital inflammatory syndrome is still a challenge.

Katherine Lane, MD, Burlington, Vt.

Idiopathic orbital inflammatory syndrome, also known as orbital pseudotumor, is a syndrome of non-specific inflammation of orbital tissue(s) with no identifiable local or systemic cause. IOIS can involve virtually any orbital tissue individually, or in combination. Foci of inflammation include the extraocular muscles, the lacrimal gland, the episcleral tissue, the orbital fat, the orbital apex and the cavernous sinus, and this anatomic localization of inflammation is the basis for one of the most commonly employed classification schemes.[1]

Overall, IOIS is the third most common orbital disorder, behind thyroid eye disease and lymphoproliferative disease, but perhaps due to its heterogeneous presentation and response to treatment, large-scale clinical studies are lacking, and our understanding of the disease process is still evolving.

Clinical Diagnosis

The classic presentation of IOIS includes the abrupt onset, often over the course of hours, of periorbital pain associated with edema, erythema and chemosis. Other common features include proptosis, diplopia and visual changes. A thorough workup is essential in all patients presenting with these orbital signs, beginning with a detailed review of systems, a full ophthalmic exam and dedicated orbital imaging. Although CT is often more readily available, MRI with and without gadolinium characterizes the location and extent of inflammation more accurately. Baseline blood work and serologic studies for patients with suspected IOIS may include a complete blood count with differential; erythrocyte sedimentation rate; C-reactive protein; angiotensin converting enzyme; cytoplasmic antineutrophil antibody; antinuclear antibody; rapid plasma reagin; thyroid function studies; and possibly a Lyme titer in specific patients living in endemic areas. While these studies cannot "rule in" IOIS, they may be helpful in ruling out other entities.

Beyond this initial workup, complete agreement on management is not currently available. One of the biggest hurdles to consensus to the understanding of IOIS is what, precisely, is the diagnosis? The inflammatory signs and symptoms of IOIS (pain, chemosis, erythema, etc.) most likely represent the clinical manifestations of a variety of autoimmune and cell-mediated processes.[2] But is "inflammation" a valid diagnosis, or is it merely a tissue response related to some other process[3] either not yet described by medicine or not yet elucidated by available testing?

This controversy divides clinicians broadly among two camps. Some consider the typical clinical presentation, when supported by positive findings on appropriate imaging studies and without another attributable cause, to be almost diagnostic. A "corticosteroid trial" followed by the rapid and complete resolution of a patient's signs and symptoms helps to support the diagnosis. Other experts believe that an orbital biopsy should be attempted in all patients prior to the initiation of steroid treatment of potential IOIS, provided the tissue in question is easily accessible.[3] They argue that "inflammation" is not a diagnosis, but may be a sign of a potentially dangerous underlying tissue process.

Although seemingly at odds, in practice these two groups are not to-

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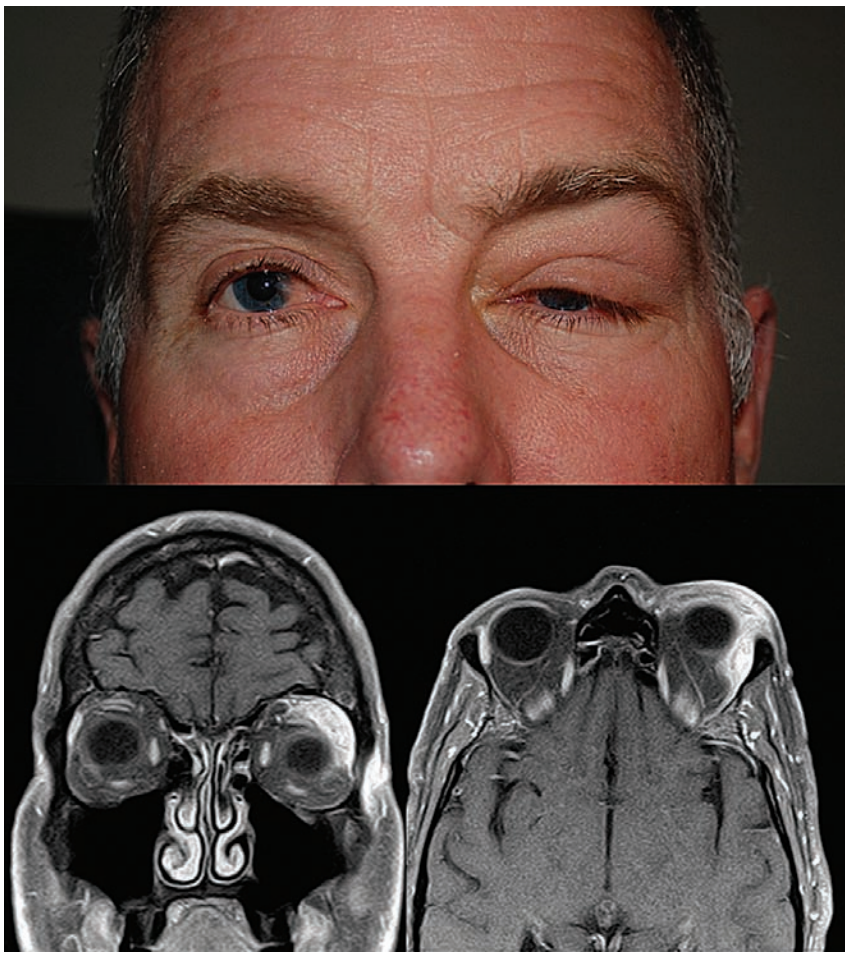
tally divergent. Clinicians who choose to use a corticosteroid trial as part of a diagnostic and therapeutic protocol may argue that orbital exploration exposes the typical IOIS patient to unnecessary surgical risk;[2] however, these experts often turn to orbital biopsy for patients with an atypical presentation, those who do not experience an immediate and sustained response to corticosteroids and those whose symptoms recur on steroid taper.[4]

Pathology

Pathologically, the most common description of IOIS is that of "nonspecific inflammation." Histology most often demonstrates a paucicellular infiltrate of lymphocytes, plasma cells and histiocytes. Particular cases may, however, show more specific patterns such as lymphoid follicles with germinal centers, destruction of normal tissue structures, granulomas and sclerosis. In his 2005 ASOPRS Foundation Lecture, Gerald J. Harris, MD, delineated a pathologic construct for IOIS,[2] helping to improve our understanding of the disease process (and its variations in both clinical practice and as seen in pathologic specimens) by correlating the specific cells present in surgical specimens with particular clinical symptoms. For example, macrophages activated by pro-inflammatory cytokines cause lysis of cells, escalating a cascade of inflammation and causing tissue injury and fibrosis which can result in the clinical symptoms of orbital pain, swelling and impaired function.[2]

This insight into the "pathologic construct," coupled with improving pathologic abilities to identify and measure cytokine levels and activities, has opened the door to further research into specific inflammatory mediators involved in IOIS. One such study demonstrates that gamma interferon and interleukin-12 levels are markedly elevated in IOIS when compared to normal, non-inflamed tissue profiles.[10] More studies will likely follow, the results of which will not only contribute to our understanding of the pathology of IOIS, but also may identify targets for treatment with therapeutic biologic agents.



Clinical and radiographic images of a patient with "typical" idiopathic orbital inflammatory syndrome. Top, clinical image showing proptosis, hypoglobus and ptosis. Bottom MRI coronal (right) and axial (left) images showing superior lateral orbital infiltration.

