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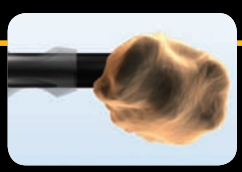

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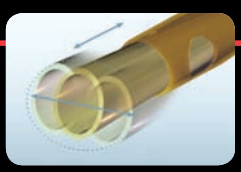

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REVIEW NEWS
Volume XX • No. 7 • July 2013

Nottingham Researchers Suggest A New Layer in the Cornea

Scientists at the University of Nottingham, UK, have discovered a previously undetected layer in the cornea. The breakthrough, announced in a study published in *Ophthalmology*, could help surgeons to dramatically improve outcomes for patients undergoing corneal grafts and transplants.

The new layer has been dubbed the Dua's Layer after the academic Professor Harminder Dua who discovered it.

Professor Dua, a professor of ophthalmology and visual sciences, said: "This is a major discovery that will mean that ophthalmology textbooks will literally need to be re-written. Having identified this new and distinct layer deep in the tissue of the cornea, we can now exploit its presence to make operations much safer and simpler for patients.

"From a clinical perspective, there are many diseases that affect the back of the cornea which clinicians across the world are already beginning to relate to the presence, absence or tear in this layer."

The newly discovered layer is between the corneal stroma and Descemet's membrane. Although it is just 15 µm thick, it is incredibly tough and is strong enough to be able to withstand one and a half to two bars of pressure.

The scientists proved the existence of the layer by simulating human corneal transplants and grafts on eyes donated for research purposes to eye banks located in Bristol and Manchester.

During this surgery, tiny bubbles of air were injected into the cornea to gently separate the different layers. The scientists then subjected the separated layers to electron microscopy, allowing them to study them at many thousand times their actual size.

Understanding the properties and location of the new Dua's layer could help surgeons to better identify where in the cornea these bubbles are occurring and take appropriate measures during the operation. If they are able to inject a bubble next to the Dua's layer, its strength means that it is less prone to tearing, meaning a better outcome for the patient.

The discovery will have an impact on advancing understanding of a number of diseases of the cornea, including acute hydrops, Descematocele and pre-Descemet's dystrophies.

The scientists now believe that corneal hydrops, a bulging of the cornea caused by fluid build up that occurs in patients with keratoconus, is caused by a tear in the Dua layer, through which water from inside the eye rushes in and causes waterlogging.

Better Gene Delivery from Cal Scientists

Researchers at the University of California, Berkeley, have developed an easier and more effective method for inserting genes into eye cells that could greatly expand gene therapy to help restore sight to patients with blinding diseases ranging from inherited defects like retinitis pigmentosa to degenerative illnesses of old age, such as macular degeneration.

Unlike current treatments, the new procedure—which takes as little as 15 minutes—is surgically non-invasive, and it delivers normal genes to difficult-to-reach cells throughout the entire retina.

Over the last six years, several groups have successfully treated people with a rare inherited eye disease by injecting a virus with a normal gene directly into the retina of an eye with a defective gene. Despite the invasive process, the virus with the normal gene was not capable of reaching all the retinal cells that need fixing.

"Sticking a needle through the retina and injecting the engineered virus behind the retina is a risky surgical procedure," said David Schaffer, PhD, professor of chemical and biomolecular engineering and director of the Berkeley Stem Cell Center at the University of California, Berkeley. "But doctors have no choice because none of the gene-delivery viruses can travel all the way through the back of the eye to reach the photoreceptors—the light sensitive cells that need the therapeutic gene.

"Building upon 14 years of research, we have now created a virus that you just inject into the liquid vitreous humor inside the eye and it delivers genes to a very difficult-to-reach population of delicate cells in a way that

is surgically non-invasive and safe. It's a 15-minute procedure, and you can likely go home that day."

The engineered virus works far better than current therapies in rodent models of two human degenerative eye diseases, and can penetrate photoreceptor cells in the eyes of monkeys, which are like those of humans.

Dr. Schaffer and his team are now collaborating with physicians to identify the patients most likely to benefit from this gene-delivery technique and, after some preclinical development, hope soon to head into clinical trials, he said.

The study was published on June 12 in the journal *Science Translational Medicine*.

Three groups of researchers have successfully restored some sight to more than a dozen people with Leber's congenital amaurosis, which leads to complete loss of vision in early adulthood. They achieved this by inserting a corrective gene into adeno-associated viruses (AAV), a common but benign respiratory virus, and injecting the viruses directly into the retina. The photoreceptor cells take up the virus and incorporate the functional gene into their chromosomes to make a critical protein that the defective gene could not, rescuing the photoreceptors and restoring sight.

Unfortunately, the technique cannot be applied to most blinding diseases because the needle often causes retinal detachment, making the situation worse. Yet the standard AAV used in eye and other types of gene therapy can't penetrate into tissue to reach the photoreceptors and other cells, such as retinal pigment epithelium, that need to be fixed. The retina is about 100,000 times thicker than an AAV, which is about 20 nanometers across.

Years ago, Dr. Schaffer set out to find a way to "evolve" AAV to penetrate tissues, including eye and liver, as a way to deliver genes to specific cells. To date he has generated 100 million variants of AAV—each carrying slightly different proteins on its coat—from which he and his colleagues selected five that were effective in penetrating the retina. They then used the best of these (7m8) to transport genes to cure two types of hereditary blindness for which there are mouse models: X-linked retinoschisis, which strikes only boys and makes their retinas look like Swiss cheese; and Leber's congenital amaurosis. In each case, when injected into the vitreous humor, the AAV delivered the corrective gene to all areas of the retina and restored retinal cells nearly to normal.

When injected into the eye of a normal monkey, the virus penetrated cells spottily across the retina but almost completely in the fovea. Current viruses do not penetrate foveal cells at all.

Dr. Schaffer predicts that the virus can be used not only to insert genes that restore function to non-working genes, but can knock out genes or halt processes that are actively killing retina cells, which may be the case in age-related macular degeneration.

Study Tabs Cost Of Inefficient Drug Use at $200 Billion

Avoidable costs of more than $200 billion are incurred each year in the U.S. health-care system as a result of medicines not being used responsibly by patients and health-care professionals, according to a new study by the IMS Institute for Healthcare Informatics. This represents 8 percent of the country's total annual health-care expenditures and amounts to millions of avoidable hospital admissions, outpatient treatments, pharmaceutical prescriptions and emergency room visits for patients.

The report—Avoidable Costs in U.S. Healthcare: The $200 Billion Opportunity from Using Medicines More Responsibly—examines six areas that contribute to unnecessary costs: medication nonadherence, delayed evidence-based treatment practice, misuse of antibiotics, medication errors, suboptimal use of generics and mismanaged polypharmacy in older adults. Together, these areas lead to unnecessary utilization of health-care resources involving an estimated 10 million hospital admissions, 78 million outpatient treatments, 246 million prescriptions and four million emergency room visits annually. The study found significant opportunities for improvement—to ensure that patients receive the right medicines at the right time, and take them in the right way.

"As our study makes clear, drugs are often not used optimally, resulting in significant unnecessary health system spending and patient burdens," said Murray Aitken, executive director, IMS Institute for Healthcare Informatics. "Those avoidable costs could pay for the health care of more than 24 million currently uninsured U.S. citizens."

The report finds that progress is being made to address some of the challenges that drive wasteful spending in many parts of the U.S. health-care system. Medication adherence among large populations of patients with hypertension, hyperlipidemia and diabetes has improved 3 to 4 percent since 2009. In addition, the proportion of patients diagnosed with a cold or the flu who inappropriately received antibiotic prescriptions has fallen from 20 percent to 6 percent since 2007. And, patients are now receiving lower-cost generic alternatives to branded medications, when available, 95 percent of the time.

The report's key findings include:

• Medication nonadherence drives the largest avoidable cost. Patients not adhering to their doctors' medication guidance experienced complications that led to an estimated $105 billion in annual avoidable health-care costs.

While the underlying reasons for nonadherence are varied and longstanding, the growing use of analytics and collaboration among providers, pharmacists and patients appear to be advancing both the understanding and effectiveness of intervention programs.

• Delays in applying evidence-based treatment to patients lead to $40 billion in annual avoidable costs. The study analyzed four disease areas where patients either are not diagnosed early or treatment is not initiated promptly. The largest avoidable impact is seen in diabetes, where such delays increased outpatient visits and hospitalizations. A reduction in this source of avoidable costs is possible if insurance coverage is expanded, and at-risk patients are able to receive appropriate screening and diagnostic testing.

• Some signs of improvement are evident in the responsible use of antibiotics. The misuse of antibiotics contributes to antimicrobial resistance and an estimated $34 billion each year in avoidable inpatient care costs. An additional $1 billion is spent on about 31 million inappropriate antibiotic prescriptions that are dispensed each year, typically for viral infections. There are encouraging signs that efforts to drive responsible antibiotics use are paying off, particularly in the declining number of prescriptions for the common cold and flu–viral infections that do not respond to antibiotics.

• Efforts are under way to address the underlying causes of avoidable spending and to improve medication use, with initiatives advancing across the health-care landscape, including novel interventions, critical assessments of established solutions and pioneering models of stakeholder cooperation. Many of these initiatives involve a greater role for pharmacists, an integrated approach to addressing patient issues, alignment of financial incentives, and greater use of health-care informatics to guide decision-making and monitor progress. REVIEW

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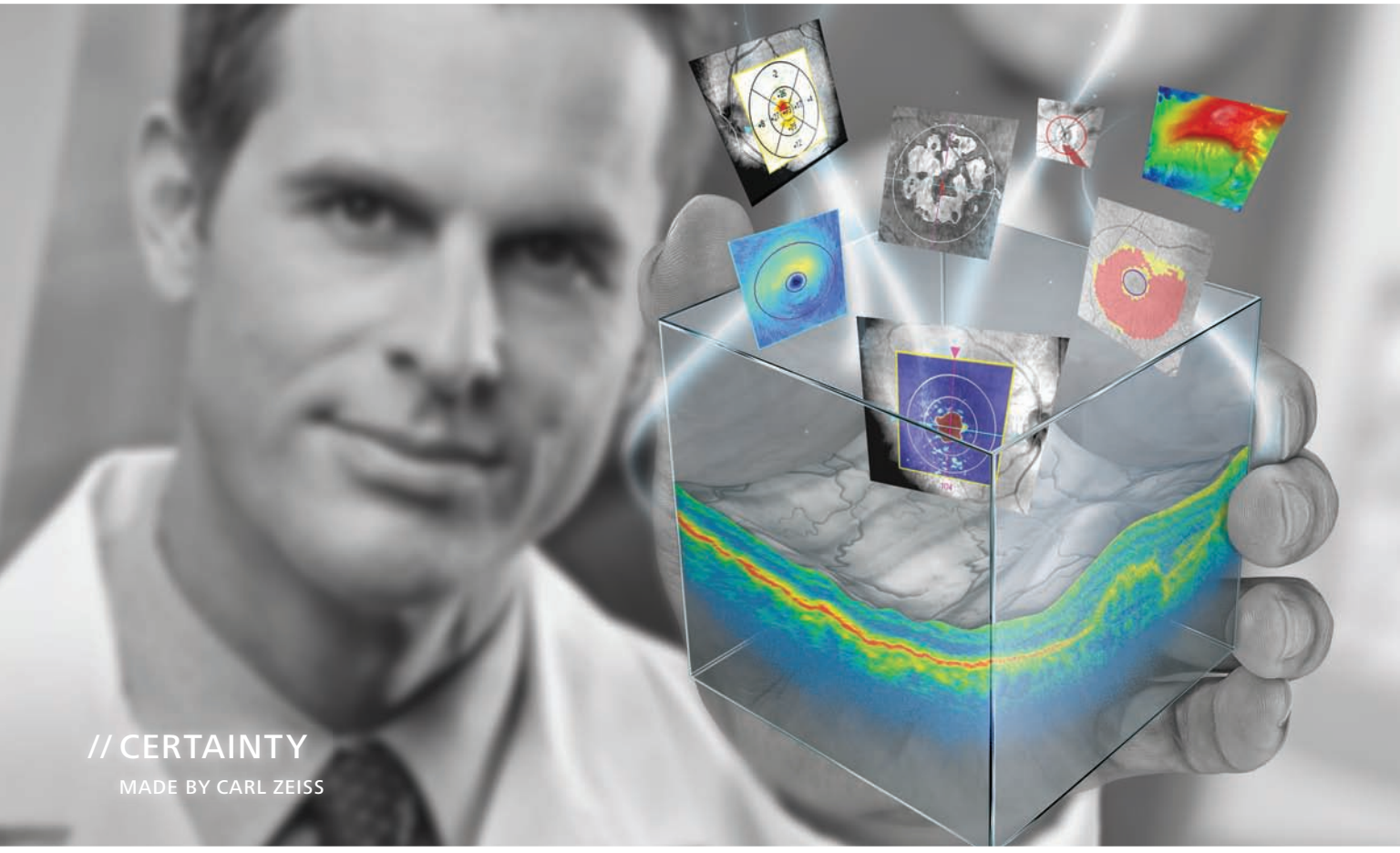

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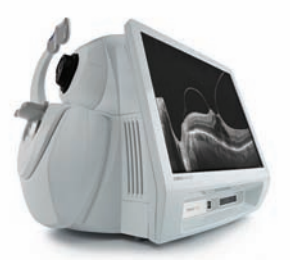

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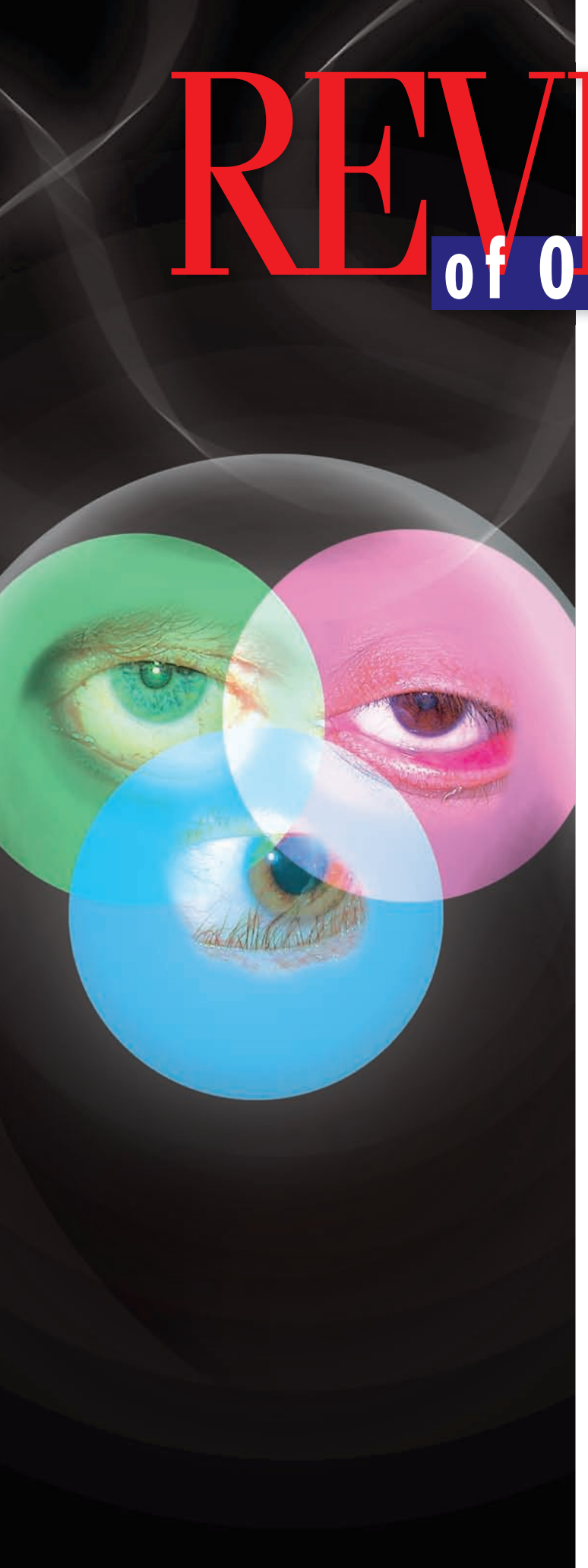

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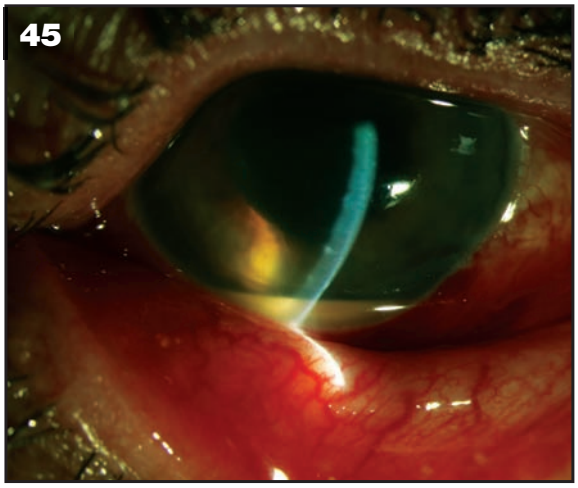

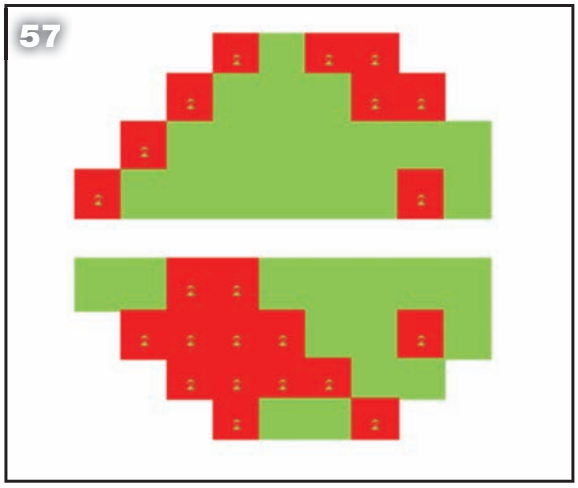

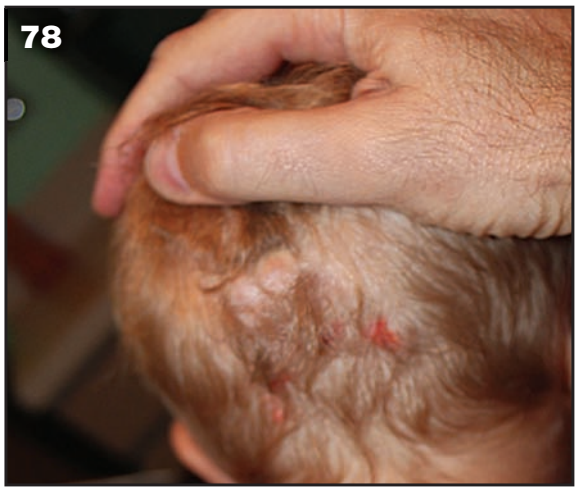

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REVIEW Editor's Page

Christopher Glenn, Editor in Chief

Plastics Demand Up, Along With Scrutiny

With all of the focus in recent years on the younger cataract patient, it would be easy to lose sight of what's going on with the more conventional, "standard-age" cataract patient of—pick a number—70 or more years of age. We decided to address that with a specific article this month (p. 38) on meeting the needs of these patients, and with our cover story (p. 20). The latter deals with the oculoplastic considerations and potential complications in the elderly cataract patient.

It's no revelation that elderly patients tend to have more issues with their lids, their lashes, their tear ducts and other extraocular problems that may need to be addressed in conjunction with their cataracts. What might be a revelation to some, though, is the increasing degree of Medicare billing for lid surgery. A report in late May by the Center for Public Integrity, a nonprofit investigative news organization, finds that from 2001 to 2011, eyelid lifts charged to Medicare more than tripled to 136,000 annually, with billing in the period quadrupling to $80 million a year, and the number of physicians performing the surgeries doubling.

At issue is medical necessity. As Medicare does not cover purely cosmetic, elective procedures, the case must be made that the patient is suffering a functional visual deficit because of the condition.

The report takes pains to point out that factors such as rising patient awareness of plastic surgery options thanks to reality television, and changing demands of patients in this age group play a role in the surge. But it adds that "Surgeons who bill Medicare for large numbers of eyelid surgeries dot a map of the United States. Yet 11 of the 20 highest billers in 2008 were in Florida, which is both an elderly mecca and the country's foremost magnet for questionable Medicare billing."

One top biller in South Florida, according to the data, "billed Medicare more than $800,000 in 2008 for about 2,200 eyelid lifts," for an average of six a day, including weekends. This same doctor was also a top biller in 2006 and 2007.

The other shoe fell this week and it's something all surgeons who participate in Medicare need to know about. In order to obtain the data that served as the basis for the report, the Center's reporters had to agree to maintain the anonymity of any individual surgeons about whose billing practices they would report. A federal judge this week struck down a decades-old injunction barring public access to a confidential database of Medicare insurance claims, essentially removing that cloak of anonymity. The AMA has suggested that it will appeal the decision, and it's uncertain how far the ruling extends but the implications for surgeons' privacy could be substantial.

Again, no one has suggested any widespread gaming of the system by plastic or ophthalmic surgeons. But those who might be just lost some cover.


Breaking New Ground In Meibography

New options are making it easy to visualize the condition of a patient's meibomian glands, with no patient discomfort.

Christopher Kent, Senior Editor

As interest in the causes and treatment of dry eye continues to grow, interest in the meibomian glands—which secrete lipids that help prevent excessive evaporation from the tear film—has grown as well. Recently, several new developments in meibography have made it easier to evaluate and monitor the condition of the glands.

"Meibomian gland dysfunction is a major cause of dry eye," notes Reiko Arita, MD, PhD, clinical researcher in the department of ophthalmology at the University of Tokyo School of Medicine, and an associate professor at Keio University. "However, conventional meibography is performed in a limited number of clinics, probably because of the necessity for examiner expertise, as well as patient discomfort induced by the direct application of a transilluminating light probe to the eyelid."

To create a less-invasive option, Dr. Arita's team has developed two noncontact meibography systems. The first, designed to attach to a slit lamp, includes an infrared filter and an infrared charge-coupled video camera. "In this system, a transilluminating probe is not necessary, making it more patient-friendly," he explains. "The structure of the meibomian glands can easily be observed in both the upper and lower eyelids of patients without causing patient discomfort.

"Using this system we've reported some new findings," he continues, "including the shortening of meibomian glands in contact lens wearers, meibomian gland duct distortion in patients with perennial allergic conjunctivitis, and the dropout of meibomian glands in patients with obstructive meibomian gland dysfunction. The system is also useful for differentiating aqueous-deficiency dry eye from lipid-layer-deficiency dry eye. Moreover, we found meibomian gland dropout in patients who have used anti-glaucoma eye drops for more than six months."

Taking the Next Step

Despite its advantages, the slit-lamp system has some downsides. "Because there are many kinds of slit lamps all over the world, this system can't be used in all facilities," he notes. "Also, it can't be used to examine the meibomian glands of patients who can't use the chin rest, such as infants or inpatients with severe systemic diseases."

Most of the limitations of the slit-lamp system have now been eliminated with their latest iteration: a portable, handheld, pen-shaped meibography device, manufactured by Topcon. "Our mobile, pen-shaped device comprises an infrared LED light source (wavelength 940 nm), a highly sensitive video camera for the acquisition of a clear image, and computer imaging software," he says. "It's connected to a monitor or a personal computer. It provides a panoramic view of all of the meibomian glands along the upper or lower eyelid. To avoid catoptric [reflected] light, the body of the pen-shaped device is held vertically toward the eyelid. None of the subjects have reported glare, discomfort or pain during the meibography procedure.

"Using this mobile pen-shaped meibography device, we can observe meibomian glands in patients who can't sit up," he continues. "We can visit a home for the aged and diagnose meibomian-related diseases. We can also monitor the changes in the meibomian glands of both healthy

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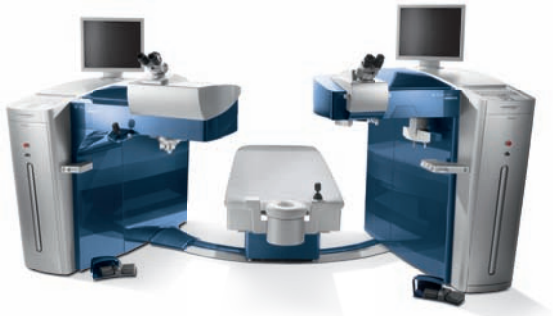

WaveLight® FS200 Femtosecond Laser Software Version AQUA

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1. Based on typical treatment parameters; data on file.

For important safety information about this product, please refer to the adjacent page.

WaveLight®

Health Care Professional Information Sheet-All WaveLight® ALLEGRETTO WAVE® EX500 System Indications

The WaveLight® ALLEGRETTO WAVE® / ALLEGRETTO WAVE® Eye-Q Excimer Laser System

CAUTION: Federal (USA) law restricts this device to sale by, or on the order of a physician.

Statements regarding the potential benefits of wavefront-guided and Wavefront Optimized® laser-assisted in-situ keratomileusis (LASIK) are based upon the results of clinical trials. These results are indicative of not only the WaveLight® ALLEGRETTO WAVE® / ALLEGRETTO WAVE® Eye-Q Excimer Laser System treatment but also the care of the clinical physicians, the control of the surgical environment by those physicians, the clinical trials' treatment parameters and the clinical trials' patient inclusion and exclusion criteria. Although many clinical trial patients after the wavefront-guided and Wavefront Optimized® procedure saw 20/20 or better and/or had or reported having better vision during the day and at night, compared to their vision with glasses or contact lenses before the procedure, individual results may vary. You can find information about the clinical trials below and in the Procudure Manuals for the WaveLight® ALLEGRETTO WAVE® / ALLEGRETTO WAVE® Eye-Q Excimer Laser System.

