**Demystifying viral eye disease**

Clinicians must discern which antiviral drugs may be best approach in managing patients with these conditions

**IN VIEW:**
CMV iritis and corneal endotheliitis presentation may include small keratic precipitate (KP) and KP corrals, iris atrophy, low-grade anterior chamber inflammation, and cytomegalo virus in the aqueous. While patients may not be systemically immunocompromised, they are probably locally immunocompromised.

(Image courtesy of Todd P. Margolis, MD, PhD)

**By Michelle Dalton, ELS; Reviewed by Todd P. Margolis, MD, PhD**

**ANTIVIRAL MEDICATIONS** inhibit viral replication and are thus used to treat viral infections. Their use for the management of viral keratitis is no exception. But with some viral eye disease, like adenoviral keratitis, “observation” may be treatment enough, said Todd P. Margolis, MD, PhD, the Alan A. and Edith L. Wolff Distinguished Professor and Chairman, Ophthalmology and Visual Sciences, Washington University at St. Louis, St. Louis, MO.

When patients present with herpes simplex virus (HSV) epithelial keratitis, “the first question has to be how you’re going to manage it, since there are several different options.”

If you do nothing, the immune system clears the disease in about 9 days, Dr. Margolis said. “But if you debride and patch—which has been done for thousands of years—the time for the cor-
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16 STEROIDS CAN BE AN EFFECTIVE DME TREATMENT
An anti-VEGF injection might be the favored treatment method, but there’s room for steroids as a first-line approach.

References

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Ocular effects of autoimmunity
Eight ways we may be closer to understanding how problems arise

By Peter J. McDonnell, MD
director of the Wilmer Eye Institute,
Johns Hopkins University School of Medicine, Baltimore, and chief medical editor of Ophthalmology Times.

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AUTOIMMUNE diseases such as rheumatoid arthritis, systemic lupus erythematosus, ankylosing spondylitis, and Sjogren’s syndrome afflict an estimated 100 million persons worldwide.

As an ophthalmologist, I detest these problems because they frequently cause eye disease; their etiology remains a mystery, and our therapeutic outcomes are often disappointing.

Corticosteroids represent a blunt tool to try to minimize the suffering these bodies endure from their traitorous immune systems and pile on with their well-known side effects. Adding an expensive monoclonal antibody to the marinade might or might not prove helpful in some patients, but any amelioration of the disease certainly comes at the expense of yet more potential therapy-induced adverse reactions.

With dry eye disease in particular, which commonly occurs in the setting of Sjogren’s syndrome, our therapies are substantially better than those used to treat systemic autoimmune disease. Topical corticosteroids often improve signs and symptoms, and we have two FDA-approved agents that work by reducing the injurious effects of T-cells on the lacrimal gland and ocular surface.

GETTING CLOSER TO UNDERSTANDING

Mountains of data generated by genetic analysis and analyzed by bioinformatics experts using supercomputers are pointing to a potential culprit: Epstein-Barr virus (EBV, HHV-4).

A few tantalizing facts:

1. After initial exposure, the virus can hide in our bodies at levels too low for our host defense mechanisms to detect and eradicate.
2. People who have been infected with Epstein-Barr virus but are otherwise normal have >2% of their T cells reacting to the virus. As two experts recently observed: “With the tens of thousands of organisms against which the ordinary person must continually defend themselves, this is an astonishingly high proportion of the host’s T cell repertoire.”
3. EB infection increases a child’s risk of developing systemic lupus erythematosus by 50-fold.
4. Patients with Sjogren’s syndrome have “ectopic lymphoid structures” in their salivary glands and these serve as a unique home for Epstein-Barr virus latency and subsequent reactivation.
5. A recent paper in the journal Nature shows that a protein produced by EB virus-infected cells (EBNA2) binds to nearly half of the chromosomal loci known to increase the risk of development of systemic lupus erythematosus.
6. Similar EBNA2 binding to DNA risk alleles with effects on gene expression are shown to exist in multiple sclerosis, rheumatoid arthritis, inflammatory bowel disease, type 1 diabetes, juvenile idiopathic arthritis and celiac disease.
7. Acting as a transcription factor, this viral EBNA2 protein regulates gene expression in a manner that appears to explain much of the risk related to the development of these important and common autoimmune diseases.
8. There are drugs available that have the ability to bind to and inhibit the EBNA2 protein. This indicates that, if EB infection is the inciting mechanism for Sjogren’s syndrome and these other autoimmune disease, it may be possible to block the virus-generated protein from interacting with our human chromosomes and condemning patients to a lifelong struggle with one of these terrible problems.