Management

The goal of treatment in all cases of IOIS is to intercept the systemic inflammatory cascade in order to halt its progression, prevent permanent damage to the orbital contents and reduce patient discomfort. Typically the treatment algorithm begins with the use of oral or parenteral corticosteroids (starting oral dose should be between 1.0 and 1.5 mg/kg/day, or approximately 80 mg of prednisone a day for a 70 kg adult) and/or NSAIDs.[2] Some clinicians advocate the use of intralesional steroid injections.[5] In patients with steroid-sensitive disease who are intolerant of steroid-related side effects, orbital radiation has been used with some success.[6] Neither of these treatment modalities differentiates between specific and non-specific types of inflammation, however. Side effects of prolonged steroid treatment are well-known and include electrolyte imbalances; osteoporosis; elevated serum glucose levels; sleep disturbances; and mood disorders, among others. Ocular complications as a result of radiation therapy are rare but not

insignificant, and include keratoconjunctivitis, cataract formation and retinopathy.

Immunosuppressive agents, including anti-metabolites (e.g., methotrexate, azathioprine), alkylating agents (e.g., cyclophosphamide, chlorambucil) and T-cell inhibitors (e.g., cyclosporine, tacrolimus), are increasingly used as steroid-sparing agents.[2,4,7,8] These medications may be better-tolerated than corticosteroids in some patients; however, they are equally non-specific, and often require ongoing serologic monitoring and close clinical follow-up.

An increasing understanding of the immunopathology of IOIS may improve our ability to target more specific elements of the inflammatory cascade, reducing co-morbidities associated with global immunosuppression. This has lead to a trend towards the use of immunomodulators that target specific cytokines that mediate the inflammatory response, such as tumor necrosis factor-alpha (TNF-a), (e.g., infliximab).[9] The recent discovery of elevated levels of gamma interferon, TNF-a, and interleukin-12 in biopsy-proven IOIS may improve our ability to more specifically treat this process in the future.[10]

Because the initial diagnosis of IOIS is often made on clinical grounds without tissue verification, a period of prolonged observation after the resolution of a patient's acute symptoms is advisable. Although recurrences are possible, they are not the norm. A recurrence of inflammation in the same or different anatomic location should arouse suspicion, and may prompt biopsy to rule out masquerade syndromes. Having a very candid conversation with patients about this possibility at initial diagnosis can help to ensure cooperation with this prolonged surveillance.

That the diagnosis of IOIS remains a challenging subject despite our growing understanding of the molecular basis of disease should invoke a certain level of caution in the treating physician. A brief review of the history of IOIS will reveal a diagnosis in transition over the past half century; patients once categorized under the umbrella term of "orbital pseudotumor" may now be diagnosed with sarcoidosis or Wegener's granulomatosis. It is not unreasonable to assume that future serologic tests may further whittle down this group now classified as idiopathic. REVIEW

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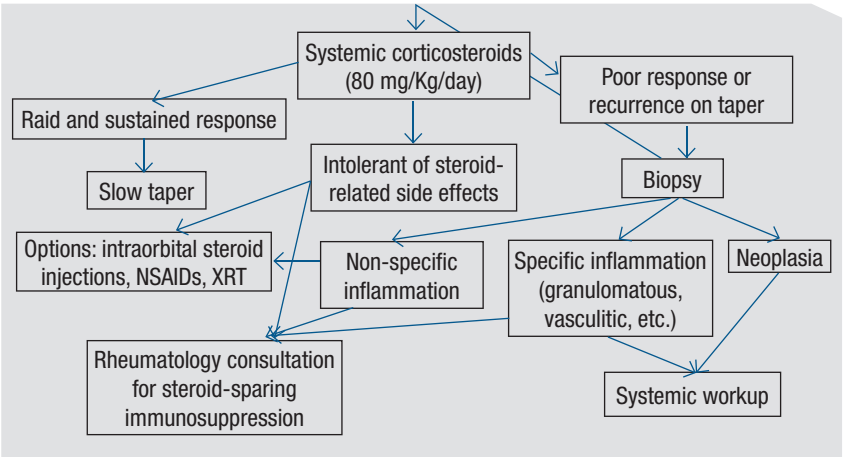
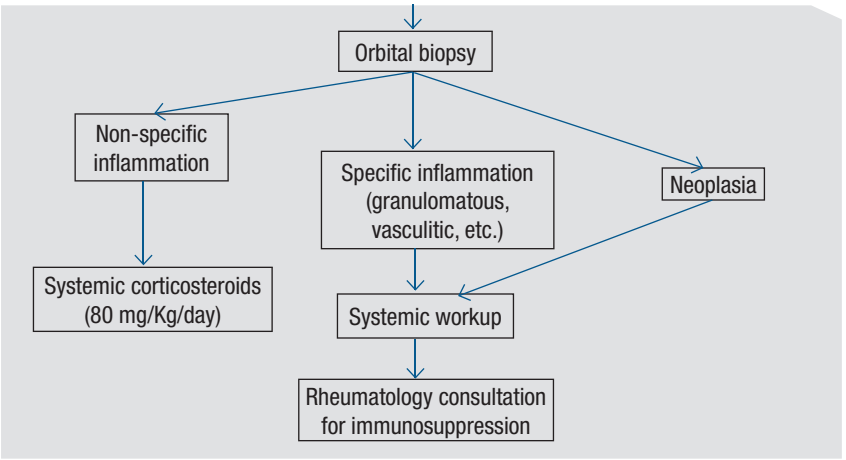
Typical IOIS (onset, symptoms, imaging)



Atypical IOIS (onset, symptoms, imaging)



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An Expert Review Of the SATs

A surgeon describes the SATs—surface ablation techniques—that help him get the best outcomes with PRK.

Jesper Hjortdal, MD, PhD, Aarhus, Denmark

Sitting down to perform refractive surgery is like taking a test; everything you've studied and practiced in wet labs now has to be brought to bear on the case in front of you, with the patient's satisfaction as your grade. The method you use for epithelial debridement, your centration technique and your postop regimen will all count either for or against you. Here, I'll describe the surface ablation techniques that have worked for me and my fellow surgeons in our university clinic, and take a look at what some of the research says about different SATs.

PRK's Place

As with many practices, PRK is no longer our go-to surgery in all our cases, and instead occupies a place reserved for certain patient presentations and levels of myopia. For most cases that come to our clinic, we use either the new femtosecond-based, small-incision lenticule extraction procedure, or LASIK. For select patients, though, PRK is simply a better fit. Such patients have low myopia, below approximately -3 D, and one or more of the following characteristics:

- an occupation that involves a high risk of receiving an injury to their eyes, especially blunt injuries, such as the military or sports;
- epithelial basement membrane dystrophy or even miniscule signs of EBMD that tell you the patient has a risk of developing an epithelial abrasion with LASIK;
- young age, because young patients, on average, do slightly better than older ones in terms of corneal haze development; and
- subclinical keratoconus or a family history of keratoconus.

In addition to PRK being able to treat the patients described above more safely than LASIK, PRK has certain advantages over LASIK that make it appealing. These include:

- no surgical complications associated with creating a flap;
- no flap folds;
- no epithelial ingrowth;
- no risk of late dislocation of the flap;
- no ectasia; and
- a shorter period of dry-eye symptoms.

The dry-eye advantage was shown in a study from 2012. In it, researchers treated 68 eyes of 34 patients with either LASIK or PRK, randomized by ocular dominance. Patients completed a questionnaire preoperatively and at each postoperative visit evaluating symptoms of dry eye, dry-eye severity, visual fluctuations and foreign body sensation. Both groups had significant increases in the frequency of dry-eye symptoms after surgery, with LASIK having a higher frequency at both one and three months. By the one-year visit, though, there was no increase in dry-eye symptoms over baseline in either group.[1]

The Procedure

Here is the way we approach key junctures of the PRK procedure, from preop prep to follow-up.