As with any surgical procedure, there are risks associated with the wavefront-guided and Wavefront Optimized® treatment. Before treating patients with these procedures, you should carefully review the Procedure Manuals, complete the Physician WaveLight® System Certification Course, provide your patients with the Patient Information Booklet, and discuss the risks associated with this procedure and questions about the procedure with your patients.

INDICATIONS: The WaveLight® ALLEGRETTO WAVE® / ALLEGRETTO WAVE® Eye-Q Excimer Laser System is indicated to perform LASIK treatments in patients with documented evidence of a stable manifest refraction defined as less than or equal to 0.50 diopters (D) of preoperative spherical equivalent shift over one year prior to surgery, exclusive of changes due to unmasking latent hyperopia in patients 18 years of age or older: for the reduction or elimination of myopic refractive errors up to -12.0 D of sphere with and without astigmatic refractive errors up to

-6.0 D; for the reduction or elimination of hyperopic refractive errors up to +6.0 D of sphere with and without astigmatic refractive errors up to 5.0 D at the spectacle plane, with a maximum manifest refraction spherical equivalent (MRSE) of +6.0 D; and in patients 21 years of age or older for the reduction or elimination of naturally occurring mixed astigmatism of up to 6.0 D at the spectacle plane.

LASIK is an elective procedure with the alternatives including but not limited to eyeglasses, contact lenses, photorefractive keratectomy (PRK), and other refractive surgeries. Only practitioners who are experienced in the medical management and surgical treatment of the cornea, who have been trained in laser refractive surgery including laser system calibration and operation, may use the device as approved. Prospective patients, as soon as they express an interest in an indicated LASIK procedure and prior to undergoing surgery, must be given the WaveLight® System Patient Information Booklet and must be informed of the alternatives for refractive correction including eyeglasses, contact lenses, PRK, and other refractive surgeries.

Clinical Data Myopia: The WaveLight® ALLEGRETTO WAVE® / ALLEGRETTO WAVE® Eye-Q Excimer Laser System for LASIK treatments of myopic refractive errors up to -12.0 D of sphere with and without astigmatic refractive errors up to -6.0 D at the spectacle plane was studied in clinical trials in the United States with 901 eyes treated, of which 813 of 866 eligible eyes were followed for 12 months. Accountability at 3 months was 93.8%, at 6 months was 91.9%, and at 12 months was 93.9%.

The studies found that of the 844 eyes eligible for the uncorrected visual acuity (UCVA) analysis of effectiveness at the 3-month stability time point, 98.0% were corrected to 20/40 or better, and 84.4% were corrected to 20/20 or better without spectacles or contact lenses.

The clinical trials showed that the following subjective patient adverse events were reported as moderate to severe at a level at least 1% higher than baseline of the subjects at 3 months post-treatment: visual fluctuations (12.8% at baseline versus 28.6% at 3 months). Long term risks of LASIK for myopia with and without astigmatism beyond 12 months have not been studied.

Clinical Data Hyperopia: The WaveLight® ALLEGRETTO WAVE® / ALLEGRETTO WAVE® Eye-Q Excimer Laser System for LASIK treatments of hyperopic refractive errors up to +6.0 D of sphere with and without astigmatic refractive errors up to 5.0 D with a maximum MRSE of +6.0 D has been studied in clinical trials in the United States with 290 eyes treated, of which 100 of 290 eligible eyes were followed for 12 months. Accountability at 3 months was 95.2%, at 6 months was 93.9%, and at 12 months was 69.9%.

The studies found that of the 212 eyes eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 95.3% were corrected to 20/40 or better, and 67.5% were corrected to 20/20 or better without spectacles or contact lenses.

The study showed that the following subjective patient adverse events were reported as much worse by at least 1% of the subjects (in order of increasing frequency) at 6 months post final treatment: glare from bright lights (3.0%); night driving glare (4.2%); light sensitivity (4.9%); visual fluctuations (6.1%); and halos (6.4%). Long term risks of LASIK for hyperopia with and without astigmatism beyond 12 months have not been studied.

Clinical Data Mixed Astigmatism: The WaveLight® ALLEGRETTO WAVE®/ ALLEGRETTO WAVE® Eye-Q Excimer Laser System for LASIK treatments of naturally occurring mixed astigmatism of up to 6.0 D at the spectacle plane has been studied in clinical trials in the United States with 162 eyes treated, of which 111 were eligible to be followed at 6 months. Accountability at 1 month was 99.4%, at 3 months was 96.0%, and at 6 months was 100.0%.

The studies found that of the 142 eyes eligible for the UCVA analysis of effectiveness at the 3-month stability time point, 95.8% achieved acuity of 20/40 or better, and 67.6% achieved acuity of 20/20 or better without spectacles or contact lenses.

The clinical trials showed that the following subjective patient adverse events were reported as moderate to severe at a level at least 1% higher than baseline of the subjects at 3 months post-treatment: sensitivity to light (43.3% at baseline versus 52.9% at 3 months); visual fluctuations (32.1% at baseline versus 43.0% at 3 months); and halos (37.0% at baseline versus 42.3% at 3 months). Long term risks of LASIK for mixed astigmatism beyond 6 months have not been studied.

Clinical Data Wavefront-guided Treatment of Myopia: The WaveLight® ALLEGRETTO WAVE® / ALLEGRETTO WAVE® Eye-Q Excimer Laser System used in conjunction with the WaveLight® ALLEGRO Analyzer® device. The device uses a 6.5 mm optical zone, a 9.0 mm ablation/treatment zone, and is indicated for wavefront-guided LASIK: 1) for the reduction or elimination of up to -7.0 D of spherical equivalent myopia or myopia with astigmatism, with up to -7.0 D of spherical component and up to 3.0 D of astigmatic component at the spectacle plane; 2) in patients who are 18 years of age or older; and 3) in patients with documentation of a stable manifest refraction defined as ≤0.50 D of preoperative spherical equivalent shift over one year prior to surgery was studied in a randomized clinical trial in the United States with 374 eyes treated; 188 with wavefront-guided LASIK (Study Cohort) and 186 with Wavefront Optimized® LASIK (Control Cohort). 178 of the Study Cohort and 180 of the Control Cohort were eligible to be followed at 6 months. In the Study Cohort, accountability at 1 month was 96.8%, at 3 months was 96.8%, and at 6 months was 93.3%. In the Control Cohort, accountability at 1 month was 94.6%, at 3 months was 94.6%, and at 6 months was 92.2%.

The studies found that of the 180 eyes eligible for the UCVA analysis of effectiveness at the 6-month stability time point in the Study Cohort, 99.4% were corrected to 20/40 or better, and 93.4% were corrected to 20/20 or better without spectacles or contact lenses. In the Control Cohort, of the 176 eyes eligible for the UCVA analysis of effectiveness at the 6-month stability time point, 99.4% were corrected to 20/40 or better, and 92.8% were corrected to 20/20 or better without spectacles or contact lenses.

The clinical trials showed that the following subjective patient adverse events were reported as moderate to severe at a level at least 1% higher than baseline of the subjects at 3 months post-treatment in the Study Cohort: light sensitivity (37.2% at baseline versus 47.8% at 3 months); and visual fluctuations (13.8% at baseline versus 20.0% at 3 months). In the Control Cohort: halos (36.6% at baseline versus 45.4% at 3 months); and visual fluctuations (18.3% at baseline versus 21.9% at 3 months). Long term risks of wavefront-guided LASIK for myopia with and without astigmatism beyond 6 months have not been studied.

CONTRAINDICATIONS: LASIK treatments using the WaveLight® ALLEGRETTO WAVE® / ALLEGRETTO WAVE® Eye-Q Excimer Laser System are contraindicated if any of the following conditions exist. Potential contraindications are not limited to those included in this list: pregnant or nursing women; patients with a diagnosed collagen vascular, autoimmune or immunodeficiency disease; patients with diagnosed keratoconus or any clinical pictures suggestive of keratoconus; and patients who are taking one or both of the following medications: isotretinoin (Accutane®1), amiodarone hydrochloride (Cordarone®2).

WARNINGS: Any LASIK treatment with the WaveLight® ALLEGRETTO WAVE® / ALLEGRETTO WAVE® Eye-Q Excimer Laser System is not recommended in patients who have: systemic diseases likely to affect wound healing, such as connective tissue disease, insulin dependent diabetes, severe atopic disease or an immunocompromised status; a history of Herpes simplex or Herpes zoster keratitis; significant dry eye that is unresponsive to treatment; severe allergies; and unreliable preoperative wavefront examination that precludes wavefront-guided treatment. The wavefront-guided LASIK procedure requires accurate and reliable data from the wavefront examination. Every step of every wavefront measurement that may be used as the basis for a wavefront-guided LASIK procedure must be validated by the user. Inaccurate or unreliable data from the wavefront examination will lead to an inaccurate treatment.

PRECAUTIONS: Safety and effectiveness of the WaveLight® ALLEGRETTO WAVE® / ALLEGRETTO WAVE® Eye-Q Excimer Laser System have not been established for patients with: progressive myopia, hyperopia, astigmatism and/or mixed astigmatism; ocular disease; previous corneal or intraocular surgery, or trauma in the ablation zone; corneal abnormalities including, but not limited to, scars, irregular astigmatism and corneal warpage; residual corneal thickness after ablation of less than 250 microns increasing the risk for corneal ectasia; pupil size below 7.0 mm after mydriatics where applied for wavefront-guided ablation planning; history of glaucoma or ocular hypertension of > 23 mmHg; taking the medication sumatriptan succinate (Imitrex®3); under 18 years (21 years for mixed astigmatism) of age; over the long term (more than 12 months after surgery); corneal, lens and/or vitreous opacities including, but not limited to, cataract; iris problems including, but not limited to, coloboma and previous iris surgery compromising proper eyetracking; taking medications likely to affect wound healing including, but not limited to, antimetabolites; treatments with an optical zone below 6.0 mm or above 6.5 mm in diameter; treatment targets different from emmetropia (plano) in which the wavefront-calculated defocus (spherical term) has been adjusted; myopia greater than – 12.0 D or astigmatism greater than 6 D; hyperopia greater than + 6.0 D or astigmatism greater than 5.0 D; mixed astigmatism greater than + 6.0 D; and in cylinder amounts > 4.0 to < 6.0 D.

Due to the lack of large numbers of patients in the general population, there are few subjects with cylinder amounts in this range to be studied. Not all complications, adverse events, and levels of effectiveness may have been determined.

Pupil sizes should be evaluated under mesopic illumination conditions. Effects of treatment on vision under poor illumination cannot be predicted prior to surgery. Some patients may find it more difficult to see in such conditions as very dim light, rain, fog, snow and glare from bright lights. This has been shown to occur more frequently in the presence of residual refractive error and perhaps in patients with pupil sizes larger than the optical zone size.

The refraction is determined in the spectacle plane, but treated in the corneal plane. In order to determine the right treatment program to achieve the right correction, assessment of the vertex distance during refraction testing is recommended. Preoperative evaluation for dry eyes should be performed. Patients should be advised of the potential for dry eyes post LASIK and post wavefront-guided LASIK surgery. This treatment can only be provided by a licensed healthcare professional.

Adverse Events and Complications for Myopia: Certain adverse events and complications occurred after the LASIK surgery. Two adverse events occurred during the postoperative period of the clinical study: 0.2% (2/876) had a lost, misplaced, or misaligned flap reported at the 1 month examination.

The following adverse events did NOT occur: corneal infiltrate or ulcer requiring treatment, corneal edema at 1 month or later visible in the slit lamp exam; any complication leading to intraocular surgery; melting of the flap of >1 mm2; epithelium of >1 mm2 in the interface with loss of 2 lines or more of BSCVA; uncontrolled IOP rise with increase of >5 mmHg or any reading above 25 mmHg; retinal detachment or retinal vascular accident; and decrease in BSCVA of >10 letters not due to irregular astigmatism as shown by hard contact lens refraction.

The following complications occurred 3 months after LASIK during this clinical trial: 0.8% (7/844) of eyes had a corneal epithelial defect; 0.1% (1/844) had any epithelium in the interface; 0.1% (1/844) had foreign body sensation; 0.2% (2/844) had pain; and 0.7% (6/844) had ghosting or double images in the operative eye.

The following complications did NOT occur 3 months following LASIK in this clinical trial: corneal edema and need for lifting and/or reseating the flap/cap.

Adverse Events and Complications for Hyperopia: Certain adverse events and complications occurred after the LASIK surgery. Only one adverse event occurred during the clinical study: one eye (0.4%) had a retinal detachment or retinal vascular accident reported at the 3 month examination.

The following adverse events did NOT occur: corneal infiltrate or ulcer requiring treatment; lost, misplaced, or misaligned flap, or any flap/cap problems requiring surgical intervention beyond 1 month; corneal edema at 1 month or later visible in the slit lamp exam; any complication leading to intraocular surgery; melting of the flap of > 1 mm2; epithelium of > 1 mm2 in the interface with loss of 2 lines or more of BSCVA; uncontrolled IOP rise with increase of > 5 mmHg or any reading above 25 mmHg and decrease in BSCVA of > 10 letters not due to irregular astigmatism as shown by hard contact lens refraction.

The following complications occurred 6 months after LASIK during this clinical trial: 0.8% (2/262) of eyes had a corneal epithelial defect and 0.8% (2/262) had any epithelium in the interface.

The following complications did NOT occur 6 months following LASIK in this clinical trial: corneal edema; foreign body sensation; pain, ghosting or double images; and need for lifting and/or reseating of the flap/cap.

Adverse Events and Complications for Mixed Astigmatism: Certain adverse events and complications occurred after the LASIK surgery. No protocol defined adverse events occurred during the clinical study. However, two events occurred which were reported to the FDA as Adverse Events.

The first event involved a patient who postoperatively was subject to blunt trauma to the treatment eye 6 days after surgery. The patient was found to have an intact globe with no rupture, inflammation or any dislodgement of the flap. The second event involved the treatment of an incorrect axis of astigmatism which required retreatment.

The following adverse events did NOT occur: corneal infiltrate or ulcer requiring treatment; corneal epithelial defect involving the keratectomy at 1 month or later; corneal edema at 1 month or later visible in the slit lamp exam; epithelium of > 1 mm2 in the interface with loss of 2 lines or more of BSCVA; lost, misplaced, or misaligned flap, or any flap/cap problems requiring surgical intervention beyond 1 month; decrease in BSCVA of > 10 letters not due to irregular astigmatism as shown by hard contact lens refraction; any complication leading to intraocular surgery; melting of the flap of > 1 mm2; uncontrolled IOP rise and retinal detachment or retinal vascular accident.

None of the following complications occurred at 3 months after LASIK during this clinical trial: corneal edema; corneal epithelial defect; any epithelium in the interface; foreign body sensation, pain, ghosting or double images; and need for lifting and/or reseating of the flap/cap.

Subjects were asked to complete a patient questionnaire preoperatively and at 3-months, 6-months, and 1-year postoperatively.

Adverse Events and Complications for Wavefront - guided Myopia: Certain adverse events and complications occurred after the wavefront-guided LASIK surgery. No adverse event occurred during wavefront-guided treatments during this clinical study.

The following adverse events did NOT occur: corneal infiltrate or ulcer requiring treatment; lost, misplaced or misaligned flap or any flap/cap problems requiring surgical intervention beyond 1 month; corneal edema at 1 month or later visible in the slit lamp exam; any complication leading to intraocular surgery; melting of the flap of > 1 mm2; epithelium of > 1 mm^2 in the interface with loss of 2 lines or more of BSCVA; uncontrolled IOP rise with increase of > 5 mmHg or any reading above 25 mmHg; and decrease in BSCVA of > 10 letters not due to irregular astigmatism as shown by hard contact lens refraction.

The following complications occurred 3 months after wavefront-guided LASIK during this clinical trial: corneal epithelial defect (0.6%); foreign body sensation (0.6%); and pain (0.6%).

The following complications did NOT occur 3 months following wavefront-guided LASIK in this clinical trial: corneal edema; any epithelium in the interface; ghosting or double images; and need for lifting and/or reseating of the flap/cap.

ATTENTION: The safety and effectiveness of LASIK surgery has ONLY been established with an optical zone of 6.0 – 6.5 mm and an ablation zone of 9.0 mm.

Reference the Directions for Use labeling for a complete listing of indications, warnings and precautions.

1. Accutane® is a registered trademark of Hoffmann-La Roche Inc.
2. Cordarone® is a registered trademark of Sanofi S.A.
3. Imitrex® is a registered trademark of Glaxo Group Limited

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infants and those with congenital diseases such as congenital ectodermal dysplasia and congenital insensitivity to pain with anhidrosis."

In a recent study, Dr. Arita's group compared the new handheld device to the slit-lamp system they had previously developed.[1] "We used both systems to visualize the upper and lower eyelids of healthy volunteers and patients with meibomian gland dysfunction, contact-lens wearers with dryness and patients with allergic conjunctivitis," he says. "The quality of images using the mobile meibography device was similar to those captured using the slit-lamp meibography system."

The handheld device currently costs about $3,000 and is available for import, but has not been approved by the Food and Drug Administration.

Reiko Arita, MD, PhD

A new handheld, pen-shaped, non-contact meibography device developed in Japan allows acquisition of clear, panoramic images and video without patient discomfort. The device can be connected to a monitor or personal computer for viewing or recording images.

Other New Options

"We need to have new ways to perform meibography," agrees Sruthi Srinivasan PhD, BS Optom, FAAO, research assistant professor at the Centre for Contact Lens Research at the University of Waterloo in Ontario. Her group has been conducting meibomian gland research, first using the Oculus Keratograph 4 and more recently the newer Oculus K5M. "Some of the older meibography methods were more research-oriented, and not clinician-friendly," she notes. "They tended to involve bulky equipment and be time-consuming, and there was some discomfort for the patient. Video processing was difficult as well—we never got a full picture of the lid in one shot, so we had to stitch them together. The new devices take a full picture of the lid in one shot."

Asked why they initially chose to pursue meibography using the Oculus Keratograph 4, Dr. Srinivasan explains that it has multiple capabilities. "The device was primarily designed to get a topographical map of the cornea, but it also allows pupillometry, tear film scans, measuring tear breakup time and tear meniscus height," she says. "The Oculus K4 didn't have a dedicated meibography option, so we used the infrared illumination that was available for pupilometry to capture infrared meibography images." Her group used the K4 to conduct their initial meibography study, published in 2012.[2] The study demonstrated the feasibility and effectiveness of this tool for in-clinic meibography.

"The new model [K5M] includes dedicated meibography software, allowing us to take meibography images more easily," she says. "Also, the working distance has been increased to enlarge the field of view; the infrared diodes have been rearranged; and the images are optimized for clarity and much easier to obtain. In addition, this instrument gives you a variety of tools in a single platform. That's why we find it more beneficial than other stand-alone meibography tools."

Dr. Srinivasan notes that a clinician-friendly meibography device will help both patients and clinicians. "Clinicians can explain the condition more easily to patients if they have a picture," she says. "They can correlate the signs and symptoms to the patient's experience. It will also allow clinicians to take a series of pictures over time, to determine whether the glands are changing.

"Using the current Oculus keratograph is very simple," she continues. "Patients rest their head on the chin rest, and you use a cotton tip applicator to gently evert the lower or upper lid. You click on the meibography option, and that opens up a window onscreen. Sometimes you may need an assistant to hold the lid in place, but if you're an experienced user, you can probably do it yourself. Then it's as simple as clicking a button to capture a photo or video."

Dr. Srinivasan says the instrument isn't currently able to perform digital analysis and quantification of images, but this can be done using other software. "There are numerous subjective grading scales for this purpose," she explains. "But we can use a program like ImageJ to outline the areas of gland loss and then calculate the gland loss as a percentage of the total area of the lid, which is more objective." She admits that digital quantification is probably more than is needed for clinical use. "But if you want a precise quantification of percentage loss," she says, "it is possible to achieve." REVIEW

Dr. Arita is an advisor to Topcon. The Centre for Contact Lens Research has conducted funded research studies on behalf of Oculus during the past three years, but Dr. Srinivasan personally does not have a financial relationship to Oculus or the instruments described.

1. Arita R, Itoh K, Maeda S, et al. A Newly Developed Noninvasive and Mobile Pen-Shaped Meibography System. Cornea 2013;32:3:242-247.
2. Srinivasan S, Menzies K, Sorbara L, Jones L. Infrared imaging of meibomian gland structure using a novel keratograph. Optom Vis Sci 2012;89:5:788-94.

In the Spotlight:
Bacitracin Ophthalmic Ointment USP

Learn about the presurgical use of this antibiotic and find out why one renowned ophthalmologist insists on it for endophthalmitis prophylaxis.

Think what you will about people who are particular about doing things a certain way and only that way, but paying extreme attention to detail just might be a key to avoiding one of the most dreaded surgical complications: endophthalmitis. Robert H. Osher, MD, a Cincinnati-based cataract surgeon, has had only one run-in with this sight-threatening condition in 35 years. Here, he shares his disciplined approach to cataract surgery, which he attributes to his tremendous track record. "I pay meticulous attention to the lids and lashes; use appropriate lid hygiene and medications, which include Bacitracin Ophthalmic Ointment USP on the lashes; carefully sterilize the field during surgery; pay careful attention to incision construction; and never underestimate the tragic severity of endophthalmitis," he says. And he has been very satisfied with his regimen, which we will learn more about later.

Bacitracin: Tried and True

In cataract surgery, preoperative regimens, which typically consist of doses of antibiotics, are necessary for preventing intraocular infection. It is indicated for the treatment of superficial infections involving the conjunctiva and/or cornea caused by Bacitracin-susceptible organisms and should not be used in patients who have a history of hypersensitivity to Bacitracin.

The ointment can be applied to the conjunctiva or lid margins. It has proven therapeutic utility in a variety of superficial ocular infections, including blepharitis and conjunctivitis.[1] Furthermore, it has profound activity against common Gram-positive pathogens.[1-3] What makes this product even more attractive is its convenient dosing (one to three times daily)[1] and the fact that it qualifies as a tier-1 co-pay on most insurance plans.[4]

Although it has been available for decades (in topical form since the early 70s), it has never been administered as a routine systemic antibiotic. Says Dr. Osher, "I may be one of a few ophthalmologists who use Bacitracin, but I think it's an outstanding drug against Gram-positive bacteria." In fact, its limited use has kept the drug's susceptibility profile relatively unchanged, making it an effective option, especially when treating Gram-positive pathogens such as *Staphylococcus* and *Streptococcus*. Dr. Osher has been using Bacitracin for 35 years and backs this statement up. Drawing on his own experience, he notes that "It has an excellent resistance profile and is highly effective against Gram-positive pathogens, particularly the most common ones (e.g., *Staphylococcus aureus* primarily, but also *Streptococcus* and methicillin-resistance *S. aureus*)."

He also believes that it's a great drug and is very safe. Thanks to Bacitracin's unsurpassed safety profile, allergenicity and side reactions are practically non-existent.[1]

Bacitracin's Key Role in Cataract Surgery

Bacitracin is typically used preoperatively to prevent bacterial infections of the eye and/or surgical site by either killing susceptible bacteria or inhibiting their growth. Following is a look at how this medication fits into Dr. Osher's complete cataract surgery routine, starting with his preoperative regimen.

"[Bacitracin] has an excellent resistance profile and is highly effective against Gram-positive pathogens."

Preoperative. "When I first evaluate patients," Dr. Osher begins, "I pay careful attention to the lids, lashes and lacrimal apparatus." In his experience, he has found that virtually 90% of patients have some evidence of blepharitis (e.g., secretions on the lashes or vascularized lids/lashes with meibomian secretions). So, the first thing he does preoperatively is explain to the patient at the initial evaluation that the lids and lashes are in the neighborhood next to the eye and that everyone has their own secretions that they can't see in the mirror but that he can see under a microscope. "And we have to control the normal bacteria to avoid any chance of infecting the eye during surgery," he continues. "I initiate a hygienic cleansing regimen in which the patient mechanically debrides and cleanses his lashes and lid margins with baby shampoo (and rinse well) every day while in the shower."

Fast-forward to the day before surgery, when Dr. Osher gives the patient a fourth-generation fluoroquinolone in the

eye for prophylaxis. The evening before surgery, he has each patient apply Bacitracin ointment to the lashes and lid margins. "I've been using this approach since 1978," he says. "I believed, even then, that by coating the lashes with Bacitracin, we would have an excellent chance of weakening—if not killing—the bacteria present on every operating field." Simply put, "the lid hygiene reduces the bacteria present, which are then pulverized by the Bacitracin," Dr. Osher reasons.

The day of surgery, he pulses the fluoroquinolone and transitions the patient to the operating room for a careful povidone-iodine prep, followed by meticulous coverage and isolation of the lids and lashes with eye drapes that he originally designed in the early 1980s for this purpose. Then he takes it one step further. "We place a drain in the lacrimal lake between the upper and lower lid and the medial canthus where fluid pools," he explains, noting that he never allows fluid to come back over the eye. Instead, any fluid is wicked out of the sterile field and into the drainage bag. Then, Dr. Osher takes it yet another step further. Using Steri-Strips (3M), he covers any lids and lashes that are exposed at the lateral canthal angle so that neither skin tissue nor lashes are ever touched by any instrument, injector, etc.

What about his intraoperative approach? It's equally obsessive-compulsive, he admits.

Intraoperative. "The surgery itself is every bit as important as the prophylaxis and preparation," says Dr. Osher, emphasizing that you have to have meticulous incision construction. He still believes in a three-plane, near clear, 2.2-mm flared incision using knives and blades that he designed. The last steps Dr. Osher performs include exchanging the fluid in the anterior chamber with sterile fluid using an irrigating and aspirating tip. This way, "whatever is left in the eye is sterile," he explains. "I always carefully confirm the watertightness of the incision." Additionally, he leaves the eye with a normal intraocular pressure so there is no gradient to allow fluid into the eye.

Postoperative. Immediately following the procedure, Dr. Osher instills the fluoroquinolone in the patient's eye and has him continue the antibiotic for five more days. Bacitracin is just one of the components that comprise the whole system that he uses. "I believe that this disciplined approach works," he says. "And when you have a winning team, you don't change the lineup."