Future ophthalmologists will no doubt look back at how we treat many patients today and shake their heads at our ignorance. Every generation of doctors does this. Wouldn’t it be great to know why so many people are afflicted with diseases like Sjogren’s syndrome and have a new, specific way to treat them?

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**Important Safety Information**
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In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.

Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration. Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information, see accompanying Brief Summary of Safety Information on the adjacent page and Full Prescribing Information on Xiidra-ECP.com.
Brief Summary: Consult the Full Prescribing Information for complete product information.

Indications and Usage: Xiidra® (lifitegrast ophthalmic solution) 5% is indicated for the treatment of the signs and symptoms of dry eye disease (DED).

Dosage and Administration: Instill one drop of Xiidra twice daily (approximately 12 hours apart) into each eye using a single-use container. Discard the single-use container immediately after using in each eye. Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.

Contraindications: Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients in the formulation.

Adverse Reactions: Clinical Trials Experience: Because clinical studies are conducted under widely varying conditions, adverse reaction rates observed in clinical studies of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. In five clinical studies of dry eye disease conducted with lifitegrast ophthalmic solution, 1401 patients received at least 1 dose of lifitegrast (1287 of which received lifitegrast 5%). The majority of patients (84%) had ≤3 months of treatment exposure. 170 patients were exposed to lifitegrast for approximately 12 months. The majority of the treated patients were female (77%). The most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.

Postmarketing Experience: The following adverse reactions have been identified during postapproval use of Xiidra. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Rare cases of hypersensitivity, including anaphylactic reaction, bronchospasm, respiratory distress, pharyngeal edema, swollen tongue, and urticaria have been reported. Eye swelling and rash have been reported.

Use in Specific Populations: Pregnancy: There are no available data on Xiidra use in pregnant women to inform any drug associated risks. Intravenous (IV) administration of lifitegrast to pregnant rats, from pre-mating through gestation day 17, did not produce teratogenicity at clinically relevant systemic exposures. Intravenous administration of lifitegrast to pregnant rabbits during organogenesis produced an increased incidence of omphalocele at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD], based on the area under the curve [AUC] level). Since human systemic exposure to lifitegrast following ocular administration of Xiidra at the RHOD is low, the applicability of animal findings to the risk of Xiidra use in humans during pregnancy is unclear.

Animal Data: Lifitegrast administered daily by intravenous (IV) injection to rats, from pre-mating through gestation day 17, caused an increase in mean preimplantation loss and an increased incidence of several minor skeletal anomalies at 30 mg/kg/day, representing 5,400-fold the human plasma exposure at the RHOD of Xiidra, based on AUC. No teratogenicity was observed in the rat at 10 mg/kg/day (460-fold the human plasma exposure at the RHOD, based on AUC). In the rabbit, an increased incidence of omphalocele was observed at the lowest dose tested, 3 mg/kg/day (400-fold the human plasma exposure at the RHOD, based on AUC), when administered by IV injection daily from gestation days 7 through 19. A fetal No Observed Adverse Effect Level (NOAEL) was not identified in the rabbit.

Lactation: There are no data on the presence of lifitegrast in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to lifitegrast from ocular administration is low. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for Xiidra and any potential adverse effects on the breastfed child from Xiidra.

Pediatric Use: Safety and efficacy in pediatric patients below the age of 17 years have not been established.

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

Nonclinical Toxicology: Carcinogenesis, Mutagenesis, Impairment of Fertility: Carcinogenesis: Animal studies have not been conducted to determine the carcinogenic potential of lifitegrast. Mutagenesis: Lifitegrast was not mutagenic in the in vitro Ames assay. Lifitegrast was not clastogenic in the in vivo mouse micronucleus assay. In an in vitro chromosomal aberration assay using mammalian cells (Chinese hamster ovary cells), lifitegrast was positive at the highest concentration tested, without metabolic activation. Impairment of fertility: Lifitegrast administered at intravenous (IV) doses of up to 30 mg/kg/day (5400-fold the human plasma exposure at the recommended human ophthalmic dose [RHOD] of lifitegrast ophthalmic solution, 5%) had no effect on fertility and reproductive performance in male and female treated rats.