• ***Prep and debridement.*** We prepare the patient with two drops of topical anesthetic and then place a drop of antibiotic. In our region, the antibiotic we use is chloramphenicol but U.S. surgeons are likely to use something different. We then use a blunt, 8-mm corneal marker to delineate the area from which I'll be removing epithelium. The surgeon applies an alcohol solution in that 8-mm zone for a few

seconds, then uses a blunt Beaver blade to scrape away the epithelium, making sure to remove any remaining epithelial cells. We prefer the alcohol/scrape method to mechanical debridement both because it's worked well in our hands and because of the findings from a randomized study. In this bilateral clinical study, researchers used confocal microscopy to compare mechanical epithelial debridement with alcohol-assisted debridement. They found that mechanical debridement retarded epithelial healing time and decreased stromal keratocyte density.[2]

• ***Centration.*** We then position the patient under the laser and use a combination of the laser's own automatic centration and a manual adjustment. First, the laser zeroes in on the center of the pupil. The surgeon then moves it one-third of the way toward the corneal apex. The light reflex there is from a part of the cornea that's perpendicular to the laser when the patient is fixated on the fixation light.

• ***The bandage lens question.*** Many surgeons will use a bandage contact lens that the patient is to wear for a few days after the PRK. In our experience, after two or three days patients will start to feel some discomfort from the lens. There's also a possibly increased risk for infiltrates with the use of a contact lens immediately after PRK.[3,4] Because of these factors, we have simply felt that it's safer to perform PRK cases the way we have been doing them, without a bandage lens. The patient will, however, have more pain postop without a contact lens in the eye, which we hope to counter with postop q.i.d. non-steroidal anti-inflammatory drops, such as diclofenac, for the first two or three days, as well as oral painkillers.

In addition to the NSAID, we'll send the patient home with chloramphenicol and fluorometholone drops, both q.i.d. for two weeks. They then taper those drops to b.i.d. for two weeks.

• ***Mitomycin-C.*** For very low myopia, we don't use this powerful antimetabolite. However, if we were to ablate more than 50 µm, we'd soak a 7- or 8-mm diameter sponge in 0.02% MMC and apply it to the stroma for 20 seconds. We then flush it with saline.

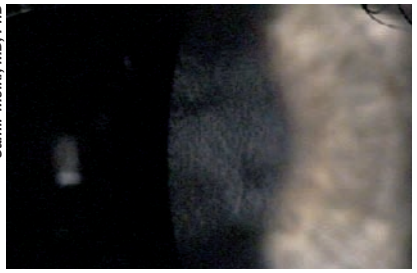
• ***Follow-up.*** Our situation is a little different in that our patients often come a good distance to see us, so we want to see them on the first day postop, just to look for anything unusual and to assure them that it's normal to have some pain. They then return home and, at one week, are seen by their local ophthalmologist to make sure their epithelium has healed. If it hasn't healed at that point, their ophthalmologist will call us and we'll suggest a way to proceed, which may involve placing a bandage contact lens. If everything is OK at one week, we'll see them at three months.

We counsel patients to expect some visual acuity fluctuations during those postop months. And, if we've done a higher-level ablation for some reason, they should be prepared for some slightly blurred vision at three months due to possible haze. This development is normal and the haze will disappear with time. Typically, patients will also be slightly overcorrected initially, and then their vision will move toward the target refraction. They should be informed that whatever refraction they have at one week most likely won't be their final result.

PRK and SMILE

Even though PRK is an older procedure and SMILE is one of the newest, it turns out they may be able to complement each other. In a few of our SMILE patients, there will be some irregular astigmatism or microfolds in the corneal cap that might be visually significant. In such cases, we'll do a trans-epithelial PRK.

In trans-epithelial PRK, we use the laser in phototherapeutic keratectomy mode to ablate the epithelium, stopping the ablation at the stroma. At that point, we switch the laser over to PRK mode to place the refractive ablation on the stroma. If the patient has microfolds, a trans-epithelial PRK gives you a good chance at smoothing them out.



Samir Melki, MD, PhD

Corneal haze can be a consideration in higher levels of PRK correction.

Using the laser in PTK mode to ablate the epithelium takes a bit of artistry, rather than just pure science. To do it, you first program the laser to cut away 60 or 70 µm, and begin the ablation. You have to watch the cornea carefully. When you see a change in reflection on the corneal surface, you know you're through the epithelium and can stop the PTK and start PRK.

PRK is typically described as a very safe way to perform a refractive laser treatment since it doesn't involve the creation of a LASIK flap and has been used for many years. However, PRK also carries the risk of keratitis if a patient doesn't follow through with his postop drops. So, even though PRK is effective and very safe, it's not without risk, which is always important to keep in mind. REVIEW

Dr. Hjortdal is a clinical professor at the University of Aarhus and president of the European Eye Bank Association.

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Evaluating Exclusions For Refractive Surgery

The Cole Eye Institute evaluated the exclusion criteria used to screen patients for refractive surgery, finding that abnormal cornea topography and low or insufficient corneal thickness remain the most common reasons for excluding patients from LASIK or photorefractive keratectomy. Factors such as cataract, too high of correction and severe dry eye were other common reasons for exclusion.

Charts of patients who were screened for initial refractive surgery by a single surgeon at the Cole Eye Institute between 2007 and 2012 were reviewed, resulting in a total of 1,067 refractive candidates enrolled in the study. Mean patient age was 39 ±12 (range: 17 to 78 years); 519 patients (48.6 percent) were male and 548 (51.4 percent) were female. Refractive surgery was performed in 657 patients (61.6 percent); PRK was considered the best option for 106 (9.9 percent). Of the screened patients, 410 (38.4 percent) did not have refractive surgery, and 134 of these patients (12.6 percent) were considered to have contraindications for both LASIK and PRK.

Among the excluded patients, 69 were male (51.5 percent) and 65 were female (48.5 percent), with a mean age of 40 ±14 (range: 18 to 78 years). Abnormal corneal topography (34.3 percent) and low or insufficient corneal thickness (23.1 percent) were the most common reasons for exclusion. Other factors for exclusion included: high myopia (10.5 percent); insipient or definite cataract (9.7 percent); high hyperopia (3.7 percent); need to wear reading glasses after surgery (3.7 percent); and severe dry eye unresponsive to treatment (3.7 percent).

Cornea 2014;33:1051-1055.
Torricelli A, Bechara S, Wilson S.

Avoiding Recurrence of Epithelial Ingrowth After LASIK

In order to avoid the recurrence of epithelial ingrowth after LASIK, Spanish researchers recommend cleaning the corneal interface (epithelial cyst extraction) and suturing the corneal flap. Doing so appears safe and led to an extremely low recurrence of epithelial ingrowth.

From a total of 7,520 LASIK refractive eyes, 13 eyes with epithelial ingrowth were identified and treated in this retrospective, noncomparative interventional case series. The main outcome measures were uncorrected distance visual acuity; corrected distance visual acuity; refractive cylinder; spherical equivalent; regrowth of epithelial cells; and complications.

Mean patient age was 46.9 years. The mean preoperative logMAR UDVA was 0.34 (standard deviation: 0.19). At two months, the mean postoperative logMAR UDVA was 0.18 (SD: 0.17) and at one year was 0.12 (SD: 0.18; p=0.01). Two months and one year postoperatively, the mean logMAR CDVA was 0.05 (SD: 0.08) and 0.03 (SD: 0.06), respectively (p=0.03). The mean spherical equivalent before surgery was 0.3 D (SD: 1.09). The mean spherical equivalent two months and one year after surgery was -0.07 (SD: 0.53) and -0.004 (SD: 0.18; p=0.04). The mean CYL before surgery was -0.92 D (SD: 1.09); the mean CYL two months and one year after surgery was -0.6 (SD: 0.84) and -0.18 (SD: 0.75; p=0.26). No epithelial ingrowth recurrence was observed up to one year after epithelial removal.