The Best Laid Plans ...

All surgeons want to perform a perfect operation, but even if all goes well, there's still a small chance of a postop complication occurring. The primary source of intraocular infection is often caused by bacteria from the patient's own ocular surface. Thus, meticulous preparation of the patient for surgery—including prophylactic measures such as lid hygiene and the use of drugs like Bacitracin—is one of the most important factors in reducing the risk of endophthalmitis. Take it from a cataract surgeon whose 35 years of "amazing luck" speaks for itself. ■

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4. http:www.fingertipformulary.com/drugs/Bacitracinopthalmicointment/

Dr. Osher is Professor of Ophthalmology at the College of Medicine of the University of Cincinnati and is Medical Director Emeritus of the Cincinnati Eye Institute. He has received the Lifetime Achievement Award and the Kelman Award from the AAO, as well as the Binkhorst Award and the Innovators Award from the ASCRS. He has no financial relationship with Fera Pharmaceuticals.

"The morbidity of endophthalmitis is enough to make you never want to see it ever again."

One Encounter Too Many

Endophthalmitis is a rare but serious postoperative complication of cataract surgery and can have devastating effects on a patient's vision. In 35 years of performing cataract surgery with his current system, Dr. Osher has only had one case of endophthalmitis.

The patient, who had ocular cicatricial pemphigoid, had cataract surgery performed in Boston, and lost his first eye. In 1990, after six months of immunosuppression at Harvard, he was referred to Dr. Osher for surgery in the second eye. He says the surgery was unique "because I did a clear corneal incision to avoid touching the conjunctiva, which can be lethal in cicatricial pemphigoid." He recalls that the patient's vision was 20/40 the first day after surgery and 20/20 at the one-week visit. In the second week, the patient arrived in Cincinnati with an endophthalmitis due to *Streptococcus viridans*.

This one case made a lasting impression on the surgeon. "The morbidity of endophthalmitis is enough to make you never want to see it ever again," he says with emotion.

Cataract Surgery: The Oculoplastic Factor

Christopher Kent, Senior Editor

Many conditions affecting the eyelid and orbit can increase the risks associated with cataract surgery. Here's help managing them.

When examining a potential cataract patient, most cataract surgeons focus on the condition of the lens, cornea and retina—and rightly so. But other factors, such as the condition of the lids and tear ducts, can also affect the outcome of cataract surgery.

With that in mind, four surgeons with extensive oculoplastic experience share their thoughts on which oculoplastic issues are most likely to impact cataract surgery, and what a surgeon should do when they arise.

Upper Eyelid Concerns

Generally, ptosis doesn't increase the risk of cataract surgery; in fact, there is some argument for waiting until after the cataract surgery to deal with it. However, in severe cases it may need to be repaired first.

Jonathan Dutton, MD, PhD, FACS, professor and vice chair of ophthalmology at the University of North Carolina at Chapel Hill, notes that if ptosis is mild and primarily a cosmetic issue, most cataract surgeons won't choose to do anything about it. "However, many patients who are going to have cataract surgery are sent to me to bring the lid up because it's so low that it's blocking their vision," he says. "Doing cataract surgery will have limited benefit if your lid is still in the way of your vision afterwards. So if the patient has significant ptosis, it probably ought to be fixed before the cataract surgery."

Julie Ann Woodward, MD, associate professor of ophthalmology and dermatology and chief of the Oculoplastic and Reconstructive Surgery Service at Duke University School of Medicine in Durham, N.C., notes another issue of concern. "A patient may have dermatochalasis, where the redundant upper eyelid skin is heavy and lying on top of the eyelashes," she says. "This can create conditions favorable for blepharitis because there's a warm, sticky environment that's conducive to bacterial growth underneath the flap of skin.

"In that situation, the cataract surgeon should refer the patient for a blepharoplasty to have the hooded tissue removed," she says. "This often improves the blepharitis so that the chance of infection after cataract surgery is decreased."

One factor that needs to be considered before correcting ptosis is the patient's dry-eye status. "If a surgeon refers a patient to us for ptosis repair and the patient has very dry eye, sometimes we'll recommend either no ptosis surgery at all or a very conservative ptosis repair," says Dr. Woodward.

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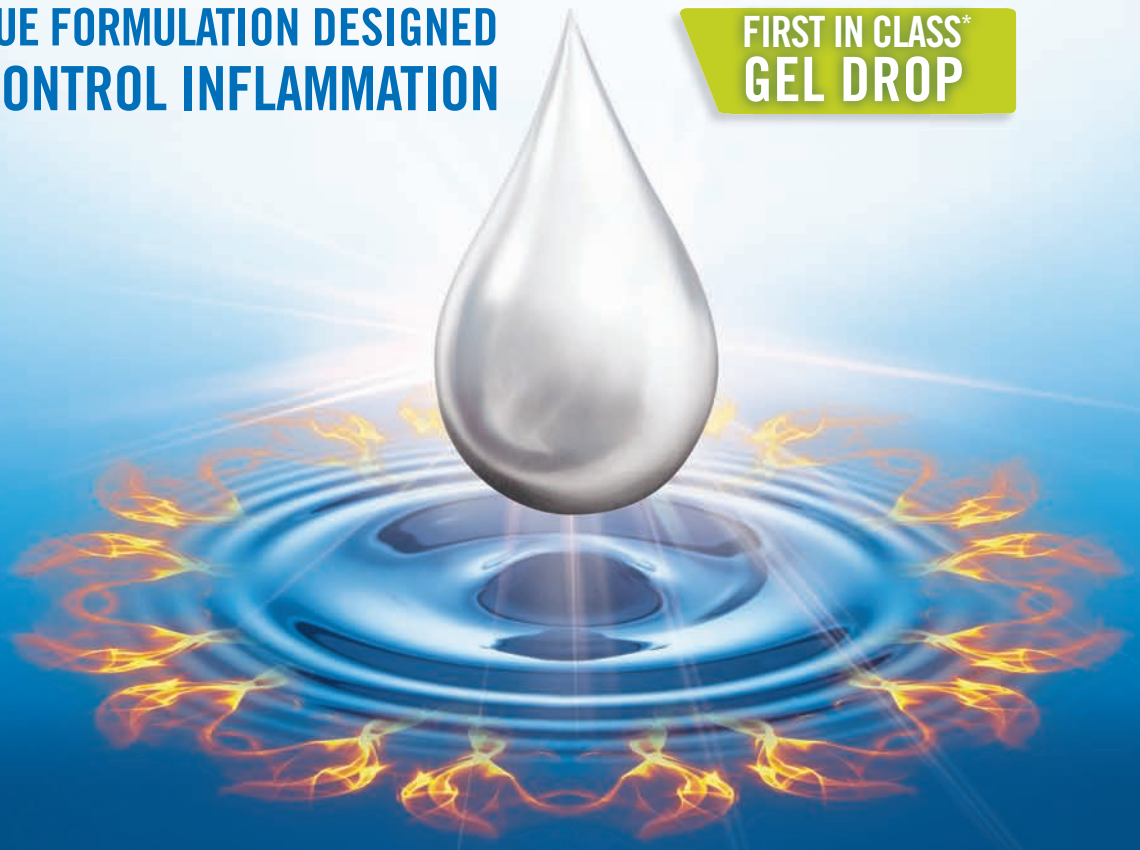

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- LOTEMAX® GEL is a corticosteroid indicated for the treatment of post-operative inflammation and pain following ocular surgery

Important Risk Information about LOTEMAX® GEL

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

Please see brief summary of full prescribing information on adjacent page.

*Ophthalmic corticosteroid.

References: **1.** LOTEMAX GEL Prescribing Information, September 2012. **2.** Fong R, Leitritz M, Siou-Mermet R, Erb T. Loteprednol etabonate gel 0.5% for postoperative pain and inflammation after cataract surgery: results of a multicenter trial. *Clin Ophthalmol.* 2012;6:1113-1124. **3.** Data on file, Bausch & Lomb Incorporated.

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

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

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Intraocular Pressure (IOP) Increase

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

Cataracts

Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing

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

Bacterial Infections

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

Viral Infections

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

Fungal Infections

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

Contact Lens Wear

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

ADVERSE REACTIONS

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Teratogenic Effects: Pregnancy Category C.

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

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

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

Nursing Mothers

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

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment Of Fertility

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

PATIENT COUNSELING INFORMATION

Administration

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

Risk of Contamination

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

Contact Lens Wear

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

Risk of Secondary Infection

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

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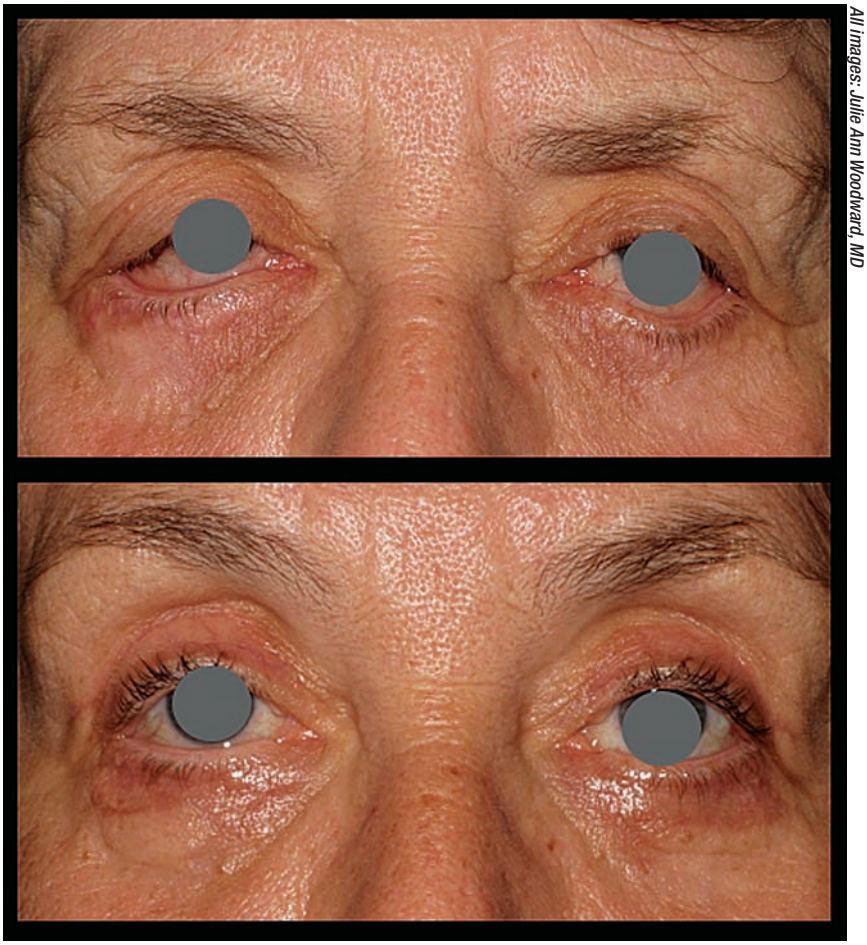
"We'll explain to the patient that we can only lift the eyelid 1 or 1.5 mm to avoid worsening the dry eye. The more we correct the ptosis in this situation, the worse the patient's dry eye will become."

Dr. Dutton concurs. "The more you open the palpebral fissure by correcting the ptosis, the more dryness the patient will have," he says. "That's why some oculoplastic surgeons do a Schirmer's test on every patient over 40 or 50. It's not a great test, but it gives you some idea of tear function. In any case, if I see a patient with any kind of dry-eye issue and I'm planning ptosis surgery, I'm very conservative. I'll lift the lid up just enough to clear the pupil so the patient can see. You don't want to make these patients bright-eyed and bushy-tailed the way you might a younger patient, because you could be throwing the patient into a much more symptomatic dry-eye situation."



All images: Julie Ann Woodward, MD

Surgery to correct ptosis and ectropion (above: before and after corrective surgery) can result in a change of K-reading and refraction. Nevertheless, surgery to repair ptosis is often postponed until after cataract surgery because the cataract surgery may cause an increase in the ptosis in some patients.

Making the Droop Worse

"One thing I see all the time—and this is fairly well-documented—is upper lid ptosis a month or two, sometimes a year after the cataract surgery," notes Dr. Dutton. "In the literature there have been debates about whether the cataract surgery is responsible for the ptosis; the consensus is that it probably is. During cataract surgery you put a speculum in and rotate the eye down to get at the superior limbus. There are adhesions between the superior rectus and the levator muscle in the orbit; when you pull one of them in one direction and the other in the other direction, you can theoretically damage those adhesions, causing ptosis. Because of the nature of cataract surgery, there's not a lot we can do to prevent it."

"There are many theories as to why this may happen," adds Guy G. Massry, MD, who practices at Beverly Hills Ophthalmic Plastic Surgery in Beverly Hills, Calif. "Some believe the mechanical stretching of the lid during surgery may cause a little droop afterwards. Years ago, when cataract surgeons gave a lot of numbing injections around the eye, they thought a toxic reaction to the medication might be causing the muscle to malfunction a little bit. It could simply be that the patient's improved vision allows her to observe a subtle droop she didn't notice before.

"In any case, if a patient comes in for cataract surgery with a few millimeters of ptosis, I wouldn't repair it until after the cataract is done," he says. "If you fix it to make the lids equal, the patient could develop a little droop again after the cataract surgery, requiring a second ptosis surgery."

Dr. Woodward agrees. "Cataract surgery has about a 1-percent chance of worsening eyelid ptosis," she says. "If patients need ptosis surgery, we usually recommend that they get their cataract surgery first. Of course, in some cases the ptosis is so severe that the surgeon finds it difficult to make certain measurements. In those cases we may go ahead and do the ptosis surgery first."

Lower Lids and Exposure

"Another issue to think about is lower lid ectropion, where the lower

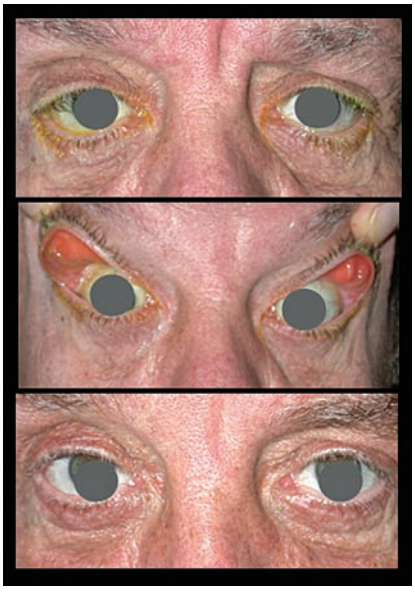
eyelid is very lax and the patient has sclera showing between the cornea and lower lid margin," says Dr. Woodward. "Patients with this issue can be more prone to exposure-related dry eye and infections. If there's a lot of sclera showing inferiorly, the cataract surgeon may suggest having the lower lid tightened so it better approximates the lower edge of the cornea prior to surgery. Normally, the lower eyelid should touch the inferior edge of the cornea or limbus and the upper eyelid should cover about 2 mm of the superior cornea.

"Ectropion is very common," she adds, "especially in cases of sleep apnea. Patients with sleep apnea tend to have floppy eyelids along with their floppy palette. They are also more likely to be eye-rubbers and have a lot of mucus in the eyes; the eyelids can flip inside-out on the pillow. Such patients should be referred to oculoplastic surgeons for lid tightening prior to any cataract surgery."

"If you're doing cataract surgery on a patient who has any difficulty closing his eyes, or has exposure symptoms, that should probably be addressed before the cataract surgery," agrees Dr. Massry. "Unlike ptosis, ectropion and entropion predispose the patient to irritation and infections after surgery. Furthermore, the individual may be asymptomatic and complication-free before surgery but start to have problems with dry eye or scratchiness afterwards. You never know how surgery will change the balance in the eye. So it's worth addressing this beforehand, in part because any exposure may increase the risk associated with cataract surgery, but also because you don't want the patient to blame related post-op problems on the cataract surgery."

Too Many Tears

"Anyone with excessive tearing should probably have that addressed before cataract surgery," says Dr. Massry. "When tears well up and sit on the eye, it's like water in a bathtub; after a while the tears can become murky and infected. If you're doing cataract surgery, that's the last thing you want."



Floppy eyelids can make patients more prone to dry eye and infections. If a patient has difficulty closing his eyes or has exposure symptoms, this should probably be addressed prior to performing cataract surgery.

John S. Jarstad, MD, medical director of Evergreen Eye Centers in Federal Way, Wash., and an adjunct professor at Pacific Northwest University College of Osteopathic Medicine, in Yakima, Wash., agrees that addressing issues such as a blocked tear duct with excessive eye watering prior to cataract surgery is crucial. (Dr. Jarstad does numerous cataract surgeries every week, but has also done thousands of oculoplastic procedures over the course of his career and continues to do them whenever circumstances permit.) "A blocked tear duct is a setup for infection," he notes. "In those cases, we'd like to see a dacryocystorhinostomy performed or tubes placed into the tear ducts to allow adequate drainage."

"Patients' eyes can tear for a number of different reasons," notes Dr. Woodward. "First, the eye can water because it's inherently dry. The dryness could be the result of not making proper mucus or oils for the hydrophobic layers that lie above and below the aqueous layer in the tear film; the eye tries to protect itself by reflexively producing extra aqueous fluid from the lacrimal gland.

"A second reason eyes can water is malposition of the punctum, which can happen with an ectropion," she continues. "An ectropion can be repaired using a number of different approaches. If the problem is just lid laxity, a tarsal strip can be performed; if the punctum itself is everted, we may perform a medial spindle operation. Sometimes a skin graft is needed to reposition the puncta.

"The third reason an eye can water is blockage in the nasolacrimal duct," she says. "If fluid doesn't flow freely through the nose, bacteria may sit in a stagnant area and then flow retrograde back out onto the eye, potentially contaminating the cataract wound. For that reason, if the patient has an eye-watering issue, he needs to be evaluated to make sure there's no nasolacrimal duct obstruction, especially if there's any evidence that the patient may have had dacryocystitis in the past. If there is a problem, we might resolve it either by inserting a Crawford tube or by performing a dacryocystorhinostomy."

In terms of deciding when tearing is sufficient to warrant intervention, Dr. Jarstad says the medical history is a big part of the answer. "Also, I ask the patient, 'Do you have tears running down your cheek?' If they say yes, I'm concerned," he says. "I also examine the tear film, staining the eye with vital dyes like rose bengal or lissamine green, and do fluorescein testing."

Additional Concerns

Cataract surgeons may encounter

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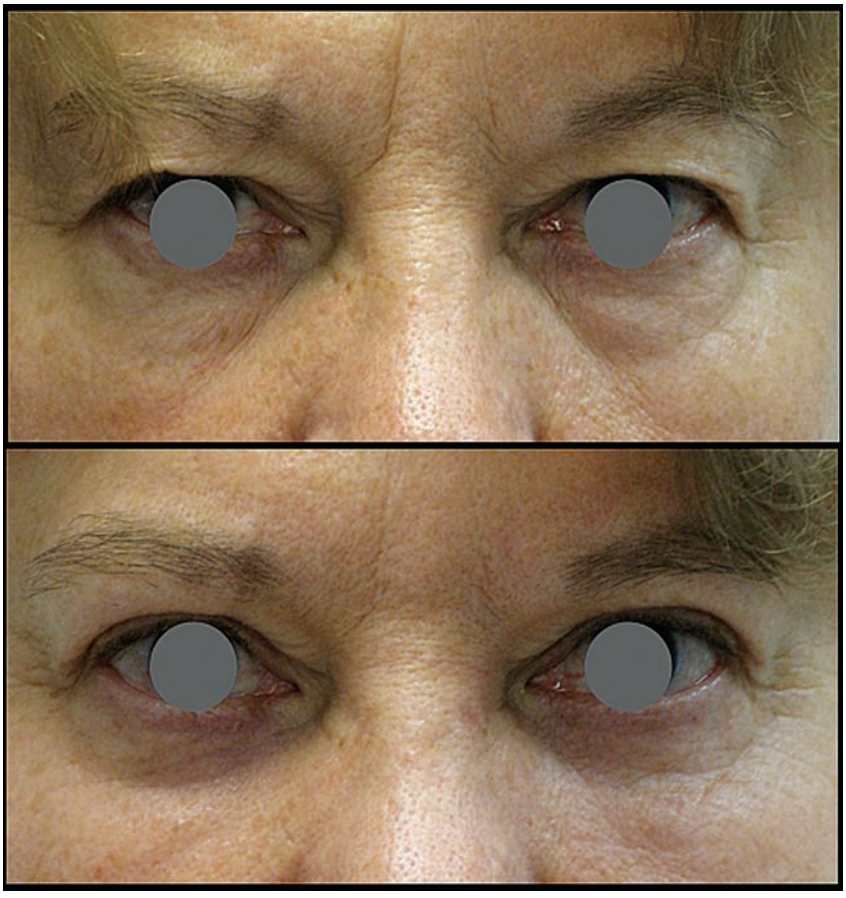
*United States Census Bureau, *"2010 Census Briefs – Age and Sex Composition: 2010, Table 2"* (2011).



An example of dermatochalasis, where the redundant upper eyelid skin is heavy and lying on top of the eyelashes (before and after correction). This can create conditions favorable for blepharitis because there's a warm, sticky environment conducive to bacterial growth underneath the flap of skin. A blepharoplasty to correct this before cataract surgery may decrease the risk of postop infection.

other issues as well:

• ***Tumors.*** "I see a lot of malignancies involving the eyelids," says Dr. Dutton. "They've often been misdiagnosed as inflammation or blepharitis. Blepharitis doesn't occur in one location, on one lid, but general practitioners sometimes make that mistake. Would an incorrectly diagnosed malignant tumor affect cataract surgery? The cataract surgeon is putting in a speculum and rubbing all over the lids; I don't know whether that could dislodge tumor cells.

"I think any ophthalmologist who sees a lesion on the lid should question the patient," he continues. "How long has it been there? Does it bleed? Especially if it's elevated, if it's ulcerated, if there's loss of lashes … those are all tip-offs that you may be dealing with a malignancy. Refer the patient to somebody who can make that diagnosis, if you can't do it yourself."

Dr. Massry agrees. "If a cataract surgeon notices any abnormal growth, whether it's on the eyelid or the eye itself, it should be addressed before the cataract surgery," he says. "Potentially it's a malignancy, and a malignancy, in some circumstances, can be associated with tremendous morbidity. It can affect vision and it can potentially spread. Cataract surgery is an elective procedure; whether or not you do it right now may affect your vision and lifestyle a little bit, but it's not a matter of vision loss or risking death. A tumor might be."

• ***Trichiasis.*** "If the eye is irritated because of the lashes coming back against the eye, the patient is going to have excess tearing," notes Dr. Dutton. "I see a lot of these patients and their corneas are abraded, which is going to affect their visual acuity. If you take out the cataract but the cornea is in that condition, the patient isn't going to be thrilled with the resulting vision. I think it makes sense to deal with this before proceeding with cataract surgery.

"One way to deal with this is to simply pluck out the offending lashes," he notes. "Sometimes the lashes will grow back in the correct position, but in most cases they'll grow back in the incorrect position, so this won't be sufficient. We prefer to use a radiofrequency tool to remove the lashes permanently. I'd do this before the cataract surgery."

When Should You Refer?

Dr. Woodward notes that whether or not a cataract surgeon refers patients to a specialist for correction of oculoplastic concerns really depends on the comfort level of the surgeon. "Years ago, doctors were jacks-of-all-trades," she says. "Many cataract surgeons felt comfortable taking care of ptosis and ectropion themselves. Today, ophthalmologists have become very subspecialized, and they're more apt to refer patients to an oculoplastic specialist.

"However, this may depend partly on your location," she adds. "In some cities, surgeons tend to stay subspecialized; in other cities, surgeons are more comfortable doing oculoplastic procedures themselves. Here at Duke University we have so many subspecialized ophthalmologists available that there's no reason for surgeons to try to do these all of these oculoplastic procedures themselves."

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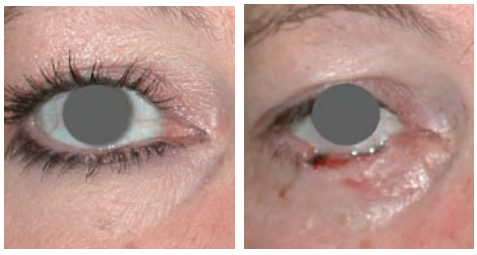
Dr. Massry agrees. "If you're talking about an eyelid problem like an entropion, ectropion or ptosis, it's all about the comfort zone and expertise of the physician," he says. "Many ophthalmologists have been around for a while and are comfortable doing basic eyelid work. However, if you're a surgeon who just does high-volume cataract all day, it may not make sense for you to do the eyelid surgery; your risk of having a complication is going to be greater than it would be for someone who does oculoplastic work all day. And plenty of specialists are available; 550 oculoplastic surgeons in this country are certified by the American Society of Ophthalmic Plastic and Reconstructive Surgery. It's really up to the surgeon to decide.

"On the other hand," he continues, "if the patient has tear duct blockage or a tumor, the surgery is a little more advanced and should probably be referred to a specialist. Ectropion, entropion and ptosis are bread-and-butter eyelid surgeries that many general ophthalmologists have been trained to do, and if the surgery doesn't work out it can probably be corrected. That's not the case with tumors or tear duct blockages, which most general ophthalmologists don't treat routinely. In those cases, I would err on the side of being cautious and refer to an oculoplastic colleague."



A cataract surgeon is in a unique position to uncover subtle but serious problems—if the focus is on the entire eye, not just the cataract. Left: This patient's makeup made it difficult to notice a basal cell carcinoma along the lower eyelid. Right: The same eye after Mohs surgery, prior to reconstruction. Noticing subtle abnormalities such as this can prolong a cataract patient's life.