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How MIGS benefits those with the greatest of needs

Charitable missions provide long-lasting care to patients in underserved areas of the world

By Stuart Sondheimer, MD; Special to Ophthalmology Times

According to a 2014 study by the American Academy of Ophthalmology (AAO), worldwide prevalence of glaucoma is expected to skyrocket, from 64.3 million in 2013, to 111.8 million by 2040. Whether due to lack of diagnosis or limited treatment, patients in the developing world will disproportionately suffer from preventable blindness due to glaucoma. Fortunately, new technology in combination with charitable missions has the chance to make a real difference for the future of glaucoma patients around the globe.

There are many challenges to treating glaucoma in developing countries, particularly in the rural areas. Frequently, patients have never had an eye examination, and are even less likely to have ever seen an ophthalmologist. Here, Stuart Sondheimer, MD, shares a moment with a patient the day after surgery.

In the United States, those prescribed ocular hypotensive medications have dismal adherence rates. We can expect that to be the case in developing countries as well, particularly because adherence is closely tied to health literacy, and rural populations generally have little understanding of a chronic disease with no immediate manifestations.

The same technology that is transforming glaucoma care in the developed world has the potential to make a major impact in these disadvantaged populations. One of the greatest benefits of microinvasive glaucoma surgeries (MIGS) is that they are designed to provide continuous, sustained lowering of pressure, and can help reduce the burden of topical medications.

They also have high-safety profiles, and are ideal in areas where medical follow-up is unlikely. Because MIGS devices are coupled with cataract surgery, they are an ideal complement to the work done by SEE International.

The non-profit organization uses volunteer ophthalmologists to provide medical services to disadvantaged individuals worldwide, focusing on cataract surgery. SEE deploys small surgical teams of volunteer ophthalmologists to local host clinic sites that are in desperate need of care.

The surgical team in San Pedro Sula, Honduras.

New technology in combination with charitable missions has the chance to make a difference.
need of help. Since they started in 1974, SEE volunteers have performed 4 million vision screenings and 500,000 ophthalmic surgeries in more than 80 countries.

SEE also fosters a network of corporate donors who provide most of the supplies. Glaukos Corp. recently donated 575 trabecular micro-bypass stents (iStents) to SEE, in addition to gonioprisms, supporting individual surgical programs, and coordinating physician training.

This past August, I had the privilege of participating in a mission to Honduras, and worked with Diego Mejia, MD, who heads the local clinic. Dr. Mejia and I operated on 20 cataract cases and implanted iStents in 12 of those cases.

An important part of missions is always to train the local surgeons. Drs. Mejia and Sondheimer operated on 20 cataract cases and implanted iStents in 12 of those cases.

The majority of the patients served in these surgical trips have no access to ophthalmic care otherwise. MIGS devices are well-suited in these settings as they are minimally invasive treatments with good long-term safety and no reliance on medications. It is comforting to know that we are restoring their vision with cataract surgery while also preventing glaucoma from having a negative impact.

However, he cautioned, “they have a learning curve. You need an experienced instructor to teach you, and a steady pair of hands. It took me around five operations before I felt comfortable implanting the stent without help.”

**CUSTOMIZING THE STENT**

In the United States, FDA guidelines dictate that a single iStent can be implanted in conjunction with cataract surgery. However, in Honduras and other countries we have more liberty to use the iStents as we see best for the patient.

Studies show that implanting two iStents in conjunction with phacoemulsification increases efficacy. A study by Ahmed and colleagues shows that two iStents plus phaco reduced unmedicated IOP more than 7 mm Hg.6

Another study by Belovay, Ahmed, and others shows the use of two or three microbypass stents with concurrent cataract surgery can achieve IOP less than 15 mm Hg.7

**References**


**PROVIDING CARE**

(Continued from page 9)

TAKE-HOME

» In parts of the world where people have limited access to ophthalmic care, MIGS and cataract procedures are able to provide long-term treatment when follow-up is unlikely.

**STUART SONDHEIMER, MD**

Dr. Sondheimer is a board-certified ophthalmologist in Skokie, IL. He specializes in LASIK and cataract surgery. Dr. Sondheimer has volunteered with SEE International since 2008, traveling to volunteer humanitarian clinics in Vietnam, El Salvador, Honduras, and Panama. Dr. Sondheimer did not indicate any relevant financial disclosures.
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PFVS new name, old problem?