Cornea 2014;33:1046-1050.
Güell J, Verdaguer P, Mateu-Figueras M, Elies D, et al.

Long-term Effect of IVI Bevacizumab for AMD on IOP

Researchers from South Korea evaluating long-term intraocular pressure changes after intravitreal injection of bevacizumab for age-related macular degeneration discovered no significantly higher intraocular elevation than baseline IOP. In addition, neither the number of injections nor pre-existing glaucoma negatively affected IOP changes.

A total of 83 eyes that received IVI of bevacizumab for AMD were enrolled in this study. Measurements of IOP were taken at baseline, six, 12, 18

and 24 months and at the last follow-up after injection; these were then analyzed for changes over time. The changes in IOP were also compared on the basis of the median number of injections. The mean number of injections was 3.71 ±1.62. There was no significantly higher elevation than baseline IOP (14.11 ±2.76 mmHg) after multiple IVI of bevacizumab ($p>0.05$). In the group that had ≥4 injections, mean IOP measurements were not higher compared with the group that had < 4 injections during the follow-up period ($p>0.05$). In the patients with pre-existing glaucoma (three eyes), there was no significant increase of IOP during the follow-up period.

J Glaucoma 2014;23:446-448.
Kim D, Nam W, Kim H, Yi K.

Reproducing SD- and TD-OCT Measurements in DME Patients

The primary objective of a new study from the Diabetic Retinopathy Clinical Research Network Writing Committee was to evaluate the reproducibility of retinal thickness measurements from optical coherence tomography images of diabetic macular edema patients obtained by time-domain (Stratus, Carl Zeiss Meditec) and spectral-domain (Cirrus, Carl Zeiss Meditec; Spectralis, Heidelberg Engineering) instruments, in an effort to formulate equations converting retinal thickness measurements from SD-OCT to equivalent values on TD-OCT. Reproducibility appears better with Spectralis than with Cirrus and Stratus. Conversion equations to transform Cirrus or Spectralis measurements to Stratus-equivalent values, within 10 percent of the observed Stratus thickness values, appear feasible. Central subfield thickness changes beyond 10 percent when using the same machine or 20 percent when switching machines, after conversion to Stratus equivalents, are likely due to a change in retinal thickness rather than measurement error.

A cross-sectional observational study was conducted in private and institutional practices. Patients with DME, defined as Stratus central subfield thickness of 250 µm or greater, participated. An additional normative cohort (individuals with diabetes but without DME) was also enrolled. Each study eye underwent two replicate Stratus scans followed by two replicate Cirrus or Spectralis scans (real-time image registration used) centered on the fovea. The Bland-Altman coefficient of repeatability for relative change in CST (the degree of change that could be expected from measurement variability) was lower with Spectralis (7 percent) compared with Cirrus (14 percent) and Stratus (12 percent within Cirrus/Stratus groups and 15 percent Spectralis/Stratus groups). For each cohort, the initial Stratus CST was within 10 percent of the replicate Stratus measurement nearly all of the time; the conversion equations predicted a Stratus CST within 10 percent of the observed thickness 86 percent and 89 percent of the time for Cirrus/Stratus and Spectralis/Stratus groups, which is similar to the agreement on Stratus re-test. The Bland-Altman limits of agreement for relative change in CST between machines (the degree of change that could be expected from measurement variability, combining within and between instrument variability) were 21 percent for Cirrus and 19 percent for Spectralis when comparing predicted vs. actual Stratus measurement.

JAMA Ophthalmol 2014;139: 1113-1122.
Diabetic Retinopathy Clinical Research Network Writing Committee.

Adalimumab as Steroid-Sparing Treatment for TED

Adalimumab and other immunosuppressive agents may have a role in the treatment of active thyroid eye disease with prominent inflammatory symptoms, mitigating some of the metabolic and psychiatric side effects of pulsed steroid treatment, according to research from the Jules Stein Eye Institute.

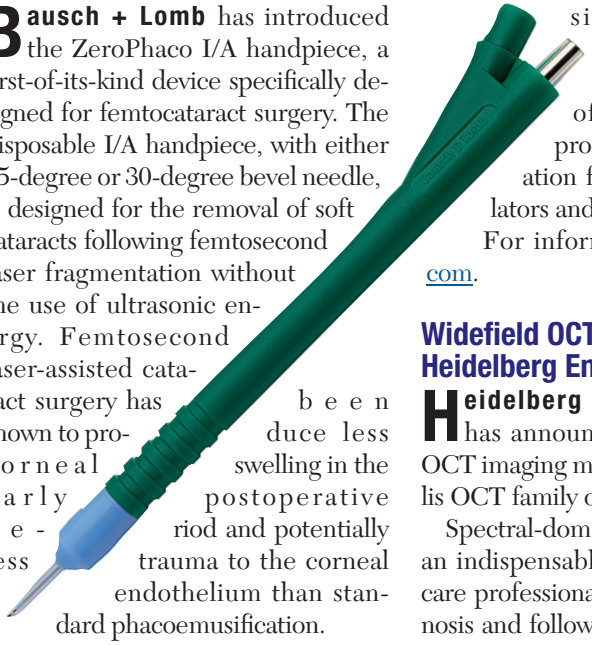
In a retrospective study of all patients (n=10) in the inflammatory phase of TED who were treated with adalimumab, a subcutaneously administered tumor necrosis factor-α antagonist, data concerning visual acuity; optic nerve function; extraocular motility restriction; binocular visual fields; and proptosis was extracted from patient charts. Masked orbital specialists reviewed clinical photographs from baseline and three-month follow-up visits, with each photograph graded on the severity of conjunctival injection; chemosis; eyelid erythema; and eyelid edema on a scale from one to four. An inflammatory score was calculated as the sum of these four elements. Groups were compared using paired *t* tests.

Six patients showed a decrease in inflammatory score while on adalimumab, three showed an increase and one stayed the same. One patient experienced a significant complication (hospital admission for sepsis). Eight patients received concomitant tapering steroids during the first six weeks of therapy as the adalimumab reached maximum efficacy. When data from all 10 patients were analyzed together, there was no significant change in inflammatory index after three months of treatment with adalimumab. However, when the five patients with a high baseline inflammatory index (>4) were considered separately, there was a significant improvement (mean decrease of 5.2 ±2.7; $p<0.01$) after adalimumab treatment. Four of five patients also reported a subjective improvement in symptoms while on adalimumab.

Ophthal Plast Reconstr Surg 2014;30:415-419.
Ayabe R, Rootman D, Hwang C, Ben-Artzi A, Goldberg R.

Designed for Femto Cataract: ZeroPhaco I/A

Bausch + Lomb has introduced the ZeroPhaco I/A handpiece, a first-of-its-kind device specifically designed for femtocataract surgery. The disposable I/A handpiece, with either 15-degree or 30-degree bevel needle, is designed for the removal of soft cataracts following femtosecond laser fragmentation without the use of ultrasonic energy. Femtosecond laser-assisted cataract surgery has been shown to produce less corneal swelling in the early postoperative period and potentially less trauma to the corneal endothelium than standard phacoemusification.