Strategies for Success

When examining a potential cataract patient, these suggestions can help avoid increased surgical risk:

• ***Don't overlook the eyelids.*** "I think it's important to pay attention to the ocular adnexa and look at the lid position," says Dr. Jarstad. "It's easy to overlook these. We're usually very focused on looking at the eyeball, checking the cornea for corneal dystrophy, checking to make sure there's no zonular weakness or pseudoexfoliation before we start, and checking the retina to make sure there won't be any surprises due to macular degeneration or some other retinal disease. But we sometimes overlook the eyelids. In particular, significant laxity or a blockage in the nasolacrimal system really should be addressed before cataract surgery. Managing these concerns will give the patient a better outcome and lower the risk of infection or a prolonged recovery."

Dr. Woodward agrees. "Of course, if a condition is severe, most cataract surgeons will notice it and address it, but sometimes they overlook it if it's mild," she says. "As a result, patients don't get treated for dermatochalasis, ectropion or ptosis, even when the patient might benefit and the cataract surgery would be safer."

"Cataract surgeons can get so busy looking at the cataract that they forget the lids, conjunctiva, tear ducts and so forth," says Dr. Dutton. "For example, I'd say that 40 to 50 percent of the patients I see who have skin cancer aren't even aware of it. Somebody has to point it out to them; they just thought the lesion was a little sore or something and paid no attention to it. The cataract surgeon is in a position to find those things at the initial examination.

"To be fair," he adds, "I have to admit that many oculoplastic surgeons pay little attention to cataracts or the retina, so this is not a problem unique to cataract surgeons."

• ***Don't assume oculoplastic issues can be addressed after the cataract surgery.*** "I think there's a tendency to assume you can take care of these issues after cataract surgery, because that's how many plastics problems are addressed," says Dr. Jarstad. "Some issues like ptosis can be affected by the cataract surgery, so it makes sense to address those later. But other issues really need to be addressed before the cataract surgery to avoid putting the patient at risk."

• ***Alert a patient of existing ptosis.*** "If a patient of yours is going to have cataract surgery and already has a droopy lid, you need to point this out beforehand so the patient doesn't blame it on your surgery," says Dr. Massry.

• ***If the upper eyelashes point straight down, ask the spouse whether the patient snores.*** "Upper eyelid lash ptosis is one of the signs of floppy eyelid syndrome," Dr. Woodward explains. "Floppy eyelid syndrome is on the spectrum of floppy palate, and these individuals frequently have sleep apnea. So if you observe that the lashes point straight down, it's important to ask the patient and even the spouse whether the patient snores. The spouse will often say, 'Yes, like a freight train,' or, 'Yes, he has a CPAP machine.' Sometimes the patient is already being treated for sleep apnea, but sometimes patients haven't been treated before. In that case it's really important for us to refer them for sleep studies, because treating sleep apnea can potentially prolong the patient's life."

• ***If appropriate, try the snapback test.*** "Occasionally you'll encounter a patient with involutional ectropion, where the eyelids are very lax and don't approximate the globe well," notes Dr. Jarstad. "Those patients are

If only you could predict how ocular inflammation will behave.

DUREZOL® Emulsion now has head-to-head data vs prednisolone acetate in patients with endogenous anterior uveitis.[1]

Scan the QR code with your smartphone or log on to **www.inflammationhappens.com** to see the results for yourself.

INDICATIONS AND USAGE: DUREZOL® Emulsion is a topical corticosteroid that is indicated for the treatment of endogenous anterior uveitis.

Dosage and Administration

For the treatment of endogenous anterior uveitis, instill one drop into the conjunctival sac of the affected eye 4 times daily for 14 days followed by tapering as clinically indicated.

IMPORTANT SAFETY INFORMATION

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

Warnings and Precautions

- Intraocular pressure (IOP) increase – Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, defects in visual acuity and fields of vision. If this product is used for 10 days or longer, IOP should be monitored.
- Cataracts – Use of corticosteroids may result in posterior subcapsular cataract formation.
- Delayed healing – The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.
- Bacterial infections – Prolonged use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, steroids may mask infection or enhance existing infection. If signs and symptoms fail to improve after 2 days, the patient should be re-evaluated.
- Viral infections – Employment of a corticosteroid medication in the treatment of patients with a history of herpes simplex requires great caution. Use of ocular steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex).
- Fungal infections – Fungal infections of the cornea are particularly prone to develop coincidentally with long-term local steroid application. Fungus invasion must be considered in any persistent corneal ulceration where a steroid has been used or is in use.
- Contact lens wear – DUREZOL® Emulsion should not be instilled while wearing contact lenses.

Adverse Reactions

In the endogenous anterior uveitis studies, the most common adverse reactions occurring in 5-10% of subjects included blurred vision, eye irritation, eye pain, headache, increased IOP, iritis, limbal and conjunctival hyperemia, punctate keratitis, and uveitis.

For additional information about DUREZOL® Emulsion please refer to the brief summary of prescribing information on adjacent page.

Reference: 1. DUREZOL® Emulsion Package Insert.

Alcon®

DUREZOL®
(difluprednate ophthalmic emulsion) 0.05%

DUREZOL®
(difluprednate ophthalmic emulsion) 0.05%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

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

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

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

CONTRAINDICATIONS
The use of DUREZOL® Emulsion, as with other ophthalmic corticosteroids, is contraindicated in most active viral diseases of the cornea and conjunctiva including epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, and varicella, and also in mycobacterial infection of the eye and fungal disease of ocular structures.

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

Cataracts
Use of corticosteroids may result in posterior subcapsular cataract formation.

Delayed Healing
The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order beyond 28 days should be made by a physician only after examination of the patient with the aid of magnification such as slit lamp biomicroscopy and, where appropriate, fluorescein staining.

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

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

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

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

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

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

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

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

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

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

Pediatric Use
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.

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

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

PATIENT COUNSELING INFORMATION
Risk of Contamination
This product is sterile when packaged. Patients should be advised not to allow the dropper tip to touch any surface, as this may contaminate the emulsion. Use of the same bottle for both eyes is not recommended with topical eye drops that are used in association with surgery.

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

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

Revised: June 2012
U.S. Patent 6,114,319

Manufactured For
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Manufactured By:
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at risk for exposure and infection after surgery. In that situation I was taught to do the snap-back test, where you pinch the lower eyelid and pull it away from the globe and let it spring back. If it takes more than a second or two to spring back and approximate the eyeball, the patient may require some eyelid tightening with a tarsal strip procedure or a wedge resection before surgery."

• ***If the patient is tearing excessively, determine the cause.*** "If the cause is mechanical, such as lid laxity or punctal stenosis, that shouldn't affect the cataract surgery," notes Dr. Dutton. "But if the tearing is due to blepharitis or a possible nasolacrimal duct infection, I'd get that fixed before cataract surgery. And if the patient is tearing but the cause isn't obvious, you might want to refer the patient just to make sure that the lacrimal drain system is OK."

• ***If something doesn't seem quite right, don't let it drop.*** Dr. Massry notes that sometimes a problem isn't obvious, so it behooves the cataract surgeon to be alert for something that just doesn't seem right. When that's the case, he advises considering a referral.

"For example," he says, "a general ophthalmologist referred a patient to me who had droopy, puffy lids. The patient said that the puffiness had been progressive, and was noticeably worse in one eye. When I examined him, I realized that a lot of the heaviness on the upper lid in the worse eye was not standard droopiness; the globe was a little more prominent and slightly inferiorly displaced. It was very subtle, but I ordered a CAT scan; it revealed a tumor in the orbit.

"There are several lessons worth noting here," he continues. "First, if something doesn't seem right, don't let it drop. And if it potentially involves an area you don't work with on a daily basis, refer to someone who manages those issues every day. When you work in a particular specialty for years, you learn to notice and identify subtle problems that would escape the notice of anyone else.

"Also, always take the patient at his word," he adds. "If he has a complaint but you don't find anything, assume he's right; something is going on. Usually if you spend the time and search carefully, you'll find the problem. If not, refer the patient. Don't let it drop just because you can't find the problem yourself."

• ***If a patient refuses corrective surgery, inform the patient of the consequences and then reconsider.*** Dr. Massry notes that occasionally a patient won't want to undergo the oculoplastic surgery. "Whether a corrective surgery is necessary for a given patient is always a judgment call on the part of the cataract surgeon," he says. "If the surgeon feels that the problem is minor or inconsequential, or the patient's a lot older and wouldn't agree to go through the extra procedure anyway, then the surgeon has to decide whether or not it's safe to do the cataract surgery given the patient's condition. It's really all about the judgment of the treating physician.

"For example, suppose a patient has had a little bit of ectropion for 20 years and doesn't want to have surgery to fix it because he's been doing fine," he continues. "It's possible that after you do the cataract surgery it will get worse and he won't be 'just fine' any more. So you have to let the patient know that it could get worse.

"In this situation, all you can do is inform patients in an ethical manner," he adds. "You can't tell them what to do; they have to make their own decision. If they won't agree to the extra surgery, then you have to decide whether you're willing to proceed."

Dr. Jarstad has encountered this as well. "I've had some patients who felt they could not endure a dacryocystorhinostomy, but they still want the cataract surgery done," he says. "That puts us in a little bit of a bind because we have to make sure that they're not at risk of infection. In this situation we treat them with antibiotic eye drops for a couple of weeks before surgery and then go ahead. In our experience that has worked, but it's definitely more risky. We've had to do this several times in the past 27 years, and so far we have not seen infections or other issues."

• ***Don't be afraid to refer.*** "The majority of patients we see are great candidates for cataract surgery," notes Dr. Jarstad. "But nowadays almost everyone has the option of referring a patient to an oculoplastic specialist or someone with experience in oculoplastics. If you don't feel you can deal with a problem, I wouldn't hesitate to refer the patient."

How Much Risk is Acceptable?

Undoubtedly, many cataract patients who might have benefitted from having oculoplastic issues addressed before cataract surgery have not, either because the condition went unnoticed, or because the surgeon felt that addressing the problem wasn't necessary. In most cases, the patients probably didn't suffer any vision loss as a result.

Nevertheless, whether proceeding in a borderline situation is ideal is open to question. "If I were doing cataract surgery, I wouldn't want to take any risk whatsoever, no matter how small," says Dr. Dutton. "I'd get everything about the eye in good shape before doing the surgery. There's no reason to do cataract surgery if the patient is going to complain afterwards that he can't see or that his eye hurts all the time.

"Patients are always going to blame you if they have any problems after you've done surgery on them, whether the problem was there beforehand or not," he adds. "So, you might as well take care of those issues first." REVIEW

The Hidden Pitfalls of Postop Enhancements

Walter Bethke, Managing Editor

How to manage patient expectations, choose a refractive target and improve vision.

Despite the best biometry, there will be the occasional cataract procedure that results in a refraction that misses the mark. Though some monofocal intraocular lens patients can just wear spectacles for small errors, there will be patients with larger errors, or multifocal IOL patients whose refractions need to be extremely accurate, who will need some sort of postop intervention to get them where they need to be. Here, experts used to dealing with these patients explain why they aren't as straightforward as they appear, and share methods to get patients seeing well again.

Preoperative Considerations

Chicago surgeon Louis Probst says that there are aspects to correcting residual refractive error that the surgeon may not have considered. Here are several issues Dr. Probst says are worth thinking about:

• ***Who was the original surgeon?*** "The cases differ depending on who did the initial cataract surgery," Dr. Probst says. "If it's your patient, it's your responsibility to make him happy and follow through as you see fit. But if it's not your patient, be aware that there's a kind of false assumption out there that the patient already had his main procedure and that these are simple 'touch-up' cases to make his vision a little better. However, these situations can get very complex, and these enhancements are far more difficult than PRK or LASIK on a virgin eye, for a host of reasons. If you didn't do the original cataract surgery and this isn't your patient, by agreeing to enhance him you'll be suddenly adopting all the issues and concerns of the patient who had a less-than-ideal outcome, and he'll become your problem. In such a situation, ask yourself if it's something you want to get involved in."

• ***Complications and/or ocular pathology.*** One of the factors that can make these cases more complex is a complication from the cataract procedure. "Though IOL surgery is very effective, it does have a complication rate," says Dr. Probst. "If the patient had a complication during his cataract procedure, this could affect his final outcome from his postop enhancement. He may not have the potential to see 20/20, yet his expectation for the enhancement is that he will see very well, if not perfectly, so this sets the bar high. However, talking to him about this before surgery can be tricky because of the lofty image of laser vision correction and LASIK in society, which leads many to believe they will

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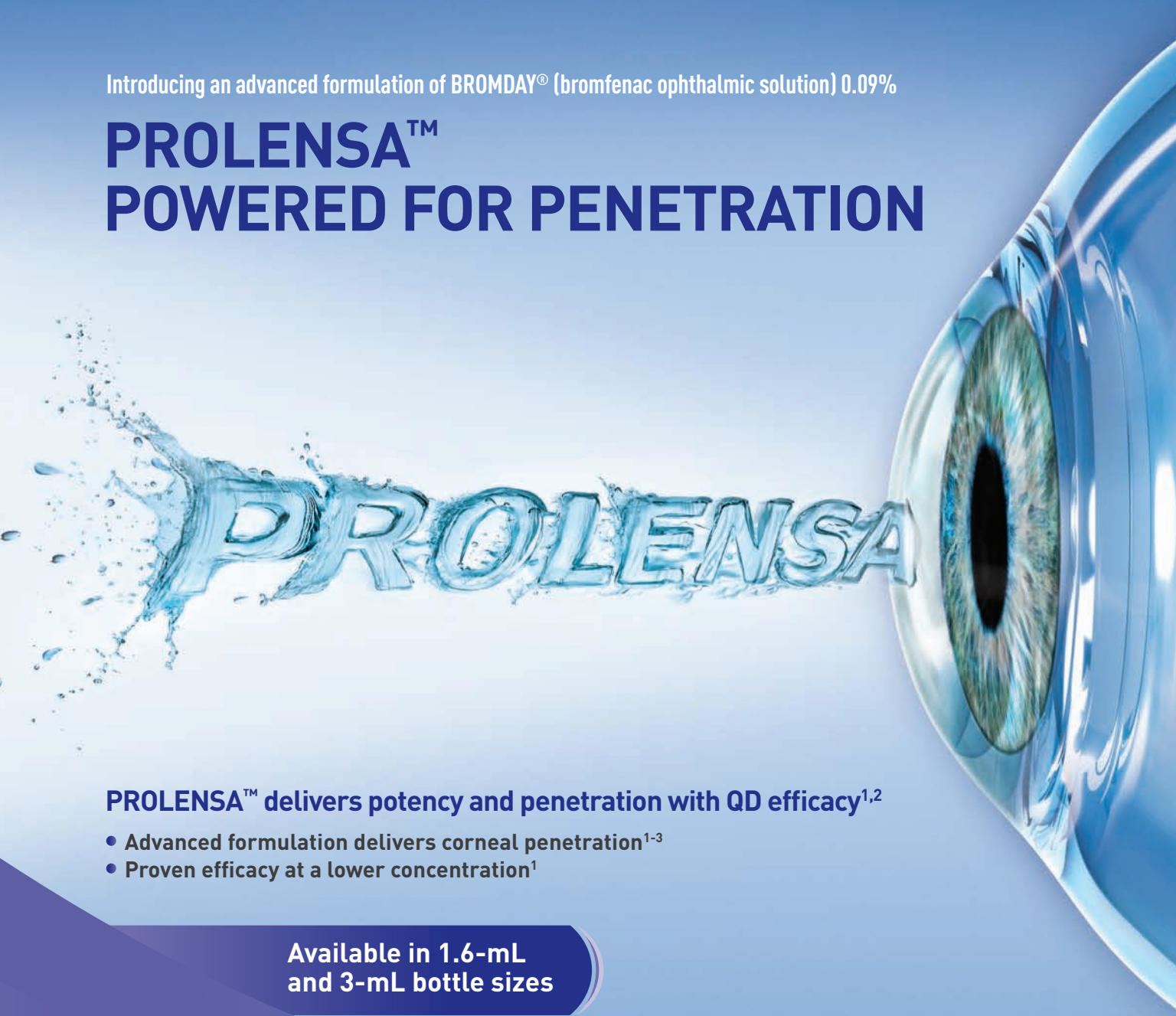

PROLENSA™ delivers potency and penetration with QD efficacy[1,2]

- Advanced formulation delivers corneal penetration[1-3]
- Proven efficacy at a lower concentration[1]

Available in 1.6-mL and 3-mL bottle sizes

IMPORTANT RISK INFORMATION ABOUT PROLENSA™

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

Dosage and Administration
Instill one drop into the affected eye once daily beginning 1 day prior to surgery, continued on the day of surgery, and through the first 14 days post surgery.

Please see brief summary of full Prescribing Information on adjacent page.

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

BAUSCH+LOMB

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

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

PROLENSA™
(bromfenac ophthalmic solution) 0.07%

PROLENSA™ (bromfenac ophthalmic solution) 0.07%

Brief Summary

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dosing

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

Use with Other Topical Ophthalmic Medications

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

CONTRAINDICATIONS

None

WARNINGS AND PRECAUTIONS

Sulfite Allergic Reactions

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

Slow or Delayed Healing

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

Potential for Cross-Sensitivity

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

Increased Bleeding Time

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

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

Keratitis and Corneal Reactions

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

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

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

Contact Lens Wear

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

ADVERSE REACTIONS

Clinical Trial Experience

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

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

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

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

Nursing Mothers

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

Pediatric Use

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

Geriatric Use

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis and Impairment of Fertility

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

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

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

PATIENT COUNSELING INFORMATION

Slowed or Delayed Healing

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

Sterility of Dropper Tip

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

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

Concomitant Use of Contact Lenses

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

Concomitant Topical Ocular Therapy

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

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see very well. You can try to counsel him otherwise, but he will still have the hope that he's going to see very well."

The same goes for situations where the patient has ocular pathology that prevents her from reaching 20/20. "For example," says Dr. Probst, "if someone's uncorrected vision is 20/40 after IOL surgery, but a retinal exam reveals that at least half of that decreased uncorrected vision is probably due to some macular pathology, and her final best-corrected vision might be 20/30, you don't want to do an LVC procedure to improve vision by just one line in the best case, while undergoing all the risks of another procedure."

• ***YAG laser.*** The possible effect of a YAG capsulotomy needs to be accounted for, say surgeons. "Once someone's had an IOL procedure, one of the reasons his vision is decreased might be because he has an opacified posterior capsule," says Dr. Probst. "If that's the case, it might be more appropriate to have the YAG performed first before doing any refractive procedure to determine whether that can improve the patient's vision."

Premium IOL Patients

Though surgeons say it's possible for monofocal IOL patients to be unhappy enough to warrant some sort of postop touch-up, in reality many already expect to wear glasses for some aspect of their vision postop. Instead, it is the premium IOL patient, who paid a good deal of money for his lenses and/or doesn't want to wear glasses, who often wants and needs to have even relatively small amounts of postop error corrected. Here are tips for managing these unique patients.

• ***Multifocal and accommodative lenses.*** "I think the multifocal IOL patient with an error is the best indication for laser refractive surgery postop," says Tucson, Ariz., surgeon William Fishkind. "A multifocal patient who comes out a little off, maybe 0.5 to 0.75 D hyperopic or 0.75 D myopic, and can't stand it, is a candidate. The lens won't work as intended and he's unhappy, and he's spent a lot of money to get that multifocality."

Of course, surgeons say that the irony is that even though the multifocal patient can be helped the most by sharpening his vision, he's also the most challenging because his vision is now multifocal.

"You'll see a higher frequency of patients needing refractive touch-ups from the multifocal group," says Nashville, Tenn., surgeon Ming Wang. "For instance, if you don't clean up a -1 D error in a multifocal patient, not only will he be nearsighted due to the error, but the myopia will prevent the lens from working as it's intended. Once you correct the refractive error, something new comes out of the lens that isn't present in a monofocal patient: the intrinsic multifocality."

So, surgeons agree that multifocal IOL patients with postop refractive error need correction, but this gives rise to another question: What refractive target do you aim for?

"A multifocal patient doesn't have a firm target," says Dr. Probst. "He has multifocal vision with distance and near targets, so picking an endpoint becomes a delicate matter. The patients themselves are also more challenging because they have more complex expectations than a single-vision patient. They're looking for distance and near vision, so you have the opportunity to fail at both. Multifocal patients require extensive discussion about what their expectations are for the enhancement: emphasis on reading or on distance?"

To help zero in on the endpoint, surgeons use the tools usually associated with preop refractive surgery: manifest refractions; anterior and posterior corneal topography and wavefront imaging. They say to discount wavefront a bit, however, since the multifocality of the lens may render it less than perfectly accurate.

Dr. Probst says the process involves a lot of discussion of the patient's activities and expectations. "Let's say we do a WaveScan on a patient with a multifocal lens and it reads a refraction of -1.5 D," he says. "Then, we do a mani-

Refractive Surgery in Virgin vs. Multifocal IOL Eyes

	35-year-old virgin eye	Older, post-multifocal eye
Postop target refraction	Plano	Varies. Some surgeons alter it based on the location of the lens's near point (e.g., ReSTOR: plano/plano; Tecnis MF: plano dominant eye/+0.5 D non-dominant). Some base it on a patient's activities.
PRK or LASIK?	LASIK for most eyes and PRK for thin and/or steep corneas	PRK avoids dry eye in this older, drier population, but may have delayed healing issues. LASIK heals fast but risks DLK, flap complications and worsening of dry eye.
Correct higher-order aberrations with custom?	Yes	No, HOAs are part of a multifocal lens's mechanism of action—use conventional LVC.
Surgical skill needed	General requirements for a LASIK surgeon	Higher level; must be able to deal with multifocal vision pre- and postop
Quality of vision	Good	Depends; the IOL creates multifocality at the cost of some contrast sensitivity
Residual refractive error	Some error is tolerated, especially low myopia	Multifocal IOL won't function adequately until refractive errors are managed.

fest refraction and find that the patient gets his best distance and near vision with -0.75 D. This makes it a little tricky determining what the target should be. It's through the trial lenses and having him look at distance and at near that you determine which correction is ideally suited to that patient's expectations. This could take multiple visits to sort through. What also bears some discussion with the patient is that the multifocal lens has already induced some loss in quality of vision, so the patient will be starting a step or two behind the virgin refractive surgery eye. If you don't explain this to him, he may attribute a loss of quality in his final vision to the enhancement rather than the original IOL surgery."

If possible, some surgeons like to do a contact lens trial. "If the patient will do it, a contact lens trial for a week or two allows him to try the corrected vision at distance and near in different situations, such as leisure, work and sports," explains Dr. Probst. "He can then identify the areas where it was good and not so good and you can adjust the target. One of the great things about this is he's participated in the decision, which he'll appreciate. Also, if the postop vision isn't 100 percent crystal clear, he'll also realize he shares some of the responsibility for it, which can be helpful at times."

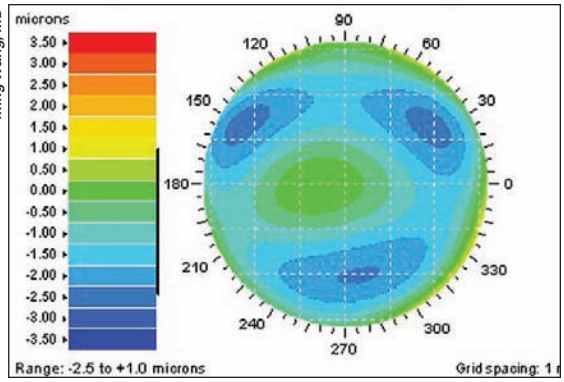
As an alternate approach, Dr. Wang says he's found that multifocal lenses and the Crystalens actually need slightly different refractive targets for postop laser enhancements. "For ReSTOR, we've found it's best to target plano in both the dominant and non-dominant eyes," he says. "This truly gives two focal points for each eye, one at distance and one at about 33 cm. For Tecnis, however, we've found that it's slightly different. The distance vision is the same as ReSTOR, but the near point is a little too close for most patients, sitting at about 25 cm, or 4 D. So for Tecnis I intentionally target a little plus in the non-dominant eye, making it around +0.5 D, the goal being to move this 25-cm focal length slightly out nearer to 33 cm.

"For Crystalens, it's different still," he adds. "When the Crystalens eventually settles into position, we've found it comes forward a little bit due to capsular contraction, so if you aim at plano you'll probably end up slightly minus. We've found the average accommodation in these patients is about +0.75 D, but for people to use a computer, which is sort of in the intermediate distance, they need maybe +1.25 D. So, in the dominant eye, I aim for +0.25 D, and in the non-dominant eye I'll aim for -0.5 D due to the 0.75 D average

amount of accommodation the lens gives."

• ***Toric IOLs.*** Errors after toric lens implantation are somewhat less involved than after multifocal procedures, but still involve some diagnostic work. Dr. Fishkind says a list of pertinent questions can help home in on the problem. "Did the lens rotate or not?" he says. "What's the effective lens position? Where is the final astigmatic refractive axis? How much is the astigmatic error? Can it be corrected with a limbal relaxing incision or a laser or does the lens need to be re-rotated back into position?"

When facing a toric lens enhancement, Dr. Probst first compares the preop and postop cylinder. "If there was a change in axis but there is still a significant amount of astigmatism, that suggests that perhaps the lens wasn't implanted in the correct axis or it rotated," he says. "Then, a lens rotation might be more appropriate. But, if it's a toric patient with little residual astigmatism who's now myopic, then LVC on the cornea would be appropriate."



An eye with a multifocal IOL will demonstrate many aberrations on wavefront analysis that are actually necessary for the lens to function properly, surgeons say.

Choosing a Procedure

Once you and the patient have determined that an enhancement is necessary, surgeons advise trying to wait at least 90 days before performing it, to allow any postop inflammation and residual astigmatism to resolve, and to ensure you know the exact amount of error you're dealing with. At that point, surgeons say the procedure you choose depends on which potential complications you'd rather avoid.

Some surgeons, like Dr. Wang, prefer PRK. "I typically do PRK because it avoids LASIK's issues with diffuse lamellar keratitis, dry eye and flap complications," he says. "It's an overall better procedure except in one category: delayed gratification. LASIK heals in days, PRK heals in weeks. However, the post-cataract patient is older than the typical refractive surgery patient, so their eyes are drier to begin with, and I don't want to induce more dry eye by doing LASIK."