Three forms of persistent fetal vasculature syndrome identified; each treated differently

By Lynda Charters; Reviewed by Michael Trese, MD

What's a name? When it comes to ophthalmology, a lot. Persistent hyperplastic primary vitreous—an old name that addresses only the status of the primary vitreous—needs updating, according to Michael Trese, MD.

Persistent fetal vasculature syndrome (PFVS), coined by Morton Goldberg, MD, seems more relevant because PFVS includes both the primary vitreous and tunica vasculosa lentis (TVL).

“PFVS is a vitreoretinal dystrophy,” said Dr. Trese, clinical professor of ophthalmology, Eye Research Institute, Associated Retinal Consultants, Oakland University, William Beaumont School of Medicine, Royal Oak, MI.

During normal development, the vessels fill the vitreous cavity. Usually the largest is the hyaloid artery from the disc to the lens in the area of the Mitendorf dot. This involutes by apoptosis beginning at 28 weeks of gestational age and is complete by the time of birth usually leaving Cloquet’s canal. The vessels that engulf the lens, the TVL, generally regress in a similar fashion, according to Dr. Trese.

Three presentations of PFVS have been recognized.

CLASSIC PFVS

The first, classic PFVS, is 90% unilateral and the affected eye is smaller than the fellow eye. Leukocoria at birth usually is when PFVS is discovered with no or a poor view of the posterior pole. The ciliary processes are pulled in.

Retinal dysplasia is the rate-limiting step for vision in all three forms of PFVS. A stalk is present from the optic nerve to the lens that can result from a tiny vessel or a larger stalk.

A variation of the classical anterior form may include multiple stalks that extend from other parts of the retina to the lens. A posterior form is characterized by a “star fish” appearance of the retina with small areas of retinal detachment around the disc that pull in to a stalk that does not reach the lens, he noted.

Surgical management of the classical form of PFVS usually is by a two-port vitrectomy.

“The white material and the capsule are removed,” Dr. Trese said. “The posterior pole determines whether or not vision will be possible.”

In some cases parts of the retina may retain some function.

THE ECCENTRIC STALK

The second PFVS presentation, the eccentric stalk, presents when the patient is 6 to 8 months of age with strabismus. A stalk can extend from the disc to the lens wrapped posteriorly with a traction retinal detachment that drags or detaches the fovea and causes the strabismus.

Following vitreous surgery, the strabismus can be reversed without muscle surgery. The lens insertion of the stalk generally does not involve the visual axis. The stalk can regress markedly when it is divided and not removed. Macroscopic or microscopic retinal dysplasia can limit vision.

During pars plana vitrectomy to manage an eccentric stalk, the eye is entered using an infusion light pipe. The light pipe is put in the eye but the infusion is off so as not to disrupt the attachment between the stalk and the posterior lens capsule; disturbing that tissue can result in development of a white cataract in a short time, he noted.

When good visualization of the interior of the eye has been achieved, vertical scissors are introduced and the stalk is divided as close as possible to the lens without damaging the capsule. In a representative case, Dr. Trese reported that 6 months postoperatively the stalk regressed completely.

“The surgeon does not have to remove the stalk in these cases with the associated potential of removing the surrounding retinal tissue,” he said.

MULTIFOCAL PFVS

The third presentation, multifocal PFVS, is new and became recognized with the introduction of widefield fluorescein angiography (FA).

“With widefield FA, we found that PFVS often has a small- to medium-sized avascular peripheral retina,” he said. “This is important.”

This new form of PFVS is characterized by areas of vessel remnants along the retinal surface and at the disc that do not behave as new vessels. They are thought to be isolated parts of the primary vitreous that did not involute. This is seen in eyes with avascular peripheral retina.

The genetically driven apoptotic involution of the PFV vessels is blocked by vascular endothelial growth factor (VEGF) as in retinopathy.

Continues on page 14: Syndrome
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Lamina cribrosa deformation may be prognostic factor in glaucoma

How much the lamina cribrosa curves inward could play role in defining history of disease

By Fred Gebhart; Reviewed by Ahnul Ha, MD

A RECENT STUDY in early-stage patients with primary open-angle glaucoma (POAG) in South Korea found a direct relationship between the degree of deformation in the lamina cribrosa and progressive loss of visual field, said Ahnul Ha, MD.