Pre-assembled with a standard infusion sleeve, the coaxial handpiece is designed to work with the Stellaris and Stellaris PC systems for lens removal using an I/A mode. The handpiece is used as a replacement for the ultrasound phacoemulsification handpiece and is green-colored to avoid confusion with the I/A handpiece for cortical cleanup. In addition to the standard incision format (for incision sizes greater than 2.4 mm), the ZeroPhaco I/A handpiece is also available for use in a MICS 2.2mm incision as well.

The ZeroPhaco I/A handpiece joins a complete family of purpose-designed, single-use Bausch + Lomb instruments for the rest of the femtocataract procedure, including fixation forceps, lens manipulators and lid speculum.

For information, visit bausch.com.

Widefield OCT Imaging from Heidelberg Engineering

Heidelberg Engineering GmbH has announced a new widefield OCT imaging modality for its Spectralis OCT family of products.

Spectral-domain OCT has become an indispensable technology for eye care professionals, aiding in the diagnosis and follow-up of patients with a variety of diseases including glaucoma, age-related macular degeneration and diabetic retinopathy.

Until recently, the area scanned during an examination has been limited to a 30-degree field of view. The new Widefield OCT module for the Spectralis expands the OCT field of view to 55 degrees. The new Widefield OCT module allows imaging of the macula, the optic nerve head and the periphery in one comprehensive examination.

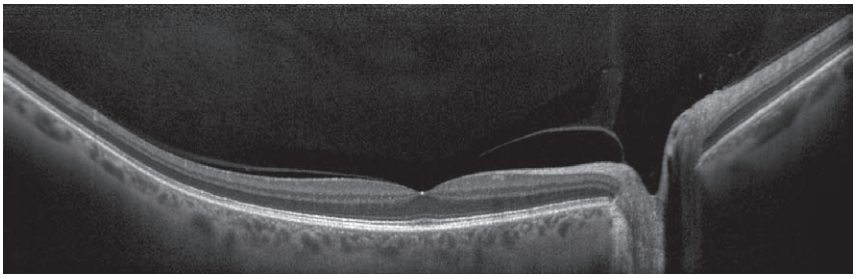
The Widefield OCT Module consists of a 55-degree widefield lens and dedicated software to acquire and process the expanded scan patterns. Customers who already own a widefield lens for Spectralis can simply purchase a software upgrade to utilize this new modality.

The Widefield OCT scans can be acquired simultaneous to all confocal laser scanning laser fundus imaging modalities available on the various models of the Spectralis product family. Widefield OCT is another module offered by the flexible and expandable OCT imaging platform of Spectralis.

For information, visit heidelbergengineering.com.

iScan for Simplified OCT

Optovue has launched its newest device, the iScan, in the United



This article has no commercial sponsorship.

States. iScan is designed to elevate the eye exam by leveraging next-generation, software-guided scanning technology.

The iScan system simplifies optical coherence tomography technology, making it accessible to a range of eye-care professionals in any practice setting. With Optovue's proprietary iWellness scan, iScan guides the patient through the entire exam and requires minimal operator involvement. The iWellness scan provides a cross-sectional view of the retinal layers, a retinal thickness map and a ganglion cell complex map. These outputs enable the doctor to identify signs of disease or otherwise confirm a patient's ocular health.

iScan is being introduced at a very attractive price point, and the revenue generated from the iWellnessExam delivers exceptional return on investment. For information, visit optovue.com.

Rayner Debuts RaySert PLUS

Rayner Intraocular Lenses Ltd. has announced the launch of the company's new injector, RaySert PLUS in the U.S. market after receiving 510(k) clearance from the Food and Drug Administration.

RaySert PLUS is designed for safe and effective implantation of the C-flex Aspheric IOL with a simple and controlled IOL delivery through a wound-assisted 2.2-mm clear cornea mini-incision. For information, visit rayner.com. REVIEW

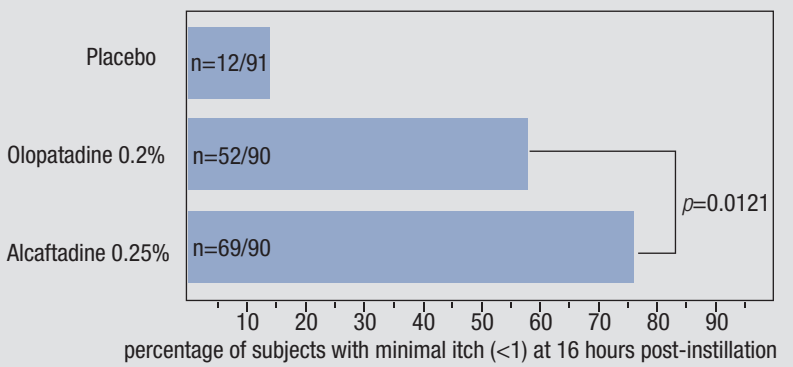
Study Compares Topical Antihistamines

Allergic conjunctivitis is the most common form of ocular allergy in the United States and around the world; seasonal and perennial allergies affect at least 20 percent of the population, and 70 percent to 80 percent of these patients report that their allergies include ocular symptoms.[1] While current treatment strategies include artificial tears, mast cell stabilizers and corticosteroids, the combination of safety, comfort and efficacy has made topical antihistamines the first choice for pharmacotherapy of AC. Among currently approved agents, only two are approved for once-daily dosing: Pataday (0.2% olopatadine, Novartis) and Lastacaft (0.25% alcaftadine, Allergan). A newly published study, supported by Allergan, provides the first direct comparison of these two topical antihistamines, focusing on the duration of relief from signs and symptoms of allergic conjunctivitis.[2]

The study is an analysis of pooled data from two double masked, randomized, placebo-controlled trials that each compared olopatadine 0.2%, alcaftadine 0.25%, and a placebo treatment using the CAC (Conjunctival Allergen Challenge) model of ocular allergy. A total of 284 subjects were included in the analysis of efficacy and safety. In the pooled analysis, mean itch scores for all time points were significantly lower in alcaftadine-treated subjects compared to the subjects receiving olopatadine (0.68 vs. 0.92; p=0.039). The clinical significance of this difference was examined by a minimal itch analysis. Subjects with minimal itch were defined as those with itch scores <1 at all time points. Following an allergen challenge 16 hours after instillation of test agents, 76.1 percent of subjects in the alcaftadine group reported minimal itch, while 58.1 percent of those in the olopatadine group reported minimal itch (p=0.0121; significant by Fisher's exact test).

Evidence from a number of studies supports the idea that chronic or severe allergy may involve long-lasting changes in the epithelial barrier of the cornea and conjunctiva, and that such changes may underlie both the symptomology of perennial allergy and the exacerbating effects of urban pollutants on allergic signs and symptoms.[3,4] A preclinical study published in 2011 examined eosinophil recruitment and epithelial barrier dynamics in a murine model of chronic allergy.[5] In this study, alcaftadine was also found to be superior to olopatadine in terms of its ability to reduce eosinophil infiltration and mitigate the changes in epithelial structural integrity. These effects may help to explain the differences seen between the two drugs in the pooled analysis by Eugene McLaurin and colleagues.[1]

Measuring Ocular Itch Relief



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3. Hughes JL, Lackie PM, Wilson SJ, Church MK, McGill JI. Reduced structural proteins in the conjunctival epithelium in allergic eye disease. Allergy 2006; 61:1268-74.
4. Runswick S, Mitchell T, Davies P, Robinson C, Garrod DR. Pollen proteolytic enzymes degrade tight junctions. Respirology 2007; 12:834-42.
5. Ono SJ, Lane K. Comparison of effects of alcaftadine and olopatadine on conjunctival epithelium and eosinophil recruitment in a murine model of allergic conjunctivitis. Drug Des Devel Ther 2011;5:77-84.