Other surgeons, such as Dr. Probst, think LASIK is better. "If you have the choice, and are comfortable with LASIK, I believe it's the better option," he says. "This is not just because of the rapid healing, which the patient will appreciate, but also for another reason that's not often appreciated by surgeons: It's possible for PRK to not go too well in older patients. These older patients often have delayed re-epithelialization and may run into problems with healing post-PRK. Sometimes, non-healing epithelial defects occur in these older patients and take weeks to heal, which is aggravating for the patient and the doctor, and puts the patient at risk for infection. In the 2011 ASCRS survey on infections after refractive surgery, the infection rate after PRK was six times higher than that after femtosecond LASIK and 2.5 times higher than microkeratome LASIK,[1] and I speculate that it might be even higher in this older group because of delayed re-epithelialization. The assumption that PRK is automatically safer isn't necessarily valid."

Whichever procedure is chosen, surgeons say that, when faced with enhancing a multifocal IOL patient, it's probably best to avoid custom ablations and perform a conventional procedure instead.

"By their very design, multifocal IOLs are supposed to cause some higher-order aberrations," says Dr. Wang. "The lenses intentionally generate some spherical aberration to cause axial dispersion, or the existence of two images, one of which is focused closer to the retina and one away from the retina. Though, classically, ophthalmology has always tried to reduce spherical aberration and axial dispersion, they are the essence of the multifocality of the IOL. Also, these lenses are almost always slightly decentered a little bit which, because of their rings, will cause a little higher-order aberration, too. If we do a custom treatment in these cases, it will erase some of the multifocality of the lens by erasing some of the higher-order aberrations. Also, the cornea is regular in these patients, so we shouldn't make it irregular by putting reverse aberrations on it to compensate for minor ones generated by the lens."

Ultimately, Dr. Probst says that, no matter how you approach these cases, they will still be challenging. "I'm a 100-percent corneal refractive surgeon," he says. "But I really try not to do too many of these cases. Many surgeons have come to me with the idea that these cases are a great opportunity to do more LASIK but, in fact, this is a very complex area that's riddled with potential pitfalls. I'm not saying you shouldn't do these cases, particularly if they're your own patients and you feel that you could help them see better, but be warned that they can turn out to be far more complex than they first appear." REVIEW

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Meeting Expectations in Older Cataract Patients

Michelle Stephenson, Contributing Editor

It's less about age, and more about attitude.

The elderly population today is diverse. Some elderly patients are very mobile and are still driving and playing golf, while other elderly patients spend their time indoors reading or doing other sedentary activities.

"The older population is one that we can really serve and make the biggest difference," says Robert M. Kershner, MD, MS, FACS. "The majority of our cataract patients are in their sixth, seventh and eighth decades of life. Their level of satisfaction for our efforts is among the highest. Thirty years ago, we waited to do surgery until it was absolutely necessary and there was no other alternative. The generation of surgeons prior to mine waited until the cataract was ripe. Our criteria for surgical intervention have changed over the years, and today's threshold for surgery is more dependent upon the patient's lifestyle than an arbitrary line on an eye chart. The criteria for proceeding with surgery in a patient who doesn't drive and sits at home all day watching TV are obviously going to be considerably different from those of the 40-year-old who works late, travels and is having night vision problems." Dr. Kershner is a professor and chairman of the Department of Ophthalmic Medical Technology at Palm Beach State College, and a consultant specialist in cataract and refractive surgery in Palm Beach Gardens, Fla.

He sees today's 80-year-olds as yesterday's 60-year-olds. They are active, healthier and living longer than previous generations. As the baby boom generation moves into the retirement years, its expectations may be higher than today's elderly patients. "There are about 78 million of them," says Dr. Kershner. "This is the generation that has always wanted everything and needed it right now. They are demanding. They believe they know what's best, they know what they want and they usually get it. That's quite a contrast from the retirement generation of a decade ago. A few years ago, we were performing 2.2 to 2.4 million procedures annually. The latest numbers are 3.1 to 3.2 million. These numbers are not because people are developing cataracts at an accelerated rate. It is because our technologies and our outcomes have improved dramatically and the population that can benefit is expanding."

Understanding Your Patient

The first step in managing expectations in the older cataract patient is to get to know him as an individual. If the patient is retired, it is

important to find out what he did as an occupation before retirement.

While many elderly patients are still active, some are not. It is important to sit down with each individual patient and ask about his needs and lifestyle. "Surgeons have to make a concerted effort to explore what their patients' lives are like, what their day-to-day needs are, and what they want to accomplish by undergoing eye surgery," Dr. Kershner says. "Surgeons often don't take the time to do that. Older surgeons think they know this group (after all, we are all in the same boat), but they are wrong. Young surgeons don't take the time to look up from their EHR screens to see who they are talking to. So much of today's exam is delegated to ancillary personnel."

He notes that, while a proper preoperative interview may add only two or three minutes to the exam for each patient, the time required to convince an unhappy patient that she made the right decision can take days, weeks or months. Perhaps the most important question you can ask a patient is what her typical day is like.

"The whole concept of 'converting' people from standard to premium I think is a terrible disservice to ophthalmologists as well as to patients. We should really be looking for what is right for an individual patient according to what his or her goals actually are."
—Lisa B. Arbisser, MD

Premium Lenses?

Dr. Kershner says that he sees the same mistakes being made over and over again when he consults with practices. "Many patients end up getting premium lenses when their needs are not going to be met by those lenses," he says. "They are being talked into doing something just because they think they should or because the doctor sounds convincing. This is a formula for failure. If the patient's needs are not addressed or their concerns discussed, your patient will seek out another physician or an attorney. The valuable lesson here is to listen to every patient, ask the right questions and hear what each patient's needs are. As the professional in the equation, we need to inquire as to their day-to-day and light-to-dark visual needs. It may be difficult to take the extra time to do the preop interview properly, but it is time well spent, not just because it can land you in court if you don't take the time, but because unhappy patients do not refer. With today's social networking, they can share their unhappiness with the world."

For some patients, a premium lens may not be the best solution. For example, if a patient plays golf, a multifocal lens may not be a good choice if the patient wants the best distance acuity. "Monovision is not particularly good for golfers because of the depth of field and stereovision needed on the green," says Dr. Kershner. "On the other hand, if the person mostly reads on a laptop or Kindle and drives infrequently at night, then she will need the best vision in the intermediate to near range. Many surgeons feel they can do good surgery, and neuroadaptation will intervene to make up the difference between a clear, well-centered intraocular lens and dysphotopsias. But, adaptation can take months if it occurs at all. It is always better to frontload the patient time. It pays for itself down the road."

Lisa B. Arbisser, MD, agrees that premium lenses are not for all patients. "When patients are asked to step out of the paradigm that Medicare has created and pay themselves, their expectations really skyrocket," she says. "That's part of why we should never be upselling people for that which they don't understand and don't need or want, because then they are likely to be unhappy. The whole concept of 'converting' people from standard to premium I think is a terrible disservice to ophthalmologists as well as to patients. We should really be looking for what is right for an individual patient according to what his or her goals actually are." Dr. Arbisser is in private practice at Eye Surgeons Associates in Iowa and Illinois and an adjunct associate professor at the Moran Eye Center at the University of Utah.

She notes that there is no perfect implant, so patients will either be given blended vision or bilateral multifocal diffractive lenses. "Nothing is going to

make them like they are 15 again so we have to manage their expectations as a result and make sure that it's very clear what the trade-offs are, that they are not widgets, and that we are not God. Only then we can meet expectations most of the time," she says.

Age Versus Attitude

Dr. Arbisser notes that managing patient expectations is often less about age and more about patient rigidity. "I think there are rigid people at age 50 and malleable people at age 85, so it's less about age and more about attitude," she says. "I always ask how patients feel about glasses. Would they be happy to have readers? Will they be willing to have prescription glasses they wear occasionally? Some people think glasses age them or are uncomfortable, and they are willing to do whatever they can to get rid of them, while others think they hide their bags and they wouldn't be recognizable without them. I offer all the choices to 80-year-olds that I offer to 55-year-olds. There are still 85-year-olds on the tennis court, at least in Iowa. I am hesitant to recommend multifocals except to those people for whom it is so critical to be rid of glasses."

She explains that patients must understand that there is a trade-off in general vision quality with multifocality, though it's the only way the vast majority of patients can be truly independent of glasses for all daily activities. Many people can deal well with this reality. "Naturally, we carefully choose only patients with healthy eyes and visual systems for these implants," says Dr. Arbisser. "Because we can't predict the future, when implanting a diffractive lens in a younger person I'm mindful of the future risk of disease development. So, in fact, I'm more confident to offer multifocals to older patients who, once they are 80 or 85 and healthy, are unlikely to ever get macular degeneration or glaucoma and so will enjoy their spectacle-free bilateral multifocality indefinitely."

She only implants multifocal IOLs in 9 to 10 percent of her patients, but she implants premium lenses in well over 30 percent because she believes that neutralizing astigmatism is a huge boon to all patients. "Even people who think they want to wear glasses and look better in glasses are well-served not to require them for function," she says. "For this reason, I have done peripheral astigmatic keratotomy since [Florida surgeon James Gills] described it years ago, have embraced toric lenses since their inception, and enjoy trading finicky manual AK for the femto laser version today."

She notes that blended vision has a much wider audience than multifocals, and she has been using this strategy for almost half of her monofocal patients for decades. "I never aim for more than 1.5 D difference between the two eyes," she says. "I think, above this disparity, there is enough aniseikonia and decrease in depth perception to cause poor adaptation and function. My blended vision patients are still encouraged to get glasses for fine near tasks or challenging night driving, but many wear them rarely. Lately, I have been using a bi-aspheric hydrophilic implant, which confers more depth of focus than my standard acrylic implant for patients who choose blended vision as a premium option. These allow me to aim for just -0.75 D or -1 D at the most for the near eye, giving wonderful binocular results. I am mindful of the higher YAG rate inherent in the hydrophilic material and other potential unknowns."

Take Extra Time

Although today's seniors may be more technology-savvy than previous generations, they are still traditional in many areas. They remember a time when doctors made house calls, and they may prefer to spend more time with the doctor than with ancillary staff.

"I take a more traditional approach with everyone, but especially with the older demographic," says Robert Arleo, MD, in private practice in Ithaca, N.Y. "They want the MD to do more and the optometrist to do less, and I think they need a little bit of education to work through the reality of how things are structured now. They view the doctor/patient relationship in a more traditional way where the doctor makes the treatment decisions," he adds.

Dr. Arleo notes that it is important to determine the patient's primary complaint and focus on improving that complaint. This population can also be more difficult to manage because many of them have other eye conditions in addition to the cataract. For example, many older patients have dry eyes, glaucoma or macular degeneration. Any of these associated conditions can limit vision to some degree.

"Many patients think that cataract surgery is going to solve everything, which is not the case for most people," he says. "I tend to shy away from multifocal lenses in this demographic. If they have been nearsighted, I really encourage them to remain at a functional level of nearsightedness unless there is a very specific reason to change that because they have lived with it for so long. I have had more people unhappy becoming emmetropic when they were nearsighted than leaving them somewhat nearsighted. I'm sensitive to that in everyone, but with the older population, it's even more important not to rock the boat too much."

In his practice, the main complaint in the older age group is difficulty driving. "So, we focus on making that

(*continued on page 73*)


Distinguishing Infection Post-Intravitreal Injection

The widespread use of anti-VEGF intravitreal injections makes early detection and treatment of postop complications crucial.

By Daniel B. Roth, MD, Kunjal K. Modi, New Brunswick, N.J.; Harry W. Flynn Jr, MD, Miami

Due to the current widespread use of intravitreal injections in clinical practice, with annual injection rates more than 160 times higher than in 1991 and more than 1 million injections performed in 2008,[1] it has become increasingly important to identify potential post-injection complications. Both noninfectious and infectious inflammation have been reported as complications of intravitreal injections.[2-4] With the increasing rates of intravitreal injections since their approval for use, the incidence of infectious endophthalmitis has been extensively studied. Recent retrospective case series have reported post-injection endophthalmitis rates between 0.022 percent and 0.16 percent.[5,6] However, in the Comparison of Age-related Macular Degeneration Treatments Trial (CATT), the rate of endophthalmitis was 0.7 percent for ranibizumab and 1.2 percent for bevacizumab.[7]

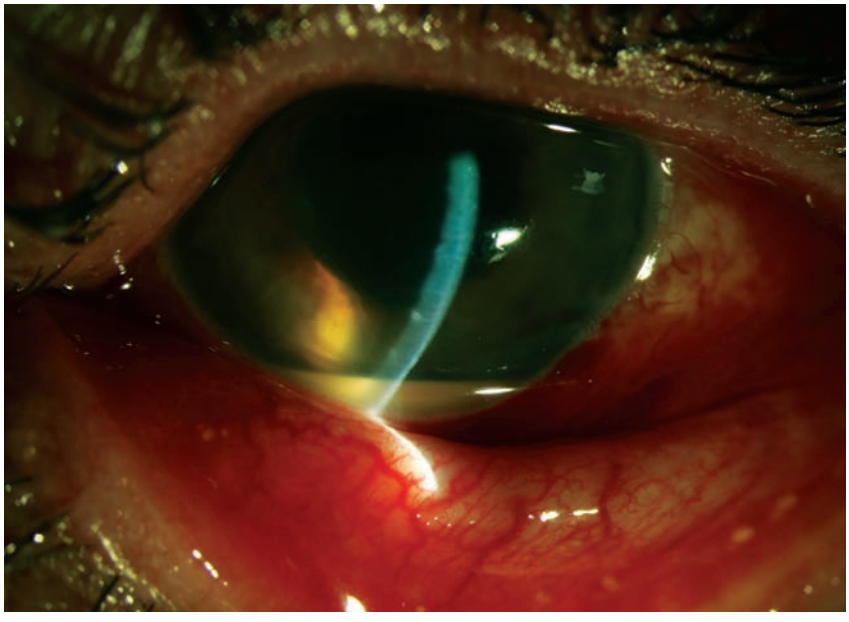

Figure 1. Infectious endophthalmitis demonstrating hypopyon and fibrin in the anterior chamber.

Noninfectious endophthalmitis (post-injection sterile inflammation, in which evidence of an infectious etiology was lacking and the milder clinical presentation seemed most consistent with sterile inflammation), has been reported after intravitreal bevazicumab at a rate of 0.09 percent to 1.1 percent and was reported at a rate of 0.2 percent in CATT.[5-10] Noninfectious inflammation may occur more often in patients with prior history of uveitis, pseudophakia and history of vitrectomy. Several reports of noninfectious endophthalmitis after intravitreal bevacizumab injections have been documented, describing an inflammatory reaction that is often painless and recovers slowly but without permanent damage.[11,12] The American Society of Retina Specialists Therapeutic Surveillance Subcommittee surveyed retina specialists' experience during a two-month period and identified 15 eyes treated with intravitreal aflibercept that presented with sterile inflammation after the injection; however some of these eyes were treated with

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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

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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.

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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.

References: 1. SIMBRINZA™ Suspension Package Insert. **2.** 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. **3.** 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. **4.** Data on file, 2013.

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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.

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

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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.

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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™, 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™, benzalkonium chloride, may be absorbed by soft contact lenses. Contact lenses should be removed during instillation of SIMBRINZA™ Suspension, but may be reinserted 15 minutes after instillation.

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

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intravitreal antibiotics as a precaution for possible infectious endophthalmitis.[13]

As these sterile inflammatory conditions lack an infecting organism, they are typically treated with steroids and observation, as opposed to topical and intravitreal antibiotics. In a recent study, eyes receiving aflibercept experienced at least some mild form of intraocular inflammation in 0.28 percent of injections *(Roth DB, et al. The Incidence of Noninfectious Intraocular Inflammation after Intravitreal Aflibercept Injection. Verbal communication, presented at the American Society of Retinal Specialists annual meeting, Las Vegas, Nev., August 27, 2012).*

Infectious endophthalmitis is defined by the presence of an infecting organism within the eye and can occur following any intraocular procedure, including intravitreal injection, surgery and trauma. Furthermore, contamination of medication batches can lead to clusters of endophthalmitis, which can have devastating visual effects. An outbreak in southern Florida occurred where 12 patients presented with symptoms of infectious endophthalmitis following intravitreal bevacizumab injection. In 10 of the 12 patients, *Streptococcus* was isolated from vitreous fluid.[14] Each of these patients was injected with bevacizumab prepared by the same private compounding pharmacy, with all but one eye resulting in count fingers or worse visual acuity at four months of follow up.

Recently, a Georgia compounding pharmacy recalled 40 lots of its bevacizumab syringes after reports of endophthalmitis due to presumed contamination.[15] This report, as well as many others, highlights the importance of adhering to the highest standards for sterile preparation of medications and injection technique, accurately identifying an infectious endophthalmitis versus a noninfectious inflammation, and treating early to avoid potential progressive vision loss from infectious endophthalmitis.[16,18]

Even in cases of infectious endophthalmitis, it is not always possible to identify the organism, either due to an inadequate sample of ocular fluids, poor specimen handling or difficulty in culturing the specific organism. Therefore, a "culture-negative" case of endophthalmitis may actually be infectious. In 25 to 30 percent of endophthalmitis cases, one is unable to identify an organism via culture. Infectious and noninfectious endophthalmitis can occasionally present in a similar manner in the

Table 1. Characteristics Differentiating Infectious from Noninfectious Endophthalmitis

More Common Features	Infectious	Noninfectious
Pain	Moderate to severe pain	Usually mild pain
Vision loss	Severe	Mild to moderate
Fibrin	Always present	Rare
Hypopyon	Very common	Usually absent
Vitreous opacity	Usually prominent	Usually mild
Conjunctival/vascular congestion	Very common	Often absent
Less Common Features	**Infectious**	**Noninfectious**
Retinal infiltrates	Occasionally present	Absent
Intraretinal hemorrhages	Common	Rare
Whitening of retinal vessels	May be present	Absent
Clinical Course	**Rapidly progressive**	**Slow improvement**

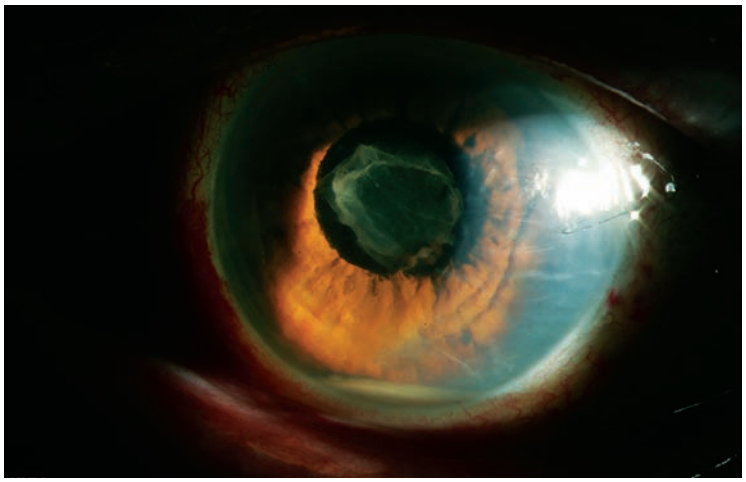

Figure 2. Infectious endophthalmitis after treatment with intravitreal antibiotics, showing retracting fibrin in the pupil and reduction in the hypopyon.

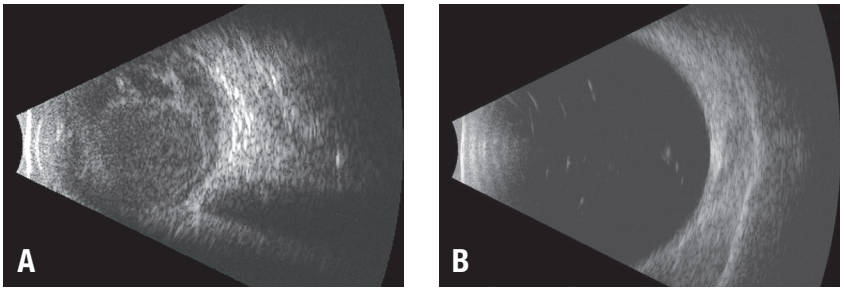

Figure 3. A. B-scan ultrasonography showing dense opacities and membranous debris in the setting of infectious endophthalmitis. B. Mild vitreous opacities in the setting of noninfectious endophthalmitis.

post-injection patient, and thus, this article aims to differentiate between infectious versus noninfectious inflammation after anti-VEGF agents, based upon signs, symptoms and clinical features.

Certain features during post-injection follow-up can be a clue to the clinician to an infectious cause: These features include presence of fibrin and hypopyon, marked anterior chamber cells and/or vitritis, decreased visual acuity, and conjunctival or scleral congested vessels. Additional, less-common features that can occasionally be helpful include presence of retinal hemorrhages, retinal infiltrates or cotton-wool spots and periphlebitis.

Hypopyon and Fibrin

Hypopyon has been reported as a presenting feature of infectious endophthalmitis in 78 percent of patients in one study *(See Figure 1)*.[5] Anterior chamber fibrin is uncommon in the setting of noninfectious endophthalmitis, but is very common in infectious endophthalmitis. Thus, hypopyon and/or fibrin are very strong predictors of an infectious process. With the inflammation associated with infectious endophthalmitis, there is an influx of polymorphonuclear leukocytes, aqueous flare from an influx of protein, and a conversion of intraocular fibrinogen into fibrin. Fibrin in the anterior chamber is an important finding in patients with endophthalmitis, and retraction of the fibrin *(See Figure 2)* after treatment is an important sign that the antibiotic therapy is effective. If an eye presents with hypopyon and fibrin, one must assume an infectious etiology until proven otherwise.

Pain

Commonly reported in these patients, pain is an early warning sign of infectious etiology. Some discomfort often occurs after intravitreal injection, but typically resolves within 24 hours. Ocular surface irritation may last longer, especially in the presence of corneal epithelial breakdown or povidone-iodine induced dryness or external inflammation after the injection procedure. Noninfectious inflammation can cause mild discomfort; however, more intense pain and deep ache after injection may suggest infectious endophthalmitis.

Pain associated with infectious disease is often described by patients as deep and more intense, but these subjective symptoms are often highly variable. Nevertheless, 75 percent of infectious cases in one study presented with the symptom of pain.[18] Symptoms usually begin within one week of injection, with an average onset 2.8 days after anti-VEGF injection in one study.[19]

Vision Loss

Along with pain in the eye, another very common presenting feature is marked vision loss, shown in the Endophthalmitis Vitrectomy Study (EVS) to be present in 94 percent of post-operative endophthalmitis cases.[20] Blurred vision is not as common in noninfectious endophthalmitis, but is typical in infectious cases. Vision loss can range from moderate to profound, depending on the virulence of the organism in infectious cases,[21] and vision loss is less marked in noninfectious cases, if significant vitritis is present. A sudden decrease in visual acuity after injection should be another early warning sign for infectious endophthalmitis. Clinicians should maintain a low threshold for follow-up for patients complaining of subjective post-injection pain or loss of vision, as they are often the first symptoms apparent to patients as a warning sign.[18,20]

Less Common Clincal Features

Several identifiable features are commonly seen in infectious endophthalmitis. Echography can measure the degree of vitreous opacities in these patients. Endophthalmitis in general is characterized by dense opacities, indicating the purulent infectious process. Noninfectious inflammation usually has less dense or minimal opacities. Another suggestive feature of infection is the presence of intraretinal hemorrhages, which are likely secondary to retinitis or localized venous occlusive disease. Retinal periphlebitis has been shown in clinical reports and animal models to occur early in the process of infectious endophthalmitis.[22] Intraretinal hemorrhages are rarely seen as a feature in noninfectious endophthalmitis, thus their presence has positive predictive value for an infectious source. Retinal infiltrates suggest an infectious source and are commonly composed of inflammatory cells and debris from the inflammatory process.

Noninfectious endophthalmitis after intravitreal injection is a self-limited process, and resolves spontaneously

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[1] Bullimore MA, The IOLMaster and Determining Toric IOL Power, 2013
[2] Leaming DV, 2012 Practice Styles and Preferences of the U.S. ASCRS Members Survey

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after a short period of observation. This entity is well-recognized to occur after intravitreal triamcinolone injections, with an incidence as high as 0.5 percent to 2 percent of injections,[23-25] and often presents with a quiet ocular surface, no fibrin and a hypopyon. This hypopyon may be true inflammatory cells or alternatively, mostly a collection of settling triamcinolone crystals, also termed a pseudohypopyon.[23]

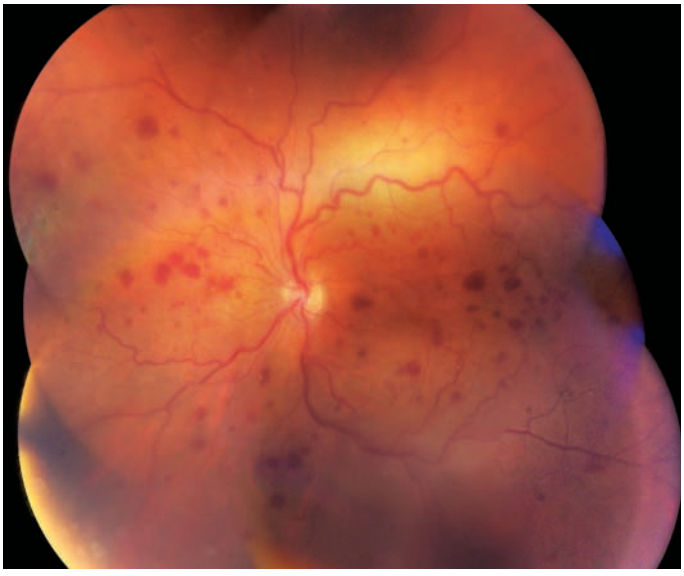

Figure 4. Intraretinal hemorrhages in the setting of infectious endophthalmitis.