Lamina cribrosa deformation can directly block cells and the disturbed blood supply can accelerate retinal ganglion cell injury, said Dr. Ha, Department of Ophthalmology, Seoul National University Hospital, Seoul, South Korea.

“We found that with greater lamina cribrosa deformation, RGC axons are increasing vulnerable to further glaucomatous injury,” Dr. Ha added. “Baseline lamina cribrosa morphology may eventually serve as a prognostic factor in patients with primary open-angle glaucoma.”

The study followed 101 eyes with early-stage POAG for a mean of 3.6 years. Researchers measured the lamina cribrosa deformation and created a lamina cribrosa curvature index (LCCI).

Measurements were based on the Bruch’s membrane opening (BMO) and anterior lamina cribrosa insertion (ALI) as fixed reference points. Variables included the distance between the BMO reference plane and the ALI, the anterior lamina cribrosa insertion depth (ALID), and lamina cribrosa depth (LCD), the maximum inward curvature in the lamina cribrosa.

The mean LCCI was computed using an average of 12 radial measurements around the periphery of the lamina cribrosa. Measurements were based on scans from swept-source OCT (DRI OCT-1 Atlantis, Topcon).

Images were enhanced with an adaptive compensation technique. Poor-quality scans were excluded.

Study patients had early-stage POAG with a mean visual field deviation of more than -5.0 dB and well-controlled IOP. Eyes with a history of intraocular surgery except uncomplicated cataract were excluded, as were eyes with posterior pole lesions that affected visual field.

The mean age of patients was just over 64 years and slightly more than half (53%) were male. Pre-treatment IOP was 16.2 mm Hg and the mean post-treatment IOP was 12.4 mm Hg, a mean IOP reduction of 23.4%.

Visual field testing showed a baseline mean deviation of -3.8 dB and a baseline pattern standard deviation of 5.1. Patients had a mean of 7.2 visual field exams over a mean follow-up period of 3.6 years, or a visual field exam roughly every 6 months.

DIVING DEEPER

Univariate analysis showed four factors associated with visual field progression: greater initial visual field PSD, mean baseline LCD, and mean baseline LCCI.

“In the multivariate analysis, only the mean baseline LCCI was statistically significant,” Dr. Ha said. “A baseline LCCI of 152.4 micrometers was identified as the significant break point. If the baseline LCCI is greater than 152.4 micrometers, the visual field progressed by -0.01 dB per year as the LCCI increased by one unit. Greater lamina cribrosa curvature places a heavier burden on the RGC axons.”

Increasing posterior lamina cribrosa bowing induced by elevated IOP creates increasing stress and strain on axons, blood vessels, and other tissues. The mechanical response of the lamina cribrosa under stress from elevated IOP is affected by age, racial differences, and variation between individuals.

The study population was uniformly Korean, but participants ranged from the late 40s to the mid-70s in age. Patients who were less than 68 years old at baseline showed slower visual field progression than patients who were older than 68.

Eyes in the younger age group showed a mean visual field deviation of -0.3 dB per year compared with -0.02 in older eyes. The age-dependent difference could be a function of mechanical changes in the lamina cribrosa over time.

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This article was adapted from Dr. Ha’s presentation at the 2017 meeting of the American Academy of Ophthalmology. Dr. Ha did not indicate a proprietary interest.

SYNDROME

(Continued from page 12)

athy of prematurity, which causes the tractional cells that contribute to retinal detachment. There is sufficient VEGF to prevent the involution of the PFV vessels completely, but insufficient VEGF to allow neovascularization and exudation, which are protected by an intact Wnt signaling system.

Dr. Trese and colleagues have been following five children who presented with multifocal PFVS when they were infants or young children. The children have avascular peripheral retina and multifocal areas of PFV in the vitreous cavity along the retinal surface seen on FA. Retinal dysplasia has been difficult to assess because good optical coherence tomography scans have not been obtained.

One of the children was found to have a Wnt signaling mutation in LRPS; these children can achieve good vision, Dr. Trese noted.

Multifocal PFVS can be treated with laser application to the avascular peripheral retina.

Patients are followed with widefield FA. No disease progression has been seen after 3 to 5 years. The three presentations of PFVS require different treatments. “The final vision is dependent on the degree of retinal dysplasia, but functional vision can be achieved,” he said.