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jmi

(continued from page 31)

J. Daniel Nelson, MD, a professor at the University of Minnesota Regions Hospital, says acclimating a patient to the room can help get a valid result. "If a patient puts a drop in the eye soon before initiating the test, or you stimulate reflex tearing with bright room lights or by shining a slit lamp in his eye, it will probably influence the result of the test," he says. "We acclimate patients to the room by having the tech ask them some questions first, to ensure that they've already been in the room for a few minutes before the test is started, and therefore they're not going to undergo any change in environment that's going to induce reflex tearing. If there's reflex tearing, or you instill a drop, it will result in an artificially low osmolarity. However, if a patient has had a drop instilled in the eye beforehand or had reflex tearing and the result comes up high—that's still a significant finding."

In a poster by TearLab investigators presented at the 2009 meeting of the American Academy of Ophthalmology, researchers found that, out of 300 patients, osmolarity correctly identified 88 percent of normal subjects, 75 percent of mild to moderate disease patients, and 95 percent of severe disease patients. "While tear osmolarity is good for testing whether a patient has dry-eye disease or not, and periodically checking on the efficacy of treatments, it doesn't differentiate between aqueous-deficient and evaporative dry eye," notes Dr. Lemp. "So, you still have to perform an exam and determine whether there is lid disease present, also."

Dr. Nelson says he frequently uses the test to identify patients with a normal result. "My particular practice is a little unusual in that I'm usually seeing people who have already been to two or three ophthalmologists for their irritated eyes and yet continue to have problems," Dr. Nelson says. "So, one of the ways the test is useful to me is if it's normal. A normal result becomes sort of an objective statement of, 'You have eye pain but it's not due to dry eye.' This helps because previous physicians have often blamed the patients' complaints on dry eye, but this tells me that probably isn't the case." REVIEW

Dr. Carlson is a consultant for TearScience and Dr. Hannush has a financial interest in Rapid Pathogen Screening. Dr. Lemp is the chief medical officer for TearLab. Dr. Massaro-Giordano has no financial interest in any of the products mentioned.

1. Chotikavanich S, de Paiva C, Quan Li D, et al. Production and activity of matrix metalloproteinase-9 on the ocular surface increase in dysfunctional tear syndrome. Invest Ophthalmol Vis Sci 2009;50:7:3203.
2. Zhou L1, Zhao SZ, Koh SK. In-depth analysis of the human tear proteome. J Proteomics 2012;75:13:3877-85.
3. Ohashi Y, Ishida R, Kojima T, et al. Abnormal protein profiles in tears with dry eye syndrome. Am J Ophthalmol 2003;136:2:291-299.

DECEMBER

1 - 4
KYOTO, JAPAN
The International Strabismological Association meeting is held every four years; the 2014 meeting will be hosted by the Japanese Association of Strabismus and Amblyopia at the Kyoto International Conference Center. The meeting is a chance for those with a special interest in strabismus from all around the world to gather to present topics in this subspecialty area of ophthalmology and to share experiences in a smaller, more personal setting. The scientific program will feature a large international group of speakers focusing on all sensory and motor aspects of strabismus, as well as other disorders of ocular motility, and promoting clinical research. For more information, visit isa2014.jp.

4 - 6
BALTIMORE
The Wilmer Eye Institute's 27th Annual Current Concepts in Ophthalmology will be held on campus in the Turner Auditorium at Johns Hopkins University. Expert faculty will present the latest developments in the management of ocular conditions, with a specific concentration on the most advanced medical and surgical treatment options within glaucoma, retina, anterior segment and refractive surgery. CME is available. For more information, phone (410) 955-2959 or visit hopkinscme.edu/pdfs/80034487pc.pdf.

FEBRUARY

5 - 8
HO CHI MINH CITY, VIETNAM
The Inaugural Asia-Australia Congress on Controversies in Ophthalmology will raise the most dynamic and controversial topics facing clinicians in the field, with the aim of reaching up-to-date and agreed-upon answers to ongoing debates in ophthalmology through evidence-based medicine and expert opinion. The Congress will emphasize issues related to the region in terms of retina, anterior segment, glaucoma, diagnostics, typical complications and distinctive responses to treatments. The official conference language is English. For more information, email cophyaa@comtecmed.com or visit comtecmed.com/cophy/AA/2015.

12 - 15
AVENTURA, FLA.
The American Society of Cataract and Refractive Surgery and American Society of Ophthalmic Administrator's Side X Side Conference, formerly known as Winter Update, will take place at Turnberry Isle Miami hotel and spa, in Aventura, Fla. This newly designed meeting has been specifically created for anterior segment eye surgeons and busy ophthalmic practice administrators who need in-depth, focused information on key topics that will allow them to integrate advanced techniques into their practices. Each year, Side X Side will focus on key innovations in the ophthalmic practice, providing in-depth "how to's" on all aspects, from discussions with patients, to preoperative screening and planning, to technique adjustments. Side X Side will incorporate the relaxed atmosphere and extensive interaction between faculty and attendees, both within sessions and at networking events, that the ASCRS/ASOA Winter Update made its own. CME and CE are available. For more information, call (703) 591-2220 or visit sidexside.ascrs.org.

MARCH

26 - 29
SORRENTO, ITALY
The 6th World Congress on Controversies in Ophthalmology will take place at the Hilton Sorrento Palace in Sorrento, Italy. This educational Congress will continue to focus on anterior segment, glaucoma and retina sections, and will also discuss controversies in other areas of ophthalmology, such as neuro-ophthalmology. The scientific program will include state-of-the-art lectures and controversial debates; outstanding world leaders as faculty will present both pro and con positions while further challenging and exploring what the optimal treatments for patients are, with emphasis on the appropriate use of new and emerging drugs. This format includes a substantial allocation of time for interactive debates and questions from the audience to each panel of experts. The official language of the Congress is English. For more information, email cophy@comtecmed.com or visit comtecmed.com/cophy/2015.

APRIL

15 - 17
SAN DIEGO
The World Cornea Congress highlights the international corneal community's endeavors in clinical and research areas. It is held every five years and is sponsored by the Cornea Society. The three-day meeting will include both invited speakers and a call for papers, as well as a poster session each day and an exhibit hall. The Congress will immediately precede the American Society of Cataract and Refractive Surgery and the American Society of Ophthalmic Administrators Symposium and Congress. For more information, visit corneasociety.org.