In noninfectious inflammation after anti-VEGF agents, a hypopyon is typically absent and the inflammatory reaction is usually mild to moderate.[19] Although a vitreous cellular reaction may be present, it usually does not obscure the view of fundus details, and it is never a dense vitritis. The B-scan echography can aid in distinguishing the level of vitritis and helping to guide the clinician to determine the nature of the vitreous opacification. Inflammation after anti-VEGF agents may be an immune reaction to the drug itself, to breakdown products in the injected material, or to an unknown contaminant.[24] In cases of noninfectious endophthalmitis, the inflammatory reaction usually resolves spontaneously, typically without deleterious visual sequelae.[27] Nevertheless, topical steroids may aid in a more rapid resolution of intraocular inflammation, ocular discomfort and visual loss. One report suggests that with multiple injections with anti-VEGF agents, there is a greater likelihood for generating an inflammatory response, as anti-VEGF agents are humanized antibodies.[11] The four patients in that series had primarily vitreous and anterior chamber cells without fibrin or hypopyon, and the inflammation resolved with topical steroids within one to two weeks.

Since it is sometimes difficult to distinguish these two conditions, clinical judgment is the most practical source of delineation. As described in Table 1, certain pertinent features can help the clinician decide whether to use intravitreal antibiotics for infectious endophthalmitis, or reassure the patient of a benign inflammatory response. The onset of symptoms in infectious endophthalmitis typically correlates with the virulence of the causative organism. The most common infective organism following intravitreal injection is *Staphylococcus epidermidis*, which has been identified in one study in approximately 65 percent of endophthalmitis isolates after anti-VEGF injection.[28] However, Streptococcal species have been reported as well, possibly due to needle contamination from oral flora at the time of injection.

Rates of endophthalmitis after intravitreal injection can be decreased by following aseptic technique protocol for the injection, reduced talking during the injection procedure[27,30] and use of a lid speculum.[5] However no difference was seen in infection rates with use of a bladed lid speculum, displacement of the conjunctiva, use of gloves or type of intravitreal agent administered.[21]

The consequences of delay in treating infectious endophthalmitis can be devastating.[16,17] Therefore, in borderline patients, it may be best to treat empirically with intravitreal antibiotics. In milder cases evaluated early in the course, treatment with frequent topical steroids can be considered, and the patient can be examined several hours later until the diagnosis becomes more well-defined. Ultimately, careful clinical examination and attention to subtle clinical features will guide the clinician to properly manage patients with early inflammation after injection and treat them appropriately. REVIEW

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ARVO Goes to The Emerald City

Highlights from the papers and posters of ARVO's first foray outside of the balmy borders of Florida.

Mark B. Abelson, MD, CM, FRCSC, FARVO, and Ora Staff, Andover, Mass.

In a dramatic change from a decades-long tradition, ARVO convened its annual meeting this May in a place other than Florida, as ophthalmologists and vision scientists headed to the Pacific Northwest for ARVO 2013. While many attendees may have felt some trepidation about the change, by the end of the week most agreed that sunny Seattle was a terrific choice. The relaxed atmosphere of the city provided a pleasant setting for scientific discourse and socializing with colleagues old and new. Plus, it wasn't hard to find a good sandwich shop, café or restaurant close by, which is always a bonus.

This month, we'll review the highlights of the meeting in various areas of vision research. (Unless otherwise specified, all of the abstract citations are from this year: IOVS 2013;54.)

AREDS2

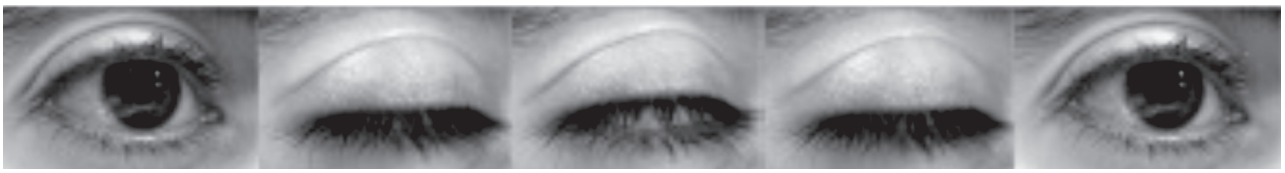
The scientific headliner of this year's meeting was the AREDS2 trial,[1] the second part of the Age-related Eye Disease Study. AREDS2 examined modifications to the vitamin formulation that AREDS had established as a valuable preventative approach for patients at risk for age-related macular degeneration. This five-year study included 4,203 participants randomized to receive: 1) 10 mg lutein + 2 mg zeaxanthin; 2) 350 mg DHA + 650 mg EPA; 3) lutein + zeaxanthin and DHA + EPA or 4) placebo. All participants also took either the original AREDS formulation or were randomized to AREDS variations (no beta carotene, reduced zinc or both).

There were no significant differences in disease progression in the four major treatment groups. The probability of progression to advanced AMD was 31 percent in the placebo group, 29 percent in the lutein + zeaxanthin group, 31 percent in the DHA + EPA group and 30 percent in the lutein + zeaxanthin and DHA + EPA group. There was also no significant difference between the two zinc concentrations tested. One subgroup, consisting of patients receiving lutein + zeaxanthin and no beta-carotene, saw an 18-percent reduction in the risk of progression to advanced AMD when compared to those who took AREDS with beta-carotene (and no lutein + zeaxanthin). Study authors also noted that this replacement of beta carotene in the original formulation with lutein + zeaxanthin reduced the risk for lung cancer in ex-smokers.

Models, Methods, Endpoints

A key aspect of therapeutic development is the refinement and optimization of methods for patient inclusion in studies and disease assessment. Ocular inflammation is an area of active effort, and many presenters reported on their attempts to improve protocol design, symptom evaluation or both.

Investigators from our research firm, Ora, used modifications to the traditional conjunctival allergen challenge protocol to elicit a more chronic, inflammatory conjunctivitis that may be a means for developing treatments for chronic allergy. *(Gomes P, et al. ARVO E-Abstract 2555)* Other refinements included updated protocols for fluorophotometry and conjunctival staining. *(Heckley C, et al. ARVO E-Abstract 6043; Lane K, et al. ARVO E-Abstract 6045)* The optimization of fluorometric measures of tear turnover was particularly in-



Video capture of blink behavior and patterns has allowed for a more comprehensive assessment of the role of blink in ocular surface disease. ***(Lafond A, et al. ARVO E-Abstract 962)***

triguing, because the authors were able to show a significant correlation between this sign of dry-eye disease and the Ocular Surface Disease Index symptomatology scale, a noteworthy accomplishment for clinical studies of this disease.

Advances in ocular surface microscopy was a dominant topic, as well. Studies of corneal nerve morphology by *in vivo* confocal microscopy demonstrated the utility of enhanced ocular surface imaging, both as a potential diagnostic tool and as a potential therapeutic endpoint. *(Sanchez Dalmau BF, et al. ARVO E-Abstract 530; You JY, et al. ARVO E-Abstract 531)* Other presentations focused on IVCM-based advances in limbal morphology and on inflammatory cell infiltration of the conjunctival vasculature. *(Baclagon ER, et al. ARVO E-Abstract 537; Angeli E, et al. ARVO E-Abstract 2557)*

A big topic in clinical methodology for ocular inflammation was the measurement of biomarkers of disease with a focus on those found in tears. A number of groups reported efforts to identify both normal and pathological values for cytokines in tears. *(Hagan S, et al. ARVO E-Abstract 955; Enriquez-De-Salamanca A, et al. ARVO E-Abstract 2072; Dionne K et al. ARVO E-Abstract 4324; Lakshman N et al. ARVO E-Abstract 4325)* While there were some disagreements on the quantitative aspects of these studies, it's clear that the technology to accurately measure picogram quantities of signaling molecules including IL-2, IL-6 and IL-8 is here, and such measurements will become an increasingly important aspect of diagnosis going forward.

Biomarker assessment was not limited to cytokine studies, and other presentations described quantification of other potential indicators or predictors of ocular disease. One study provided evidence that several micro RNAs associated with retinal degeneration can be detected in systemic circulation, and so may ultimately function as biomarkers for retinal disease. *(Peng Q, et al. ARVO E-Abstract 1947)* These short-chain nucleic acid molecules function as regulators of gene transcription in a tissue-specific manner. The potential importance of miRNAs (particularly miRNA-96 and miRNA-124) was confirmed in other presentations examining the role of these molecules in retinal degeneration. *(Langmann T, et al. ARVO E-Abstract 4517)*

There were a number of presentations that provided new insights on the measures used to assess blink rates and the importance of considering lid contact time to differentiate between normal and dry-eye subjects. *(Johnston P, et al. ARVO E-Abstract 967; Lafond A, et al. ARVO E-Abstract 962)* Other presenters examined the relationship between tear meniscus dimensions and other disease measures in subcategories of dry eye and found that in patients with aqueous tear deficient dry eye and autoimmune disease, lower tear volume is associated with worse corneal epithelial disease. *(Tung CI, et al. ARVO E-Abstract 970)*

Mucin function in dry eye was also the subject of multiple presentations. One presentation found that as the signs of dry eye worsen, soluble MUC16 values increase. *(Watson M, et al. ARVO E-Abstract 4309)* Another study used a polymerase chain reaction-based measure of MUC5A expression to screen for goblet cells in patients with limbal cell deficiency. The goal of this study was to correlate loss of this key cell type with disease severity. *(Suarez-Cortes TM, et al. ARVO E-Abstract 547)*

Ora presented novel data on the use of software analysis for the evaluation of corneal superficial punctate keratitis, an important primary endpoint for dry-eye trials. *(Rodriguez J, et al. ARVO-E Abstract 4341)* Clinical grading, typically based on a 0-to-4 point scale, poses many challenges, such as inefficiencies in reproducibility, accuracy, subjectivity and sensitivity. In a population of 665 dry-eye subjects, the software-based approach generated accurate, efficient quantification of corneal desiccation. An automated approach is useful in standardizing the SPK evaluation process and allows for clear identification of improvement due to therapeutic intervention. Automation may not be applicable in every situation, however. In another study, comparison of software-based analysis of hyperemia grading showed that while this approach may be useful for dry-eye studies, confounding factors in allergic hyperemia (such as chemosis) preclude the use of automated redness analyzers. *(Raval Y, et al. ARVO E-Abstract 2553)*

Dry eye is a disease that involves a range of functional tests of tear film stability, but despite this it's still not clear which tests are best. One group sought to address this topic by calculating the correlations of dry-eye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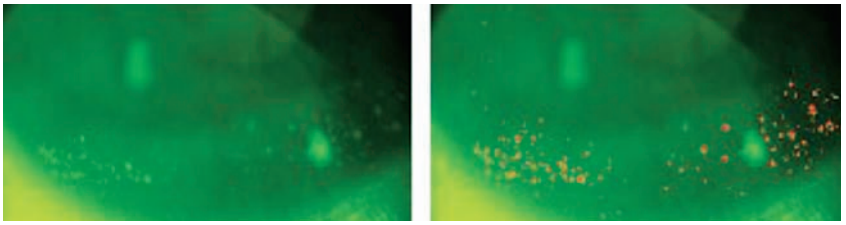

Digitization and pseudocolor enhancement can allow for automated quantification of superficial punctate keratitis. The original image is on the left, the enhanced one on the right. ***(Rodriguez J, et al. ARVO E-Abstract 4341)***

signs to signs, symptoms to symptoms, and both signs and symptoms to objective tests of tear-film stability. Contrary to many other reports, the authors reported that many signs and symptoms correlate with quality-of-life variables. In addition, they found a stronger correlation between tear turnover rate and symptoms than that seen between Schirmer's tests and symptomatology. Lid variables, however, correlated in unexpected ways, and the authors suggest that compensatory mechanisms may underlie these findings. *(Saigal S, et al. ARVO E-Abstract 4361)*

Retina, Glaucoma and Dry Eye

In addition to the preclinical presentations, ARVO always presents a good opportunity to see what may be in the pipeline of new therapeutics. We came across a number of interesting posters throughout the week, including some on Thursday, the last day of the meeting. Just in case you weren't able to stick around through the end of the week, we'll provide a recap here, as a number of the "best-in-show" posters were presented on ARVO's final day.

A group of investigators, one of whom is an employee for Aerpio Therapeutics (Cincinnati, Ohio) provided *in vitro* and *in vivo* data on the company's drug AKB-9778. *(Shen J, et al. ARVO E-Abstract 6094)* The researchers confirmed its bioactivity as a potent and selective small molecule inhibitor of vascular endothelial-protein tyrosine phosphatase. The VE-PTP enzyme, also known as human protein phosphatase β or HPTBβ, is a negative regulator of the Tie2 receptor, which is expressed on vascular endothelial cells and plays a key role in stabilizing blood vessels. Inhibition of VE-PTP restores Tie2 signaling, reducing vascular leak and pathologic neovascularization. In the study, the researchers note that, *in vitro*, "AKB-9778 promoted phosphorylation of Tie2, enhanced angiopoietin (Ang)-1 induced Tie2 phosphorylation, and stimulated phosphorylation of signaling molecules in the Tie2 pathway." *In vivo*, AKB-9778 also induced phosphorylation of Tie2. While AKB-9778 is initially being developed for diabetic macular edema, vascular stabilization may also provide benefits for a wide variety of disease states. Aerpio initiated a Phase Ib/IIa trial of AKB-9778 for the treatment of DME in September 2012.[2]

The agent ALG-1001 is being investigated in several vascular eye diseases including wet AMD, DME and symptomatic vitreomacular adhesion. ALG-1001 is a new small-molecule oligopeptide that targets multiple integrin receptor sites that play key roles in cell signaling and regulating cellular shape, motility and the cell cycle. Interim data on the Phase Ib/IIa dose-ranging, monotherapy study of the drug in wet AMD was presented at this year's ARVO.[3] *(Kaiser P, et al. ARVO-E Abstract 2177)* In the first human study of the agent, the drug appeared safe and well-tolerated and a treatment effect lasted longer than four months off-treatment. There was also a robust response in the 3.2-mg dose group of at least three months off-treatment in all subjects. A demonstrated mean best-corrected acuity improvement of eight letters as measured by ETDRS in this group corresponded to a 30-percent decrease in central macular thickness and improvement in retinal architecture.

Monday's retina posters included a meta analysis of ranibizumab safety data in patients with AMD, retinal vein occlusion or DME. *(Avery RL, et al. ARVO E-Abstract 1535)* The analysis pooled 22 Phase II, III and IIIb studies and included 10,300 patients with a mean follow-up time of 15.9 months. In the analysis, patients with DME showed higher mortality rates and a greater rate of wound healing complications than those with either AMD or RVO. No other patterns of systemic disease emerged from the study.

As our experience with therapeutic responses to either ranibizumab or bevacizumab is extended, it's important to examine the distinctions in therapeutic responses observed to these and other anti-VEGF based therapies. This was addressed in a retrospective study of aflibercept efficacy in patients who had previously received treatment with either ranibizumab or bevacizumab. *(Yonekawa Y, et al. ARVO E-Abstract 1938)* Mean central macular thickness, visual acuity and treatment history were collected from 94 patients (104 eyes) in two treatment centers. Although the follow-up was modest (average of 18 weeks), significant reduction in CMT was observed in two patient populations: patients who were refractory to ranibizumab or bevacizumab and those who received aflibercept after a recurrence of disease progression. Both groups also showed a stabilization of VA following aflibercept. Thus, despite similar mechanisms of action, aflibercept appears to be a

useful therapeutic option in patients previously treated with other VEGF antagonists.

The treatment landscape for vitreomacular adhesions changed when ocriplasmin (Jetrea; Thrombogenics NV, Leuven, Belgium) was approved by the FDA in 2012.[3] This recombinant protease targets vitreous proteins, resulting in degradation and enzymatic vitrectomy. A Phase III study sub-analysis examined the efficacy of ocriplasmin in patients designated as clinical candidates for traditional vitrectomy. *(Kuppermann BD. ARVO E-Abstract 1942)* Patients were evaluated for VMA resolution 28 days after injection of either ocriplasmin or placebo. In patients with full-thickness macular hole, closure was also assessed at 28 days. Overall, 33.2 percent of eyes treated with ocriplasmin achieved VMA resolution as compared with 11.5 percent (p=0.001) of those treated with placebo; in patients with a baseline FTMH, these rates were 50 percent and 25.5 percent (p=0.006), respectively. In addition, the study doctors report that FTMH closures were seen in 40.6 percent of the ocriplasmin-treated group as compared to 10.1 percent in the placebo group.

Building off data presented at last year's ARVO *(Van de Velde S, et al. IOVS 2012;53:ARVO E-Abstract 1977; Sijnave D, et al. IOVS 2012;53:ARVO E-Abstract 2522; Hollanders K, et al. IOVS 2012;53:ARVO E-Abstract 1974)*, Amakem Therapeutics (Diepenbeek, Belgium) presented new preclinical data on its lead drug candidate, the locally acting Rho kinase (ROCK) inhibitor AMA0076. In Dutch Belted rabbits, once-daily treatment with AMA0076 resulted in IOP reduction that was more sustained than Y-39983, a non-local ROCK inhibitor. *(Van de Velde S, et al. ARVO E-Abstract 5631)* The data demonstrated that AMA0076 elicited a sustained, 24-hour effect on lowering intraocular pressure, an effect not seen with Y-39983. Additionally, hyperemia was observed with Y-39983 at all concentrations, whereas only mild hyperemia was observed with the highest concentration (0.4%) of AMA0076. Looking ahead, Amakem initiated a Phase IIa proof-of-concept, placebo-controlled, dose-escalation study of topical AMA0076 in September 2012.

Data implicating B-Amyloid in the pathology of glaucoma, as analyzed via levels of B-Amyloid in glaucomatous retinas compared to healthy subjects, set the stage for MRZ-99030, a B-Amyloid aggregation modulator.

Data implicating β-Amyloid in the pathology of glaucoma, as analyzed via levels of β-Amyloid in human glaucomatous retinas in comparison to healthy subjects, set the stage for MRZ-99030 (Merz Pharmaceuticals; Frankfurt, Germany), a β-Amyloid aggregation modulator. *(von Thun und Hohenstein-Blaul N, et al. ARVO E-Abstract 1139)* Merz researchers found that the topically administered drug significantly reduced retinal ganglion cell apoptosis in a rodent model of glaucoma compared to vehicle control in a dose-dependent manner. *(Gravius A, et al. ARVO E-Abstract 2625)*

Multiple abstracts from Japan's Ono Pharmaceuticals highlighted ONO-9054, an isopropyl ester derivative of the free acid ONO-AG-367 classified as a dual FP/EP3 receptor agonist that may be effective in lowering intraocular pressure. *(Tomohiro K, et al. ARVO E-Abstract 766; Karakawa T, et al. ARVO E-Abstract 1998)* In dogs and monkeys, the IOP-lowering effects of ONO-9054 were more potent and longer-lasting than the effects produced by an FP receptor agonist (latanoprost), a beta-adrenergic receptor antagonist (timolol) and a fixed combination of the two. *(Nagai K, et al. ARVO E-Abstract 1986)* In a double-masked study of 48 healthy volunteers, ONO-9054 was well-tolerated and there were no apparent dose-related responses in any systemic or local tolerability parameters. *(Rowe-Rendleman C, et al. ARVO E-Abstract 440)*

Mimetogen (Montréal, Québec) presented post-hoc data from a completed trial of MIM-D3 Ophthalmic Solution. Patients with greater or more rapid exacerbation of signs and symptoms from Ora's CAE were more responsive to MIM-D3, which targets mucin-protective compensatory mechanisms. *(Ousler G, et al. ARVO E-Abstract 4343)* Additionally, the post-hoc analysis supports an association between the duration of dry eye and the response to treatment for the reduction in both signs and symptoms. *(Meerovich K, et al. ARVO E-Abstract 4340)* Patients who reported having dry eye for five to 10 years saw a significant reduction in fluorescein staining and experienced improvements in their dry-eye symptoms, as opposed to those patients who reported having dry-eye disease for durations of one to five years or greater than 10 years.

Also targeted to treat ocular surface orders such as dry eye, EBI-005 is a potent IL-1R1 inhibitor. Eleven Biotherapeutics (Cambridge, Mass.) presented clinical data from a Phase I safety study demonstrating that EBI-005 was safe and well-tolerated in normal volunteers at two dose levels when administered three times daily. *(Goldstein M, et al. ARVO E-Abstract 4319)* The positive results

of the Phase 1a study prompted a Phase 1b study in patients with dry eye. Eleven also presented preclinical toxicology data demonstrating that EBI-005 was well-tolerated in both mouse and rabbit. *(Furfine E, et al. ARVO E-Abstract 4320)*

Preclinical data on a new topically administered anti-inflammatory, cis-Urocanic acid, demonstrated a significant reduction in corneal staining using a murine model of dry eye in a study from Ora. *(Whitlock A, et al. ARVO E-Abstract 902)* The same compound also showed promise in an Ora preclinical study of allergic conjunctivitis, so we're likely to see additional studies of cis-UCA in the future. *(McLaughlin J, et al. ARVO E-Abstract 2554)*

An interesting wrinkle in the therapeutic development paradigm was described by two poster presentations on the efficacy of low-dose brimonidine as an eye-whitener. *(Chapin MJ et al. ARVO E-Abstract 2556; Horn G et al. ARVO E-Abstract 5451)* (One of the presenters is the patent holder for this use of brimonidine.) The re-purposing of this anti-glaucoma agent provides a great example of how clinicians may be the best untapped resource in the drug development landscape. It also reminds us why we like the ARVO meeting: It represents a unique opportunity for clinicians and scientists to rub elbows, share ideas and move ocular therapeutics forward. REVIEW

Dr. Abelson is a clinical professor of ophthalmology at Harvard Medical School.

1. Age-Related Eye Disease Study 2. Lutein + Zeaxanthin and Omega-3 Fatty Acids for Age-Related Macular Degeneration. JAMA 2013;309:19:2005-2015.
2. Safety and Pilot Efficacy of AKB-9778 in Subjects With Diabetic Macular Edema. http://clinicaltrials.gov/ct2/show/NCT01702441?term=AKB-9778&rank=1. Accessed May 29, 2013.
3. A Safety And Efficacy Study Of ALG-1001 In Human Subjects With Wet Age-Related Macular Degeneration. http://clinicaltrials.gov/ct2/show/NCT01749891?term=ALG-1001&rank=1. Accessed May 15, 2013.
4. Approval letter for Jetrea (ocriplasmin) Intravitreal Injection. http://www.accessdata.fda.gov/drugsatfda_docs/appletter/2012/125422Orig1s000ltr.pdf. Accessed May 29, 2013.

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Using Visual Fields to Predict Progression

Knowing which patients are at greatest risk is crucial to effective treatment. This new approach may help make that a reality.

By Joseph Caprioli, MD, Los Angeles

I think most glaucoma specialists would agree that many glaucoma patients today are overtreated or undertreated. This is not a reflection of our competence, but of our limitations when it comes to identifying which glaucoma patients are most likely to lose vision—and how quickly.

In an ideal world, we might be able to constantly monitor all of our patients and respond to changes in their condition the moment the changes appear, but this is not an ideal world. Furthermore, our constraints are likely to increase because we're going to have even more limited resources for medical care in the future; fewer doctors will be treating a growing number of patients, while dealing with decreasing health-care funding. To make the best of this situation we're going to have to focus on treating those patients who are at the greatest risk of losing vision.

To do that, we need to be able to identify those patients who are progressing quickly. The reality is that not everybody with glaucoma is going to go blind. Depending on their age and other factors, many patients who have a slow rate of progression may do well without any treatment at all. If a 70-year-old patient has a very slow rate of progression, he's not going to go blind within the next 30 years. You can leave him alone, saving him the cost and morbidity of treatment. On the other hand, a young patient who is getting worse fast is likely to lose his vision if left untreated. That's not only a bad situation for the individual, but comes with a great cost to our society (as numerous studies have shown). These patients need more aggressive treatment.

The point is that we need to get the right level of treatment to the right patients at the right time. Without having reasonably accurate estimates of progression rates, we really don't know which patients need intensive treatment and which don't.

Separating Fast and Slow

To date, most of the statistical approaches for estimating the speed of glaucoma progression have used indices that were relatively global, taking the entire visual field into account. However, experienced practitioners who are estimating progression by studying visual fields usually focus primarily on the parts of the field that seem to be getting worse. That makes sense, because non-uniform progression is the nature of glaucoma damage; different portions of the visual field behave differently. The damage from glaucoma is relatively localized and tends to appear in typical patterns.

Perhaps most important, the portion of the visual field that's damaged is likely to get worse much faster than other parts of the field that have been relatively spared by the disease. In fact, the latter areas may not change at all; that's just the nature of the pathophysiology of glaucoma. So, if you want to know whether a patient is progressing rapidly or slowly, it makes sense to focus on the parts of the visual field that are damaged, rather than on the field as a whole.