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This article was adapted from Dr. Trese’s presentation at the 2017 meeting of the American Academy of Ophthalmology. Dr. Trese has no financial interest in any aspect of this report.
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First-line treatment for diabetic macular edema (DME) is overwhelmingly anti-vascular endothelial growth factor (VEGF) drugs, with more than two-thirds of clinicians around the world prescribing them for this patient population.

Clinicians in Africa and the Middle East lead the way with 91% of clinicians prescribing anti-VEGF drugs as the primary treatment for DME, followed by the United States at 87%, Central and South America at 64%, and European clinicians at 63%.

However, there is also a role for treatment with steroids for patients who are refractory to anti-VEGF therapy with an increase of only a few letters of vision and those with persistent edema among others, said Anat Loewenstein, MD, MHA.

The disease pathogenesis—which is complex and involves both the vascular and neural components—is enhanced by increased leakage of inflammatory cytokines, explained Dr. Loewenstein, professor of ophthalmology and deputy dean of the medical school, Sackler Faculty of Medicine, Tel Aviv University, and chairman of the ophthalmology division, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel.

“Steroids that inhibit these cytokines theoretically and potentially have a role in the management of DME,” she said.

**Steroid Therapy: Yes**

Dr. Loewenstein recounted the case of a 63-year-old man with DME who had received six injections of bevacizumab (Avastin, Genentech) without improvement in the visual acuity. He did have a marked positive response to the dexamethasone intravitreal implant (Ozurdex, Allergan) and the visual acuity increased from 20/100 to 20/40 by 4 months after the implant.

In light of this, it is noteworthy that 40% of the patients analyzed in Protocol I by the Diabetic Retinopathy Clinical Research group had persistent edema that was refractory to ranibizumab (Lucentis, Genentech) at treatment week 24 and the DME persisted at 3 years in 16% of these patients.

“These patients pay a price in the change in the visual acuity from baseline (+5 letters versus +12 letters, respectively) and the changes for a two-line improvement in the visual acuity (43% versus 60%, respectively) are lower than in patients without persistent DME through 3 years,” Dr. Loewenstein said.

Similar results were seen in a post-hoc anal-
Dr. Loewenstein noted that at 12 weeks, 40% of patients had less than five letters of improvement (functional non-responders) and 35% had less than a 20% improvement in the central retinal thickness (anatomic non-responders).

Among the functional non-responders, the average additional gain in visual acuity after three injections was also small over 3 years in two-thirds of these eyes.

When patients were stratified anatomically by disease duration, Dr. Loewenstein noted that edema was present in one-third of eyes at almost every evaluation. When the stratification was based on the extent of the edema, the average thickness over 250 μm in quartile 4 was greater by a mean of 129 μm and minimal in quartiles 1 and 2.

Unadjusted comparisons showed that only the greater disease duration and not the greater extent of the edema was associated with significantly worse visual acuity outcomes at week 52 (6.3 versus 11.5).

However, when adjusting for potential confounders, a strong association was seen between both the duration of the DME and the extent of the edema and the long-term visual improvement, according to Dr. Loewenstein.

The Protocol T subanalysis highlighted the effect of persistent edema at 24 weeks. In these eyes, the visual acuity outcomes were worse in the presence of persistent edema compared with eyes without persistent edema.

Steroids also might be useful in patients who do not comply with their treatment regimens. In the case of a 48-year-old man with uncontrolled diabetes, the right and left eye visual acuities were 20/60 and 20/20, respectively. This patient was unwilling to report for monthly treatments and monitoring, and he responded well to the dexamethasone intravitreal implant.

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**Special Report**

**LEADING-EDGE RESEARCH IN ANTIBIOTIC & ANTI-INFLAMMATORY DRUGS**

**ADVANCES CONTINUE TO PROGRESS FOR TREATMENTS TO MINIMIZE, PREVENT OCULAR INFECTIONS**

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**SHEDDING LIGHT ON ANTIMICROBIAL EFFECT OF CXL, UV**

Newer approach with 222 nm works better than 365 nm UV used during CXL for keratoconus

By Vanessa Caceres; Reviewed by J. James Rowsey, MD

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It’s a given that ultraviolet (UV) light is effective at killing organisms, noted J. James Rowsey, MD. Though a 365-nm wavelength lamp often has been used, Dr. Rowsey touted the greater strength of a 222-nm UV light source technology (Far-UV Sterilray).