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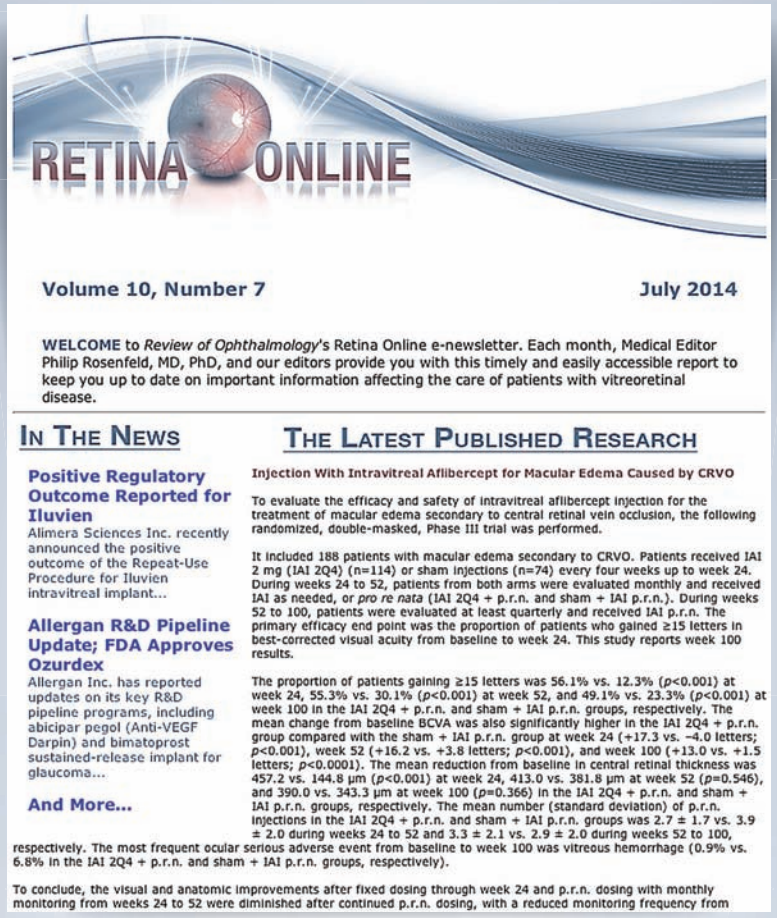

RETINA ONLINE

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.

IN THE NEWS

Positive Regulatory Outcome Reported for Iluvien
Alimera Sciences Inc. recently announced the positive outcome of the Repeat-Use Procedure for Iluvien intravitreal implant...

Allergan R&D Pipeline Update; FDA Approves Ozurdex
Allergan Inc. has reported updates on its key R&D pipeline programs, including abicipar pegol (Anti-VEGF Darpin) and bimatoprost sustained-release implant for glaucoma...

And More...

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

Once a month, Medical Editor Philip Rosenfeld, MD, PhD, and our editors provide you with timely information and easily accessible reports that keep you up to date on important information affecting the care of patients with vitreoretinal disease.

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REVIEW® of Ophthalmology

A fleshy mass, initially diagnosed as conjunctivitis, persists despite treatment, and the patient seeks assistance at Wills Eye Hospital.

Faheem Ahmed, MD

Presentation

A 56-year-old Caucasian female presented with a two-month history of a slowly enlarging fleshy mass located on the nasal conjunctiva of her right eye. The patient was initially diagnosed with conjunctivitis and treated with topical erythromycin ointment. She reported a mild reduction in size of the lesion and a change in color from red to pink on this regimen. On review of systems, the patient denied any eye pain, purulent discharge, photophobia, recent trauma or diplopia. The patient denied the presence of headache, weight loss, fever, rash, joint pain, abnormal bowel movements, urinary symptoms or recent illness.

Medical History

Past ocular history was significant for a suspicion of primary open angle glaucoma treated with a two year trial of Alphagan, which was ultimately discontinued. Medical history included hypertension; a myocardial infarction in 2007 resulting in stent placement; hyperlipidemia; ankylosing spondylitis; osteoporosis; and the diagnosis of follicular B-cell lymphoma in 2009. Past surgical history included hysterectomy in addition to the cardiac stent. Family history was positive for glaucoma. The patient was a nonsmoker. Allergies included intravenous dye, sulfa medications, shellfish and Cefprozil.

Medication list included: Losartan 50 mg by mouth daily; aspirin 5 mg by mouth daily; metoprolol 50 mg by mouth two times a day; Flexeril 10 mg by mouth daily; Plaquenil 200 mg by mouth two times daily; prednisone 5 mg by mouth daily; Protonix 40 mg by mouth daily; simvastatin 5 mg by mouth daily; sulindac 150 mg by mouth two times a day; and Plavix 75 mg by mouth daily. She noted that she had previously been on Enbrel (etanercept) 50 mg subcutaneous injections once a week for ankylosing spondylitis. The medication was discontinued when she was diagnosed with follicular B-cell lymphoma in 2009.

Examination

The patient's vital signs were stable and within normal limits. Ocular examination demonstrated a best corrected visual acuity of 20/25-1 OD and 20/25 OS without improvement on pinhole. Pupillary examination revealed equal, round pupils, reactive pupils to light, with no relative afferent pupillary defect. Extraocular motility was full bilaterally and visual fields were full to confrontation OU. Intraocular pressure by Goldmann applanation tonometry was 16 mmHg OD and 17 mmHg OS. Ishihara color plates were full 13/13 OU.

External examination revealed no evidence of proptosis and normal eyelids without edema or ptosis. Slit-lamp examination of the right eye revealed a painless mass in the medial canthus, involving the conjunctival stroma, appearing "salmon pink," and measuring approximately 15 mm x 15 mm *(See Figure 1)*. The left eye was unremarkable. Dilated fundus examination revealed normal optic nerve, macula, vessels and peripheral retina bilaterally.

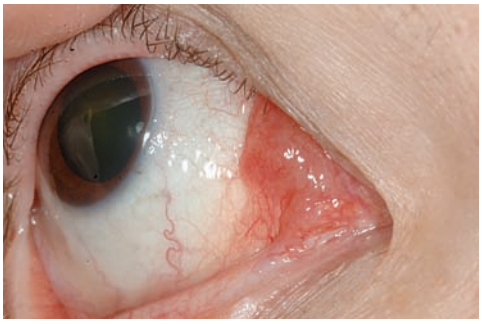

Figure 1. External photograph of the right eye demonstrating an erythematous fleshy mass in the medial canthus.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 88

Diagnosis, Workup and Treatment

Given the patient's personal history of previous B-cell lymphoma, recurrence of a malignant lymphoma in the conjunctiva was considered. Due to the nonspecific features of the lesion, the differential also included benign conjunctival masses such as reactive lymphoid hyperplasia, lymphangioma, or atypical inclusion cyst. Additional malignancies considered in a patient on chronic immunosuppression include Kaposi's sarcoma, squamous cell carcinoma and amelanotic melanoma. An infectious etiology or inflammatory condition was much lower on the differential diagnosis due to the lack of related features on examination.

MRI of the orbits was subsequently performed and was largely unremarkable. The globes and optic nerves were normal bilaterally, without abnormal enhancement. The extraocular muscles and orbital fat were unremarkable without evidence of inflammation. There was no discrete intraconal or extraconal mass. The ventricular system and cavernous sinus were normal.

Laboratory evaluation with complete blood count and basic metabolic panel were both unremarkable. Without evidence of orbital tumor on MRI and largely normal lab work, the patient underwent biopsy of the right medial canthal lesion. A 15 mm x 15 mm x 4 mm salmon-colored specimen was submitted to pathology. Histopathology revealed a follicular lymphoma, grade 1 to 2/3 with a mixed follicular diffuse growth pattern (50 percent follicular and 50 percent diffuse). An orbital specimen was negative for tumor.

Given the patient's localized findings of a conjunctival follicular lymphoma, the patient was then treated with eight weekly infusions of rituximab, a monoclonal antibody that targets CD20+ B-cell lymphocytes. Rituximab has been approved as a first-line treatment for indolent, isolated orbital adnexal lymphoma.[1] The patient tolerated the treatment without serious systemic side effects with resolution of the right conjunctival lesion *(See Figure 3)*.