With that in mind, we recently developed a software system that can analyze a sequence of visual fields, identify locations that are progressing at faster rates than the remainder of the field, and then predict future deterioration of the field based on this information. In essence, the system

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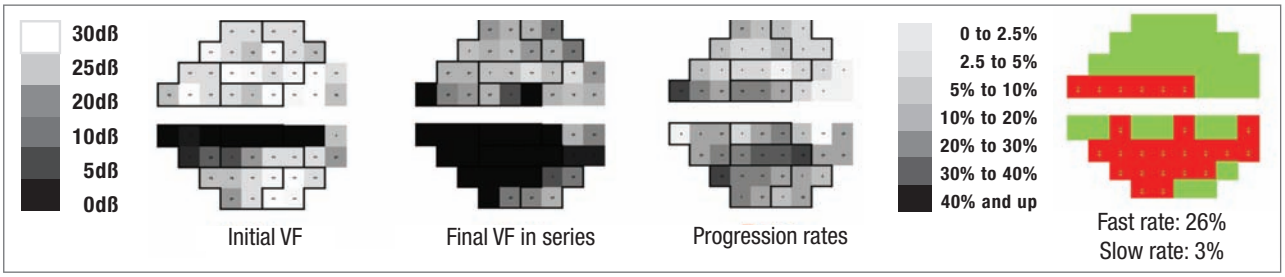


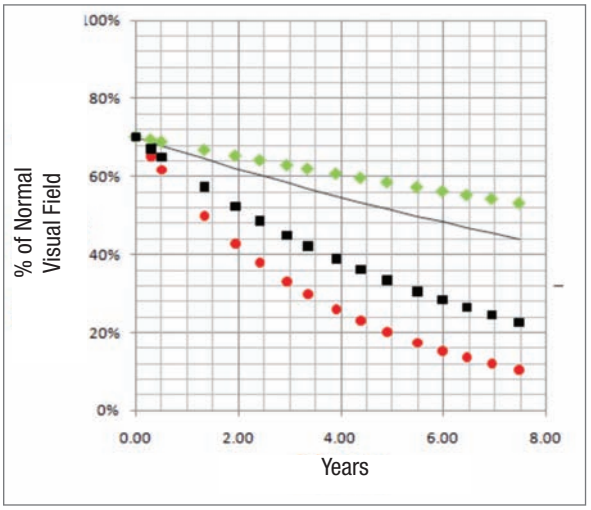
An example of using the rate of visual field decline to predict probable future outcomes in a glaucomatous eye (barring intervention). Above, left to right: grayscale of the initial visual field; grayscale of the final visual field in the series; grayscale showing the percentage rate of decay per year at each location; visual field partitioned into locations progressing more slowly (green) and faster (red). Directly below: average decay rates for slow and fast components given by the red and green dots, respectively. The black dots indicate the average rate of decay across the whole field, while the black line shows mean deviation (MD). Bottom of page: grayscale predictions for thresholds at final follow-up, at three confidence intervals.

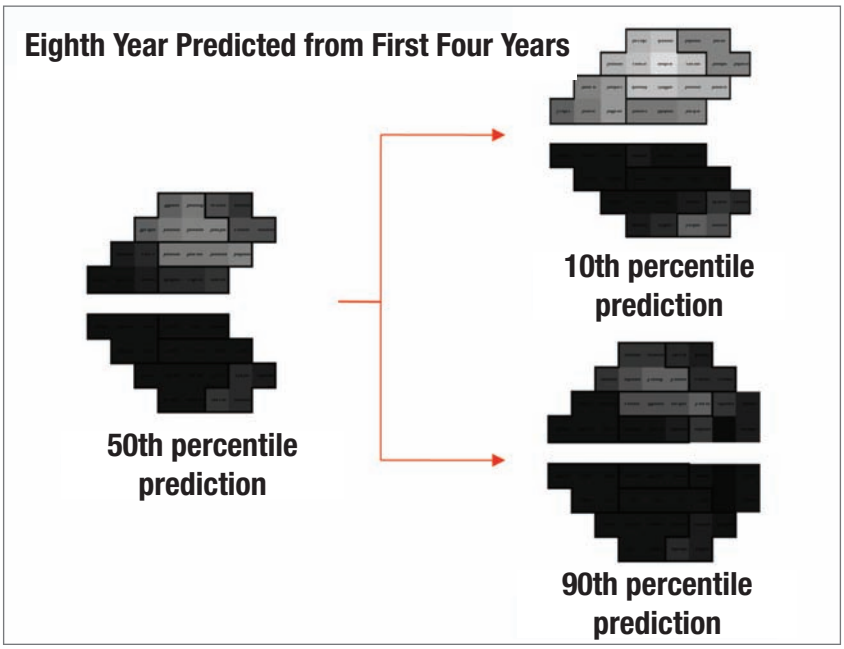
mimics what an experienced glaucoma specialist would do, but because it's digital, it can do it far more accurately. One of the fundamental problems of visual fields is that they're highly variable, so it's often difficult for a human brain to pick out the signal from the noise. But software is able to do it very quickly and reproducibly.

Using the Data

The reason that it's helpful to pay less attention to the parts of the visual field that are progressing slowly (if at all) is that much of the slower degradation in the visual field is the result of aging or cataract formation rather than glaucoma. Our system keeps that from confounding the issue by removing that gradual shift from consideration.

First, the software divides the field into areas that are getting worse relatively quickly and those that are getting worse relatively slowly, based on the preceding series of visual fields, using point-wise exponential regression (PER) analysis of threshold sensitivities. The rate of change seen in the slower areas may, to a small extent, represent glaucomatous damage, but for the most part it can be explained by the other causes. That means the deterioration seen in those areas is probably happening across the entire visual field, so the software subtracts that amount of deterioration from the entire field, leaving a net rate of progression that can be attributed solely to the disease. In fact, in most eyes the magnitude of the slow component compared to the fast component is actually pretty small, so when you subtract it out, it doesn't make a very big difference. In





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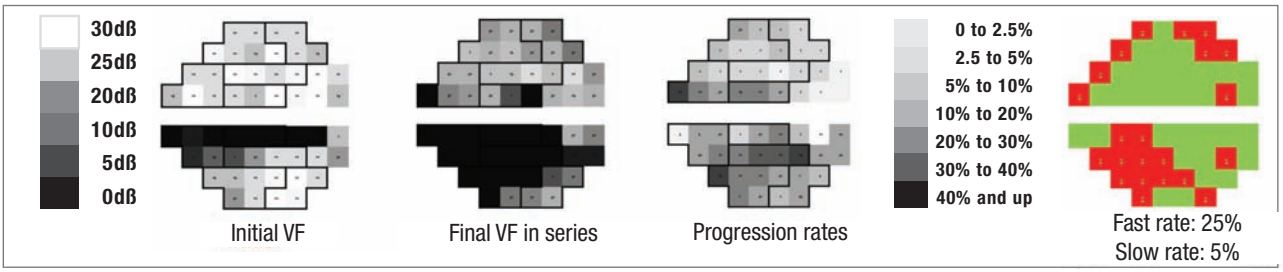


Another example of using the rate of visual field decline to predict probable future outcomes in a glaucomatous eye (barring intervention). This eye has a better prognosis than the previous example on p. 59. (For a detailed explanation of the charts, see the charts and caption on p. 59.)

some eyes, if the patient isn't too old or has already had cataract surgery, the rate of change in the slow areas approaches zero.

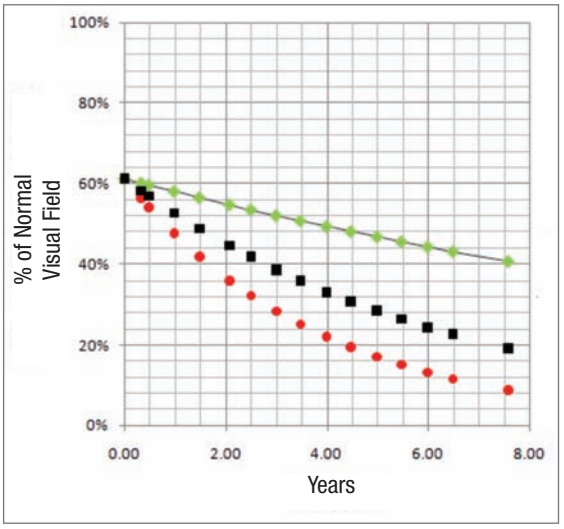
Next, the software uses this data to make predictions for what the visual field will likely look like in, say, five years if nothing changes (i.e., no change in treatment is undertaken). In other words, it projects into the future assuming that the future rate will be similar to the past rate. With statistical analysis, it produces a worst-case scenario, a best-case scenario and a most-likely scenario.

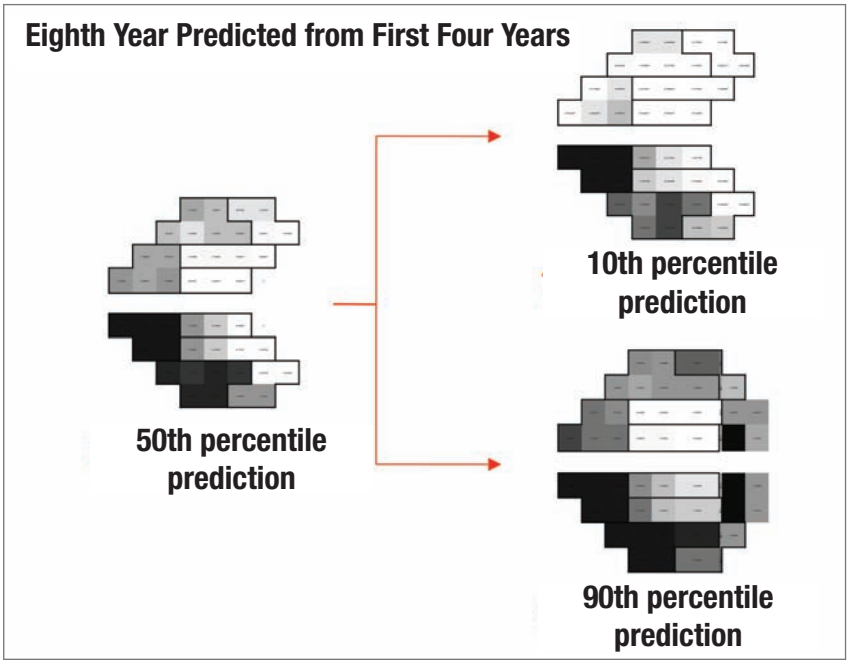
In addition to giving the physician valuable information, this is also something you can show to the patient. If the patient is getting worse fast, that will be reflected in a much worse-looking visual field in the future, even in the best-case outcome prediction; the worst case might show the patient becoming blind. (This could help reduce the problem of patient non-compliance.)

Validating the System

We've conducted two studies to validate this system as a means to separate the fast progressors from the slow progressors. The initial study involved fairly advanced patients with a lot of visual field damage from glaucoma[1]; it was based primarily on data collected during the Advanced Glaucoma Intervention Study. We included individuals with six or more years of follow-up and at least 12 visual field exams (389 eyes of 309 patients). Forecasts made by the system correlated well with the actual measured outcomes ($p<0.001$).

Two independent cohorts were also used to determine the software's ability to differentiate areas of glaucomatous damage from reduced vision caused by cataract; the difference in rate of decay between faster and slower segments of the visual field were significantly greater among the glaucoma patients than among the cataract patients (19 ±10





percent vs. 5 ±5 percent, (p<0.001).

After we completed that study, our next concern was whether the system would work as well in patients with less damage. Some of the more globally based visual field progression analyzers have low sensitivity when testing patients with early damage, and produce highly variable results when used with patients who have advanced damage. So we wanted to be sure that our system would work well across the full range of visual field sensitivity.

The second group of patients we tested, 409 eyes of 279 open-angle glaucoma patients from the database at the University of California, Los Angeles, had much less glaucoma damage.[2] Their data were also combined with the data from the first study to see how well the system worked over a broad range of damage levels. For comparison, predictive forecasts were calculated using both the mean deviation and visual field index forecasting systems; comparison of the prediction errors of the three approaches favored our system's forecasts (p<0.001). Overall, the new system was successful at identifying high-risk rapid progressors across a broad range of disease severity.

We have another study, currently in press, in which we looked at 83 patients who underwent glaucoma surgery to see what effect the surgery had on their progression rates. In brief, the data showed that the surgery produced a significant reduction in the rate of progression in the fast-progressing parts of the visual field, but essentially no change in the rate of the slower-changing parts of the field. This suggests that the slower change is likely not a result of glaucomatous damage. (In fact, some eyes showed a slightly increased rate of progression in the slower areas after trabeculectomy; that makes sense, since trabeculectomy is known to accelerate the formation of cataract in some eyes.)

It's worth noting some limitations to what these studies show. We required a minimum of five test locations in a visual field in each rate component in order to avoid mistaken identification of deterioration when none was present. How well the system would work with fewer deteriorating locations in a visual field cannot be determined from these trials. Also, it's possible that a small subgroup of patients might have slow, diffuse glaucomatous damage, which may be reflected in the "slow" component.

Not only do our studies support the validity of the software program, they support the concept that accurate prediction of future progression depends largely on paying attention to the damaged areas of the visual field, not just global analyses.

Nevertheless, the system appears to work well over the entire range of visual field damage. It's more sensitive with early glaucoma patients than existing predictive systems, and more specific when testing those with advanced glaucoma.

What's Next?

Once our system is thoroughly tested, its use should help clinicians distinguish between fast and slow progressors, directing more aggressive treatment to those patients who need it and helping to prevent unneeded treatment side effects and problems in patients who don't. The software is not part of any commercial product at present (which may be partly because it can be seen as a competing approach to existing analysis tools). However, there's nothing secret about it and we don't have any proprietary interest in it. We've already published the technique, so anybody can create similar software; there's enough detail in the published articles to tell you exactly how to do it. Furthermore, anyone who has the skills and interest can tweak what we've developed.

At this point we're still working on a Web-based version of the concept, and we expect to be ready to share it pretty soon. Once we feel that it's perfected, anyone is welcome to use it. In the meantime, as the system proves its value, we expect that manufacturers will eventually choose to incorporate it into their products.

For now, I think it's important to note that not only do our studies support the validity of the software program, they support the concept that accurate prediction of future progression depends largely on paying attention to the damaged areas of the visual field, not just global analyses. So until software for this purpose is available, I encourage clinicians to remember to focus on those areas when trying to decide which patients need intensive treatment. REVIEW

Dr. Caprioli is the David May II Professor of Ophthalmology, chief of the glaucoma division and director of the Glaucoma Basic Science and Clinical Laboratories at the Jules Stein Eye Institute in Los Angeles.

1. Caprioli J, Mock D, Bitrian E, et al. A method to measure and predict rates of regional visual field decay in glaucoma. Invest Ophthalmol Vis Sci 2001;52;7;4765-73.
2. Azarbod P, Mock D, Bitrian E, et al. Validation of pointwise exponential regression to measure the decay rates of glaucomatous visual fields. Invest Ophthalmol Vis Sci 2012;53:5403-5409.

CME

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Ophthalmologist Program
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Nurse, Technician & Office Staff Program Provided by ASORN
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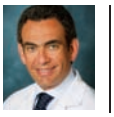


Reports from the U.S. SMILE Study

A look at the U.S. trial for the new, all-femtosecond-laser refractive procedure performed with the Visumax laser.

Walter Bethke, Managing Editor

U.S. refractive surgeons would no doubt enjoy a procedure with the rapid healing profile of LASIK but which only required one piece of equipment. They came a step closer to this goal with the submission of the first set of data for Carl Zeiss Meditec's all-femtosecond, small-incision lenticule extraction procedure to the Food and Drug Administration. Here's a look at the procedure and how it's faring in its first U.S. trial.

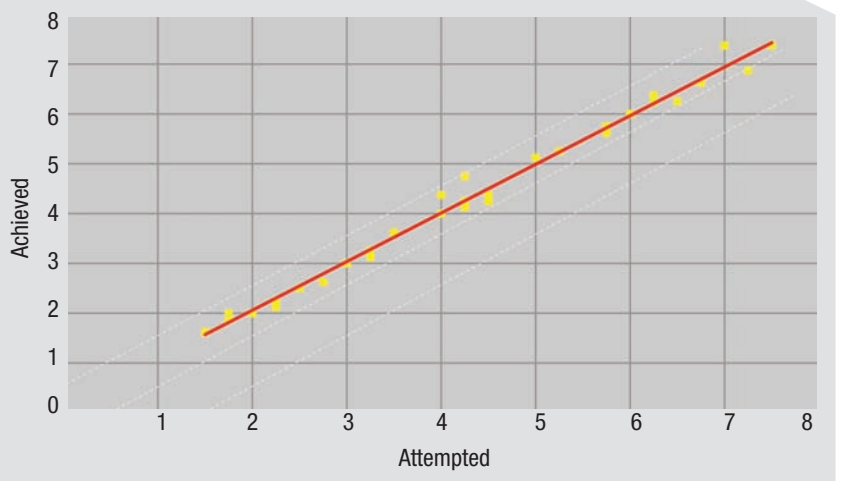
The SMILE Procedure

The SMILE procedure uses the Visumax femtosecond laser to create an intrastromal refractive change in the cornea.

"In SMILE, the surgeon uses the Visumax to create a posterior refractive pass," explains John Doan, MD, of St. Louis, one of the study's principal investigators. "He then makes an anterior intrastromal pass that's planar to the corneal surface. The posterior cut is a lenticular refractive cut and the anterior is simply the front surface of the lenticule, which has no refractive power. So, instead of vaporizing quarter-micron pieces of tissue, we're creating a three-dimensional lenticule that we extract through this small incision. The removal of this lenticule induces central flattening in the cornea that treats the myopia. In that way, it's somewhat analogous to the procedure automated lamellar keratoplasty, in which the surgeon made two passes with the microkeratome and removed a lenticule of tissue." The incision that's used to remove the lenticule is angled anywhere from 60 to 90 degrees. The lenticule itself is approximately 6.5 mm in diameter, and the outer dimension of the pocket that's created is 8 mm.

"At the conclusion of the case, we remove the lenticule and spread it out on the anterior surface of the cornea to make sure there aren't any missing pieces," Dr. Doane explains. "If there are any, your only option at that point is to create a flap and look for the missing pieces, because you wouldn't be able to see them otherwise." The postop regimen is similar to LASIK's,

MRSE Predictability (Diopters) at Three Months



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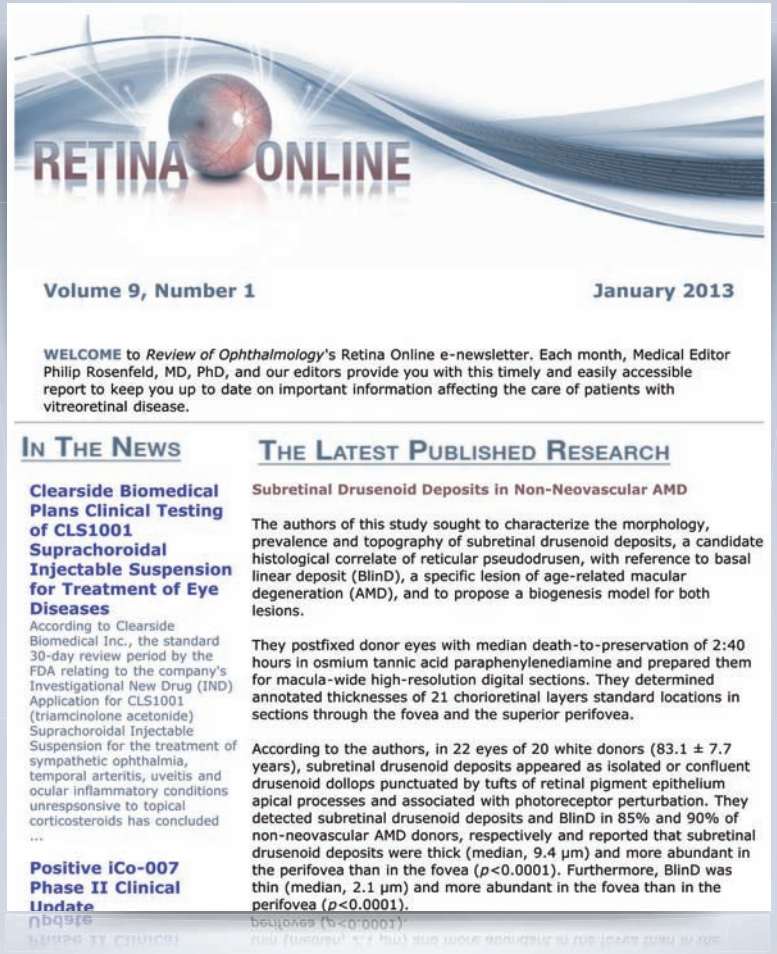

RETINA ONLINE

Volume 9, Number 1 January 2013

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

Clearside Biomedical Plans Clinical Testing of CLS1001 Suprachoroidal Injectable Suspension for Treatment of Eye Diseases

According to Clearside Biomedical Inc., the standard 30-day review period by the FDA relating to the company's Investigational New Drug (IND) Application for CLS1001 (triamcinolone acetonide) Suprachoroidal Injectable Suspension for the treatment of sympathetic ophthalmia, temporal arteritis, uveitis and ocular inflammatory conditions unrespsonsive to topical corticosteroids has concluded ...

Positive iCo-007 Phase II Clinical Update

THE LATEST PUBLISHED RESEARCH

Subretinal Drusenoid Deposits in Non-Neovascular AMD

The authors of this study sought to characterize the morphology, prevalence and topography of subretinal drusenoid deposits, a candidate histological correlate of reticular pseudodrusen, with reference to basal linear deposit (BlinD), a specific lesion of age-related macular degeneration (AMD), and to propose a biogenesis model for both lesions.

They postfixed donor eyes with median death-to-preservation of 2:40 hours in osmium tannic acid paraphenylenediamine and prepared them for macula-wide high-resolution digital sections. They determined annotated thicknesses of 21 chorioretinal layers standard locations in sections through the fovea and the superior perifovea.

According to the authors, in 22 eyes of 20 white donors (83.1 ± 7.7 years), subretinal drusenoid deposits appeared as isolated or confluent drusenoid dollops punctuated by tufts of retinal pigment epithelium apical processes and associated with photoreceptor perturbation. They detected subretinal drusenoid deposits and BlinD in 85% and 90% of non-neovascular AMD donors, respectively and reported that subretinal drusenoid deposits were thick (median, 9.4 µm) and more abundant in the perifovea than in the fovea ($p<0.0001$). Furthermore, BlinD was thin (median, 2.1 µm) and more abundant in the fovea than in the perifovea ($p<0.0001$).

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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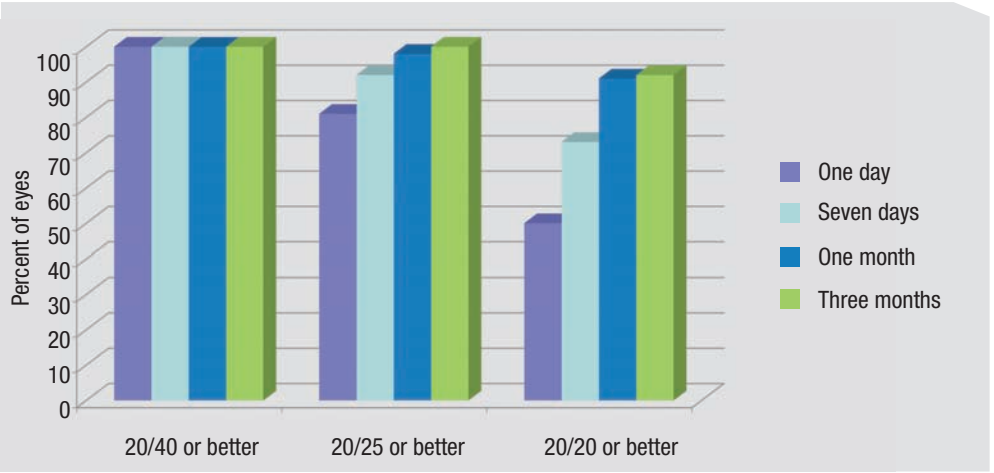
SMILE Patients' Uncorrected Vision Results



consisting of steroid and antibiotic drops for a week, with regular follow-up visits.

The Results

Though Carl Zeiss Meditec isn't sharing all of the data on the full 100 patients that have been submitted to the FDA from the SMILE study, Dr. Doane is able to discuss the outcomes of his 64 study patients.

In the trial, patients had SMILE in one eye and LASIK in the other. In Dr. Doane's 64 patients, the average sphere was -4.39 D (r: -1.5 to -7.5) and the average cylinder was -0.14 D (r: zero to -0.5 D). The average spherical equivalent refraction was -4.46 D (r: -1.63 to -7.75 D). In the 53 patients available for follow-up at a month, the average SE was -0.11 (r: -0.75 to +0.38 D), with the average sphere being zero and average astigmatism -0.21 D. For the 37 patients available at three months, the average SE was -0.06 D. All of the patients see 20/25 or better uncorrected postoperatively.

Dr. Doane says the treatment proved to be highly predictable. Using regression analysis, where an R2 value of 1 would mean perfect predictability between attempted and achieved refractions, in the SMILE study at three months the R2 value was 0.99. "What was interesting is that the predictability for 1 to 3 D treatments is just as good as LASIK," Dr. Doane says. "However, for treatments of 6 to 8 D, LASIK's predictability isn't as good as it is for 1 to 3 D, so there's a drop-off in how accurate we can be with the excimer. But this wasn't the case with the SMILE procedure. So far its refractive predictability has been just as good with 6- to 8-D corrections as it is with the 1- to 3-D treatments.

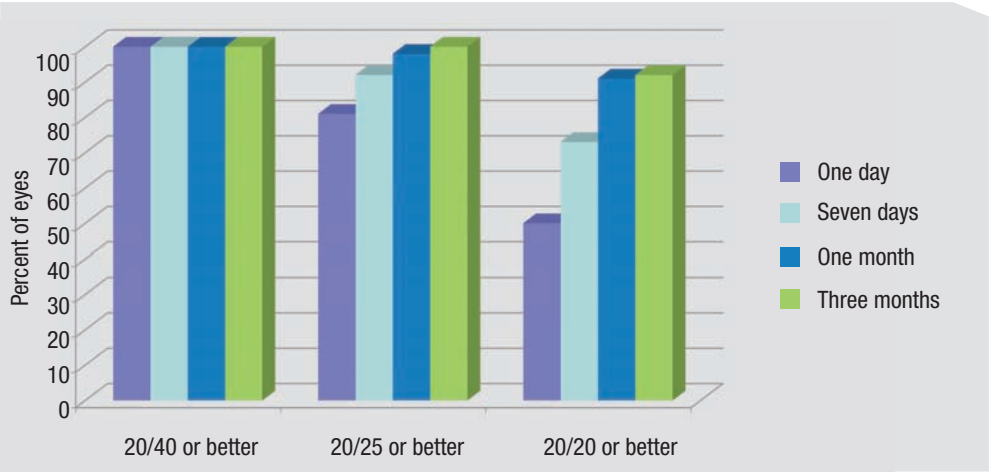
"The patients have essentially been exactly where we want them to be in terms of refraction," Dr. Doane continues. "Unlike the excimer, which needs to travel through the air before it hits the cornea and can therefore be affected by volatile substances such as particulates in the air or perfume, with the femtosecond we're docked with the cornea, so it's a completely closed system. The system is closed tighter still with SMILE because you're doing the photodisruption within the cornea."