“We know that 222 nm will kill just about everything at a very low dose, including methicillin-resistant *Staphylococcus aureus* [MRSA] and *Clostridium difficile*,” said Dr. Rowsey, St. Michael’s Eye and Laser Institute, Largo, FL. “The safety margin is enormous. It takes only 1/100th of the dose that will hurt tissue to kill yeast, bacteria, and *E. coli*.”

The 222-nm light kills most ocular pathogens in 20 seconds, making it more effective than the 365-nm ultraviolet (UV) light typically used with the corneal collagen crosslinking (CXL) regimen for keratoconus, he added.

Two years ago, Dr. Rowsey presented on the safety of the 222-nm Far-UV light on the corneal endothelium by specular microscopy. A colleague asked whether a TUNEL assay would be more auspicious.

“We did exactly that,” he said. “The 222 nm was toxic to microbes at 5 seconds, but even at an hour it was not toxic on the epithelial surface. If we photodisinfected from the outside of the cornea inward, we’re safe.”

When Dr. Rowsey and colleagues compared the use of riboflavin with or without the 365-nm light, there was no effective treatment for *E. coli*. That was in contrast to what happened with the 222 nm light which was effective for *E. coli*.

“The 222 nm is actually interfered with by the riboflavin,” he said. “It inhibits efficacy.”

Dr. Rowsey highlighted two patients who were effectively treated with the 222-nm Far-UV light.

The first patient was a 48-year-old who had MRSA prior to treatment; after 60 seconds of Far-UV light treatment, there was no MRSA.

“‘The ulcer has healed with vancomycin and a bandage contact lens following Far-UV Sterilray therapy,” he said.

He described a second patient, a 72-year-old female physician with previous radial keratotomy 25 years before. Several of her incisions had rotted away due to MRSA and *Candida*. After treatment for 60 seconds, the patient was *Candida* negative. Eventually, Dr. Rowsey was able to perform a corneal transplant.

Researchers have now treated 9 of 20 patients approved by the Institutional Review Board for use with the 222-nm light.

In addition to its immediate treatment for corneal ulcers, Dr. Rowsey believes that 222-nm treatments may be an auspicious method to sterilize donor corneas in eye banks.

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**FIGURE 1**

A. Patient with recurrent methicillin-resistant *Staphylococcus aureus* (MRSA) ulcer prior to Far-UV light treatment. B. Patient with MSRA healing after Far UV. (Images courtesy of J. James Rowsey, MD)

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**J. JAMES ROWSEY, MD**

P: 727/585-2200

This article was adapted from Dr. Rowsey’s presentation at the 2017 meeting of the American Academy of Ophthalmology. He did not indicate proprietary interest in the subject matter.
In clinical studies of ocular surgery patients, DUREZOL® (difluprednate ophthalmic emulsion) 0.05% is a potent and effective ocular steroid that has been prescribed for millions of patients.1,2

**Indications and Usage**

DUREZOL® (difluprednate ophthalmic emulsion) 0.05% is a topical corticosteroid that is indicated for:

- The treatment of inflammation and pain associated with ocular surgery.
- The treatment of endogenous anterior uveitis.

**Dosage and Administration**

- For the treatment of inflammation and pain associated with ocular surgery, instill one drop into the conjunctival sac of the affected eye 4 times daily starting 24 hours after surgery and continue 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.
- 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 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. 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.

**Most Common Adverse Reactions**

- In postoperative ocular inflammation and pain studies, ocular adverse reactions occurring in 5-15% of subjects included corneal edema, ciliary and conjunctival hyperemia, eye pain, photophobia, posterior capsule opacification, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis.
- 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, intraocular pressure, and conjunctival hyperemia, punctate keratitis, and uveitis.

**For additional information about DUREZOL® Emulsion, please see Brief Summary of Prescribing Information on adjacent page.**

**References**

DUREZOL® (difluprednate ophthalmic emulsion) 0.05%

Initial U.S. Approval: 2006

BRIEF SUMMARY: Please see package insert for full prescribing information.

1 INDICATIONS AND USAGE

1.1 Ocular Surgery
DUREZOL® (difluprednate ophthalmic emulsion) 0.05%, a topical corticosteroid, is indicated for the treatment of inflammation and pain associated with ocular surgery.