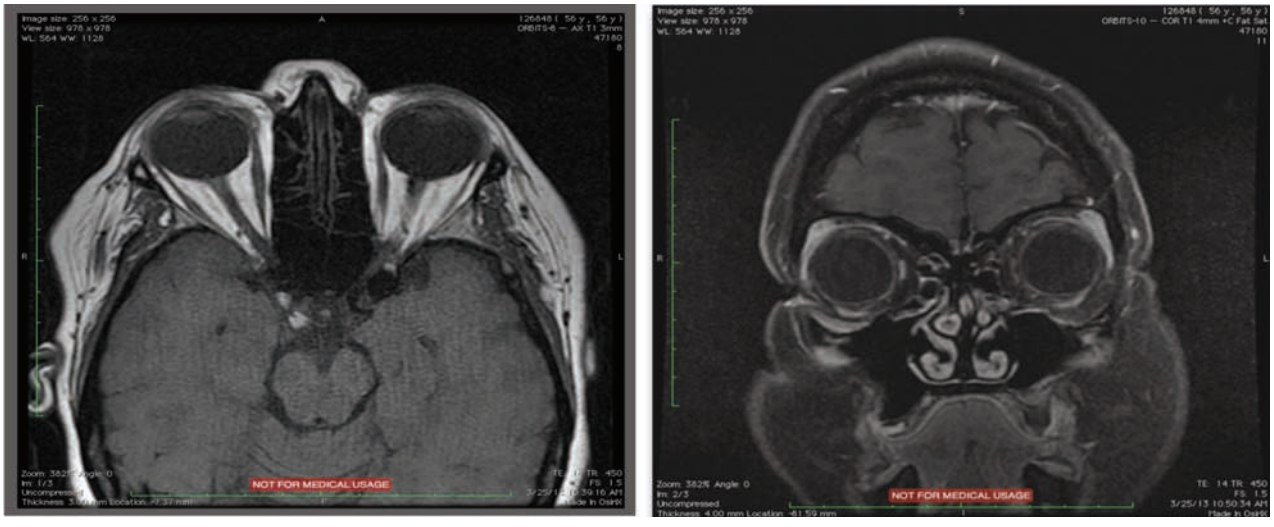

Figure 2. T1-weighted MRI axial cut (no fat suppression, no enhancement) (left) and sagittal cut (with fat suppression and enhancement) (right) showing normal orbits bilaterally.

Discussion

This patient had been diagnosed with ankylosing spondylitis in 1998 and was subsequently started on methotrexate and oral prednisone. The symptoms persisted despite this regimen, and consequently etanercept (Enbrel), a tumor necrosis factor antagonist, was added to her treatment. She used this medication for nine years without any complications. In 2009, she developed lymphadenopathy in her neck and right periorbital region. Biopsy revealed the presence of Stage IIA follicular B-cell lymphoma, a subset of non-Hodgkin's lymphoma. Etanercept and methotrexate were both discontinued immediately, and the patient was treated with rituximab for four consecutive weeks and a maintenance therapy of every month for two years.

Etanercept belongs to a class of drugs known as disease-modifying anti-rheumatic drugs (DMARDs), injectable biologic agents that function by suppressing the body's immune system. Etanercept was first released for commercial use in 1998. The Food and Drug Administration approved indications for this medication include

rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis. When patients are symptomatic despite the use of first-line anti-rheumatic medications, such as methotrexate, physicians often turn to biologic agents as the next course of therapy. DMARDs generally provide rapid onset of action and less-frequent dosing. However, this needs to be balanced against possible correlation between the use of biologics such as etanercept and the development of lymphoproliferative disorders.

According to a 2002 study performed by S. Lori Brown, PhD, and colleagues, a total of 26 cases of lymphoma were reported to the FDA after the administration of TNF antagonist therapy.[2] Eighteen cases were linked directly to etanercept with a median of eight weeks from initiation of therapy to lymphoma development. Of these 26 cases, 81 percent were non-Hodgkin's lymphoma. Furthermore, there were two instances of lymphoma regression following discontinuation of the TNF antagonist in the absence of targeted lymphoma treatment. This study, and others like it, have ultimately resulted in a new diagnostic entity termed "iatrogenic immunodeficiency-associated lymphoproliferative disorders."[2] A 2012 meta-analysis of all randomized controlled clinical trials from 2000 to 2009 found an increased risk for lymphoma, predominantly B-cell lymphoma, in patients receiving TNF antagonist therapy for rheumatoid arthritis.[3] In seven of the 14 studies, there was no incidence of lymphoma in the non-TNF antagonist group. The development of lymphoproliferative tumors did not reach statistical significance due to the rarity of lymphoma.[3]

A major caveat to consider in these two studies, however, is the fact that patents with rheumatoid arthritis are inherently at a higher risk of developing malignant lymphoma. According to a 2003 study, the overall risk for lymphoma in RA patients is doubled compared to non-RA patients.[4] This is compounded by the fact that there is a strong association between severity of inflammatory disease and the risk of developing lymphoma. TNF antagonists and biologic agents in general tend to be given to patients with more severe disease. This same inherent risk, on the other hand, was not found between ankylosing spondylitis and the development of lymphoma according to a 2006 retrospective case-control study performed in Sweden. Using the Swedish Cancer Register, Johan Askling, MD, PhD, and colleagues found no evidence to suggest that the average risk of lymphoma in patients hospitalized with ankylosing spondylitis is increased.[5]

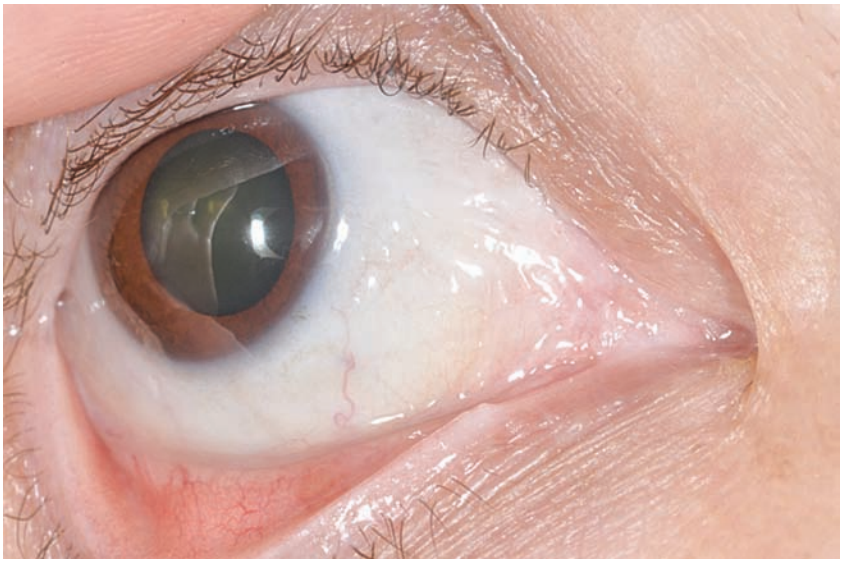

Figure 3. External photograph of the right eye demonstrating regression of the erythematous lesion after two months of rituximab infusion.

This patient with ankylosing spondylitis received etanercept for nine years before developing follicular B-cell lymphoma that was detected in 2009 and recurred again in the conjunctiva in 2013. A similar case report was published in 2011 of a 45-year-old Turkish male with ankylosing spondylitis who developed diffuse large B cell non-Hodgkin's lymphoma after 11 months of etanercept therapy.[6] Etanercept was discontinued and his cancer went into remission after receiving systemic chemotherapy.

In conclusion, there is growing evidence of a potential positive correlation between the development of lymphoma and the use of TNF antagonist biologic agents. Although it is impossible to point to etanercept therapy as the sole cause of lymphoma in this patient, it is important to raise awareness that patients on these medications could be at greater risk for lymphoma. Therefore, we must encourage physicians to use their best judgment when treating chronic inflammatory conditions with administration of TNF antagonists. REVIEW

The author would like to give special thanks and acknowledgement to Carol Shields, MD.

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