In terms of safety, Dr. Doane says none of the eyes lost two lines of vision. "There is nothing new or out of the ordinary in terms of the incidence of complications associated with typical corneal refractive surgery," he says. "There have been no infections and no epithelial ingrowth. There have been cases of mild diffuse lamellar keratitis in a few eyes as surgeons got used to the new technique, but nothing that's led to lost lines of best-corrected vision. There can be an epithelial defect, which I've seen myself, but we also see that with LASIK."

At this point, though SMILE proponents would like to think the field is moving toward all-femtosecond procedures, if an enhancement is necessary after SMILE, it's acknowledged that you still need an excimer to do it. "Right now, it appears that enhancement rates will be lower than with LASIK since it appears that SMILE is more predictable across the range of corrections," says Dr. Doane, referring to the tight R2 value. "But if you had to do an enhancement, the options are to do a PRK, so you go back to an excimer, or creating a flap and doing an ablation in the stromal bed, which also involves an excimer. There's also the possibility, though it's just in the concept stage at this point, of doing layers of photodisruptive pulses in the stroma with the femtosecond to resolve whatever minimal refractive error is there. This approach hasn't been done yet, though."

Looking down the road, Dr. Doane says Carl Zeiss Meditec is awaiting FDA approval to begin the final Phase III study of the device, and that the eventual approval may also involve compound myopic astigmatism in addition to just simple myopia. "Then we'll have to see if we can treat mixed astigmatism and if we want to treat hyperopia," he says. REVIEW

SMILE Patients' Uncorrected Vision Results



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Supplements Improve Macular Pigmentation

After a 12-month intervention, German researchers concluded that a supplement containing a fixed combination of xanthophylls (lutein and zeaxanthin) and ω-3 long-chain polyunsaturated fatty acids (LC-PUFA) significantly improved plasma antioxidant capacity, circulating macular xanthophyll levels and the optical density of macular pigment in patients with nonexudative AMD,

A total of 145 individuals with nonexudative AMD were randomly divided as follows: placebo group; group 1 (a daily capsule containing lutein 10 mg, zeaxanthin 1 mg, docosahexaenoic acid 100 mg and eicosapentaenoic acid 30 mg); and group 2 (double the dose of substances used in group 1).

After a month of intervention, the concentrations of the administered carotenoids in plasma as well as the optical density of the macular pigment increased significantly in the groups randomized to receive supplementary macular xanthophylls and ω-3 LC-PUFAs; these concentrations remained stable though the end of the study. Use of the double dose of xanthophyll and LC-PUFA supplements in group 2 resulted in a beneficial alteration of the fatty acid profile in the plasma of patients with AMD in comparison with group 1. The lipophilic antioxidant capacity in plasma was also significantly elevated.

JAMA Ophthalmol 2013;131:564-572.
Arnold C, Winter L, Fröhlich K, Jentsch S, et al.

Visual Outcome of Cataract Surgery from the ERQOCRS

Fifteen European cataract surgery clinics participated in a database study to analyze visual outcomes after cataract surgery; the data supports excellent outcomes. A majority of patients (61.3 percent) achieved a corrected distance visual acuity of 1.0 (20/20) or better. While age and sex influenced outcomes, the greatest influences were short-term postoperative complications, ocular comorbidity, surgical complications and complex surgery.

Data were drawn from case series of cataract extractions reported to the European Registry of Quality Outcomes for Cataract and Refractive Surgery database; 368,256 cataract extractions were available for analysis. Case series data was entered into the database by surgeons, by transfer from existing national registries or by electronic medical record systems. The database contains individual anonymous data on preoperative, intraoperative and postoperative measures.

The best visual outcomes were achieved in age groups 40 to 74 years, with men showing a higher percentage of excellent vision (1.0 [20/20] or better). A corrected distance visual acuity of 0.5 (20/40) or better and of 1.0 (20/20) or better was achieved in 94.3 percent and 61.3 percent of cases. Ocular comorbidity and postoperative complications were the strongest influences on the visual outcomes, but surgical complications and ocular changes requiring complex surgery also had a negative influence. Deterioration of visual acuity after the surgery (n=6,112 [1.7 percent of cases]) was most common in patients with a good preoperative visual acuity. The researchers also note that a weakness of the study could be the self-reported nature of some data to the registry.

J Cataract Refract Surg 2013;39:673-679.
Lundström M, Barry P, Henry Y, Rosen P, et al.

Corneal Thickness as Predictor Of Corneal Transplant Outcome

A new report from the Cornea Donor Study shows that in the first five years after penetrating keratoplasty, corneal thickness can serve as a predictor of corneal graft survival. However, CT is not a substitute for cell density measurement because both measures are independently predictive of graft failure.

A total of 887 patients with a corneal transplant for a moderate-risk condition (principally Fuchs' dystrophy or pseudophakic corneal edema) had postoperative CT measurements throughout a five-year follow-up time. Relationships between baseline (recipient, donor and operative) factors and CT were explored. Proportional hazards models were used to assess the association between CT and graft

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failure. Relationship between CT and cell density was assessed with a longitudinal repeated measures model and Spearman correlation estimates.

Higher longitudinal CT measurements were associated with the following: diagnosis of pseudophakic or aphakic corneal edema ($p<0.001$); intraocular pressure >25 mmHg during the first postoperative month ($p=0.003$); white (non-Hispanic) donor race ($p=0.002$); and respiratory causes of donor death ($p<0.001$). Among those without graft failure within the first postoperative year, the five-year cumulative incidence of graft failure (±95 percent CI) was 5 percent ±5 percent in those with a one-year CT ≤500 µm; 5 percent ±3 percent for CT 501 to 550 µm; and 20 percent ±11 percent for CT >600 µm. In a multivariate analysis, both one-year CT and cell density were associated with subsequent graft failure ($p=0.002$ and 0.009). CT increase was modestly associated with endothelial cell loss during follow-up (r= -0.29).

Cornea 2013;32:729-736.
Verdier D, Sugar A, Baratz K, Beck R, et al.

Patient Preferences Between Botox and Xeomin in BEB

According to doctors in Missouri, patients with benign essential blepharospasm treated with both onabotulinumtoxinA (Botox) and incobotulinumtoxinA (Xeomin) who prefer Xeomin over Botox had a statistically significant shorter treatment interval. In addition, those who preferred Xeomin thought it was more effective; patients who preferred Botox thought it had a longer duration of effect.

Fifty patients with BEB being treated with Botox were switched to Xeomin. At a scheduled follow up, patients decided to either continue with the Xeomin or switch back to Botox, and preferences regarding treatment were recorded. The preference groups were then analyzed using unpaired Student t test, with the statistical significance set at $p<0.05$.

The mean age of the 50 Xeomin patients was 64.9 years; 39 (78 percent) were women and 11 (22 percent) were men. In all, 26 (52 percent) preferred Xeomin and 24 (48 percent) preferred Botox. Those who preferred Xeomin believed that it was "more effective" (n=10; 29 percent), while those who preferred Botox concluded that it had a "longer duration" (n=11; 37 percent). The mean treatment interval was 13 weeks (SD=6.39) in those who preferred Botox, whereas it was 10.2 weeks (SD=2.15) in those who preferred Xeomin ($p=0.017$). There was no statistical difference when comparing mean disease duration, number of total treatments and number of units/treatment between the two preference groups.

Ophthal Plast Reconstr Surg 2013;29:205-207.
Chundury R, Couch S, Holds J.

Endothelial Graft Failure After Contralateral APK

Bascom Palmer Eye Institute and the Miami Veterans Affairs Hospital are the first to describe graft failure because of slow endothelial attenuation after contralateral autologous corneal transplantation (APK).

Five patients received a contralateral APK and a simultaneous allogeneic penetrating keratoplasty in the donor eye at the Bascom Palmer Eye Institute and the Miami Veterans Affairs Hospital. Median patient age at the time of surgery was 67 years (r: 58 to 88 years); four patients were male and one female; one patient was white and four were black. The surgeries were uneventful and no operative or immediate postoperative complications occurred in either eye. During follow-up (r: 18 to 54 months; mean: 35 months; median: 34 months), four autologous grafts failed because of endothelial attenuation. Identified risk factors for failure in the autologous eyes included the presence of a glaucoma tube (5/5), previous graft failure (4/5) and anterior synechiae (2/5).

Cornea 2013;32:745-750.
Martinez J, Galor A, Perez V, Karp C, et al.

Antibiotic-resistant Ocular Surface Flora After IVT Injection

Repeated use of topical moxifloxacin after intravitreal injection appears to increase antibiotic resistance in ocular surface flora. Because of this, researchers recommend that routine use of prophylactic antibiotics after IVT injection be discouraged.

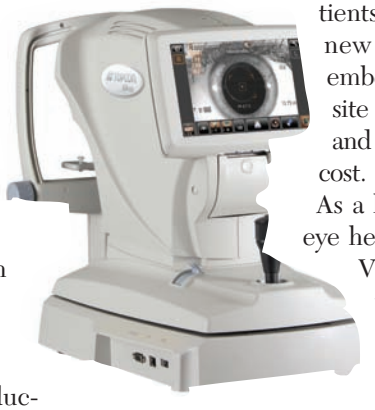
Patients 65 years and older with newly diagnosed age-related macular degeneration were recruited by seven retinal specialists from July 1, 2010 through December 31, 2011. The study group (n=84) received topical moxifloxacin hydrochloride for three days after each monthly IVT injection, while the control group (n=94) received no topical antibiotics after injection. Researchers measured the resistance to moxifloxacin and ceftazidime in cultured isolates at baseline and monthly for three months in both groups, studying the changes in the minimal inhibitory concentration of culture isolates.

In the study group, the baseline adjusted MIC increased from 1.04 to 1.25 µg/mL ($p=0.01$), the MIC for 50 percent of isolates (MIC_{50}) increased from 0.64 to 1.00 µg/mL and the MIC for 90 percent of isolates (MIC_{90}) increased from 0.94 to 4 µg/mL. In both groups, the culture-positive rate did not change significantly when adjusted for baseline. No significant change was found in the MIC level, culture-positive rate, MIC_{50} level or MIC_{90} level in the control group. Subgroup analysis found diabetes mellitus to be noncontributory to both the MIC and culture-positive rate.

JAMA Ophthalmol 2013;131:456-461. Published online February 21, 2013. doi:10.1001/jamaophthalmol.2013.2379.

Topcon Debuts New Auto Refractor Series

Topcon Medical Systems of Oakland, N.J., has released its new KR/RM-800 product line. Based on 60 years of manufacturing experience, the KR-800 Auto Kerato-Refractometer and the RM-800 Auto Refractor incorporate the very latest in design technology and ergonomics. Featuring a high-resolution 8.5-inch color touch screen, a compact modern design and an improved joystick operation due to a 23-percent reduction in weight, the KR-800/RM-800 take ease-of-use and operability to a new level.



This latest generation auto refractor series from Topcon features the proven Rotary Prism Technology, for unparalleled accuracy and reliable keratometric and refraction measurements every time. In addition, it has a built-in, easy-to-load printer and LAN and RS232 connectivity for easy integration with other ophthalmic instruments, including the Topcon CV-5000S Automated Vision Tester and EMRs. Topcon expected to begin delivering these new products at the end of June. For information, visit topconmedical.com.

Free Educational Videos for Practitioner Websites

Eye-care professionals can help their websites look polished and educational to potential and current patients with AllAboutVision.com's new eye-health videos. These embeddable videos provide website visitors with an entertaining and educational resource—at no cost.

As a leading online resource for eye health information, AllAboutVision.com is linked to by thousands of eye-care practitioners who wish to direct their patients to reliable, up-to-date information. With these new eye-health videos, practitioners can enhance their websites and take patient education to new heights.

Four videos available cover the basics of astigmatism, cataract surgery, blurry vision and preventing eye injuries. Interested practitioners should visit AllAboutVision.com's Eye Care Professional portal and fill out a video request form. In addition to the newly available eye health videos, AllAboutVision.com also offers practitioners free directory listings and a free Eye Health News Feed for Facebook pages. For information visit AllAboutVision.com.

Boost: New Line of Cosmetic Products for Sensitive Eyes

Ocusoft has introduced Zoria Boost Lash Intensifying Serum, the first in its new line of cosmetic products for sensitive eyes. Utilizing patented polypeptide technology, Zoria Boost naturally enhances and supports the eyelash growth cycle for dramatically longer, fuller and darker looking eyelashes, the company says.

The product was developed by ophthalmologist and biochemist, Lili Fan, MD, who holds numerous patents for polymeric and oligomeric biosurfactants. The drug-free formula is non-irritating and delivers noticeable results

This article has no commercial sponsorship.

without the potential side effects associated with other lash-enhancement products. It is safe for contact lens wearers and ideal for those with sensitive eyes. Simply apply Zoria Boost on the lash line before bedtime to nurture, strengthen and condition eyelashes. Zoria Boost will be marketed to and distributed by eye-care professionals without a prescription. Also available in the Zoria Cosmetics line is Zoria Mascara, a flake-free, hypoallergenic formula for sensitive eyes as well as Zoria Make-up Remover and Facial-Skin Cleanser. For information, call 1 (800) 233-5469 or visit ocusoft.com.

Publication Offers Insider's Look at Ophthalmic Pioneers

Today's ophthalmologists are more adept at saving sight than ever before. Eye surgeons of the past would marvel at the ability to remove cataracts in minutes, perform LASIK surgery, and implant retinal microchips that return sight to the blind. And yet, how well do ophthalmologists remember the innovators who preceded them? The very doctors whose inventions enable them to save sight each day?

Saving Sight: An Eye Surgeon's Look at Life Behind the Mask and the Heroes Who Changed the Way We See, is a newly released book by Andrew Lam, MD, that profiles ophthalmology's heroes: men like Ridley, Kelman, Schepens, Patz and others. "Their stories contain all the elements of a blockbuster Hollywood movie: courage; adversity; serendipity; and perseverance," says Dr. Lam. "I was surprised by how few people knew their stories, and thought that everyone should."

In *Saving Sight*, Lam blends his memoir of surgical training at Wills Eye Hospital with the stories of ophthalmology's greatest inventors. Published by Irie Books for a general audience, the author's gritty look inside the operating room reveals the stress of performing cataract surgery for the first time, the fear of failing to extract a retina-embedded foreign body, the joy of performing LASIK, the frustration of failing to re-attach a retinal detachment, and the complexities of treating ROP.

Past AAO President, William Tasman, MD, writes: "In *Saving Sight*, Dr. Lam has beautifully captured the atom-smashing accomplishments of men who transformed the world of vision. This book is a real page-turner!" Two-time Pulitzer Prize winner Richard Wilbur writes: "Dr. Andrew Lam, a distinguished retinal surgeon, has written a wonderfully readable book about the heroic lives of the great inventors in his field. The layman will be carried away by Dr. Lam's clear, colloquial story-telling, and he will also gain, as I did, a far clearer knowledge of the human eye."

Dr. Lam is a retinal surgeon with a history degree from Yale and is currently an assistant professor at Tufts University School of Medicine. Saving Sight is available at amazon.com, barnesandnoble.com or andrewlammd.com ($12.95).

(*continued from page 41*)

better and not trying to make the patient 30-years-old again," he says. In his practice, many patients are retired professors, so they often have very high expectations. However, he says that, while the baby boom generation believes that medicine fixes everything, the older population is more cognizant of the fact that they are older and are not going to have vision like they had 30 years ago.

He recommends delivering more and promising less. "You have to be careful about what you are promising about what they are going to get," says Dr. Arleo. "If I have an engineering professor who is -6, you're going to really have to twist my arm to not leave him a -3. Many of those people will be unhappy if you make them emmetropic. You may need to have different goals for them. When we do change their visual acuity, we have to really be clear about how it will affect their lifestyle. If a person is myopic but likes hiking, you may want to make him or her emmetropic. It takes a little more counseling than with someone who is 45 or 50."

Surgeons in different parts of the country may encounter different patient expectations. For example, Dr. Arleo practices in a small city with two universities. "We have a disproportionate number of very educated elderly people. They are just as tech savvy as far as researching the docs as the younger people around here. However, that may be different in other parts of the country. I think it's very specific to your location," he says.

Snowbirds who spend part of the year in Florida or Arizona or those who relocate to more temperate areas are often engaged in more outdoor activities than those in other areas of the country, so they may value distance vision more than elderly patients in colder climates.

Dr. Arleo notes that surgeons need to be a little bit more careful about instructions with older patients. "Many of these people have hearing issues. Some might be having some dementia," he says. "We are very careful about giving them specific instructions and making sure they understand everything. Many of them are juggling multiple medications, and they have multiple doctors. I think they need a little more TLC with the logistics of everything. Fix the problem, but don't try to go for it too much." REVIEW

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Products and Services

Before reading on, please see p. 78 for presenting complaint, history and examination.

Diagnosis, Workup and Treatment

While the patient was under anesthesia, an optical coherence tomography test and electroretinography were performed. The OCT revealed retinal thinning, photoreceptor loss, poor retinal lamination and macular hypoplasia. The ERG was mildly abnormal in both eyes, with both rod and cone dysfunction. The patient was noted to have an axial length of 26.25 mm by ultrasound.

The combination of high myopia, an occipital lesion, a characteristic retinal appearance and midface hypoplasia was suspicious for Knobloch syndrome, a rare autosomal recessive developmental disorder.

Discussion

Knobloch syndrome is known to be caused by a mutation in the gene encoding for collagen 18A1 (COL18A1), which is a nonfibril-forming collagen expressed in human epithelial and endothelial basement membranes throughout the body, but particularly in ocular tissues. Our patient was found to be a compound heterozygote with a previously reported truncating mutation on one allele and a novel truncating mutation on the other allele.

The distinct ophthalmic phenotype of this disorder was characterized by Arif Khan, MD, and coworkers in 2012 in a case series of eight patients with a genetically confirmed diagnosis of Knobloch syndrome. All eight children had smooth cryptless irides, high myopia and a distinctive vitreo-retinal degeneration, which consisted of RPE atrophy, prominent choroidal vessels, macular atrophy and fibrillar vitreous condensations. Six of the children had ectopia lentis, and four of the children had posterior perinuclear opacity. Systemic associations include developmental delay, renal anomalies and pulmonary hypoplasia. Although occipital defects may be absent, abnormalities include a patch of alopecia (as seen in our patient), cutis aplasia or encephalocele.

The prognosis of children with Knobloch syndrome is greatly affected by the extent of CNS malformation, systemic involvement and increased risk of retinal detachment. The prognosis is also dependent upon whether or not there is any functional isoform of collagen 18 present.

Our patient underwent a systemic evaluation, including renal ultrasound, which was normal and did not have evidence of developmental delay. Spectacle correction improved his visual acuity and nystagmus. Goals of treatment include close monitoring for retinal tears or detachment and ectopia lentis.

Identification of additional mutations that result in Knobloch Syndrome has the potential to reveal novel molecular mechanisms that control eye development. The discovery of new mutations continues to be an important contribution to the small fund of knowledge we currently have on this rare genetic entity. REVIEW

The author would like to thank Alex Levin, MD and Wadakarn Wuthisiri, MD of the Wills Eye Institute Department of Pediatric Ophthalmology and Ocular Genetics for their assistance with the preparation of this case.

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Product News

(continued from p. 73)

Hydrating Compress for Dry Eye, MGD, Blepharitis and Chalazions

The Bruder Eye Hydrating Compress, featuring MediBeads, is a microwavable moist-heat compress that does not require hydrating and rejuvenates itself naturally. Twenty to 30 seconds in the microwave will give 10 minutes of good moist heat for the eyes, and the user can apply the compress over and over again for years, the company says. It is the only microwavable eye compress that can be totally submerged in water, washed with a mild soap, air-dried and used continually. Stye Compresses are available to cover one eye only.

The compress is sold only through doctors' offices, and is available immediately. To receive a free sample and learn more about the complete line of Bruder Ophthalmic products, including Bruder Ophthalmic Surgical instruments, call 1 (888) 827-8337, ext. 218, visit bruderophthalmic.com or e-mail eyes@bruderophthalmic.com.

REVIEW

Advertising Index

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High myopia and nystagmus in a young child prompt a referral to the Wills Pediatric Ophthalmology and Ocular Genetics Department.

Alessandra Intili, MD

Presentation

A 2-year-old Caucasian male was referred to the Wills Eye Institute Department of Pediatric Ophthalmology and Ocular Genetics by an outside physician for evaluation of high myopia and the presence of nystagmus. The onset of nystagmus occurred at 2 months of age. He had been wearing spectacles since he was 7 months, with improvement of both his visual acuity and nystagmus.

Medical History

The pregnancy was uneventful and he was born full-term by spontaneous vaginal delivery. The patient had no prior surgeries, no hospital admissions and no serious injuries. Notably, a cystic area on the occiput of the skull was discovered on fetal ultrasound. A postnatal CT was performed and no communication was found between the intracranial vault and the elevated occipital lesion. Family history and pedigree revealed no evidence of parental consanguinity or a constricted gene pool. A maternal uncle reportedly had very fair skin, an inability to tan and high myopia without nystagmus. A maternal great aunt had severe developmental delay.

Examination

General examination of the patient revealed a fair-skinned, blue-eyed child with blond hair, mild mid-facial hypoplasia, and an elevated area of alopecia at the occiput *(See Figure 1)*. Ophthalmic examination revealed a cycloplegic refraction of -21.50 +3.00 X 90 in the right eye, and -23.50 +2.00 X 75 in the left. The pupils were equal, round and reactive, without a relative afferent pupillary defect. Extraocular muscle motility was full, with horizontal, symmetrical, pendular nystagmus and an additional latent component in each eye. There was a preference for a 5 to 10 degree chin down position, with a right head tilt. There was also an exotropia of 18 prism diopters at distance, and 20 diopters at near. Intraocular pressure was 11 mmHg in the right eye and 14 mmHg in the left eye. Slit-lamp examination of the anterior segment was significant for cryptless irides with radial furrows and no transillumination defects *(See Figure 2)*.

Dilated fundus examination *(See Figure 3)* of the right eye revealed abnormal fibrillar condensations in the vitreous, anomalous optic nerves, bilateral poor foveal reflexes, and diffuse retinal attenuation with a prominent choroidal pattern. There was a geographic area of macular atrophy. Pigmentary mottling was present 360 degrees around the midperiphery. There was no evidence of retinal breaks, retinal tears or lattice degeneration.

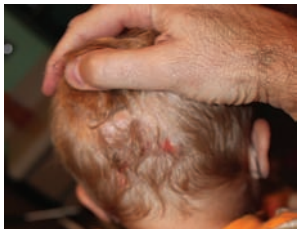

Figure 1. Posterior aspect of the patient's scalp, with a central area of alopecia overlying the putative cyst.

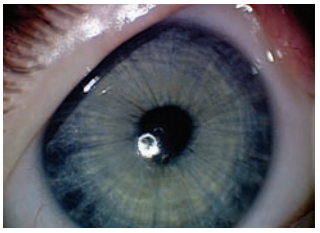

Figure 2. External photo of left eye revealing a smooth, cryptless iris.

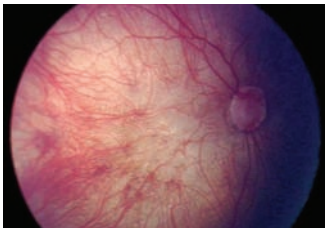

Figure 3. Color fundus photo of right eye, revealing macular hypoplasia and pigmentary mottling.

What is your differential diagnosis? What further workup would you pursue? Please turn to p. 76

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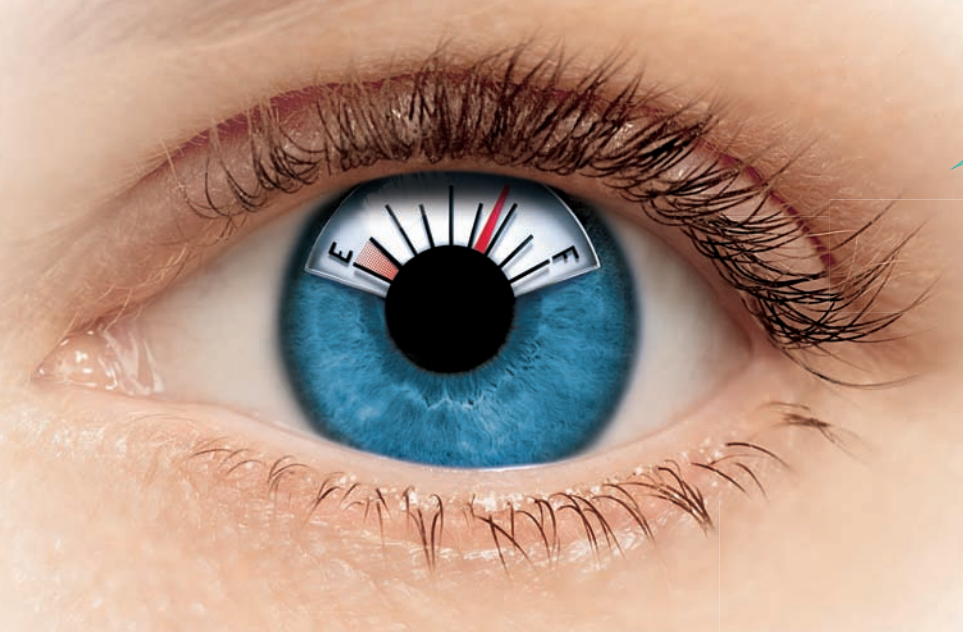

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RESTASIS® is contraindicated in patients with known or suspected hypersensitivity to any of the ingredients in the formulation.

Warnings and Precautions

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

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

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