1.2 Endogenous Anterior Uveitis
DUREZOL is also indicated for the treatment of endogenous anterior uveitis.

2 CONTRAINDICATIONS

The use of DUREZOL, 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.

3 WARNINGS AND PRECAUTIONS

5.1 Intracocular 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, IOP should be monitored.

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

5.3 Delayed Healing
The use of steroids after cataract surgery may delay healing and increase the incidence of bleb formation. In those diseases causing thinning of the cornea or sclera, perforations have been known to occur with the use of topical steroids. The initial prescription and renewal of the medication order 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.

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

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

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

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

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

6 ADVERSE REACTIONS

The following serious reactions are found elsewhere in the labeling:

- Elevated IOP [see Warnings and Precautions (5.1)]
- Posterior subcapsular cataract formation [see Warnings and Precautions (5.2)]
- Secondary ocular infection [see Warnings and Precautions (5.4)]
- Perforation of the globe [see Warnings and Precautions (5.3)]

6.1 Ocular Surgery
Ocular adverse reactions occurring in 5% to 15% of subjects in clinical studies with DUREZOL 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% to 5% of subjects included conjunctival edema, anterior chamber cells, anterior chamber flare, conjunctival edema, and blepharitis. Other ocular adverse reactions occurring in less than 1% of subjects included application site discomfort or irritation, corneal pigmentation and striae, epidermolysis, 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.

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

8 USE IN SPECIFIC POPULATIONS

8.1 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, since DUREZOL 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 should be used during pregnancy only if the potential benefit justifies the potential risk to the embryo or fetus.

8.3 Nursing Mothers
It is not known whether topical ophthalmic administration of corticosteroids could result in sufficient systemic absorption to produce detectable quantities in 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 is administered to a nursing woman.

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

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

Continued from page 1

ne to heal is 2.5 days,” Dr. Margolis said. “The drugs we currently use to inhibit viral replication, be they oral or topical, clear the epithelial keratitis in about 7 days, so the choice is really about cost and side effects of the medication.”

In his area of the country, ganciclovir gel costs about $330, whereas trifluridine costs about $150. Oral agents, including acyclovir, valacyclovir, and famciclovir, cost $20, $68, and $56, respectively, for a course of treatment.

“Oral agents are less expensive, well tolerated, and generally have fewer side effects,” he said. “They also get into the corneal stroma, anterior chamber of the eye, and trigeminal ganglion better than the topical agents, and so I tend to use these almost exclusively. There is a rare occasion when I use a topical agent.”

HSV Stromal Keratitis

Dr. Margolis suggests thinking about this as primarily an immune-mediated disease “like you would chronic uveitis.”

Treat the inflammation with topical corticosteroids, and use oral antiviral prophylaxis to prevent the virus from reactivating while the patient is using the topical immunosuppressor.

Most physicians manage the steroid treatment by putting patients on a set taper in the hopes of avoiding disease reactivation, but Dr. Margolis wants to avoid that mindset, and instead “reduce the amount of steroid until you get to the lowest level that controls the chronic inflammation,” much like chronic uveitis is managed.

He generally starts patients on a four-times-daily steroid regimen until the eye is quiet, then reduces the dosing in half once and reassessing whether the eye is still quiet in 4 to 6 weeks.

“Why wait 4 to 6 weeks?” he asked. “It’s because it can take that long for enough immune response to build up in this chronic disease for you to see it on your exam or the patient to feel it.”

Topical steroids may be needed for years in cases of stromal keratitis, which is acceptable as most recurrences of HSV stromal keratitis “are not due to recurrences of the virus but are due to inadequate steroid treatment,” Dr. Margolis said.

HSV Endothelitis

This “so-called disciform disease is really active viral disease in the anterior chamber which disrupts the corneal endothelium leading to corneal edema,” Dr. Margolis said.

Oral agents are preferred because they have better penetration into the anterior chamber.

“You can help control the inflammation with a topical corticosteroid, but think about this as an infectious disease first, and an inflammatory disease second,” he said.

Herpes Zoster Ophthalmicus

Dr. Margolis categorizes this disease as “much worse” than herpes simplex, as it can manifest with dermatologic disease, superficial ocular disease, deep ocular disease, retinal disease, or even central nervous system diseases.

Treat aggressively with systemic antivirals (acyclovir, valacyclovir, famciclovir), and manage the immune response similar to how HSV stromal keratitis is managed.

“The big difference is sometimes it takes as little as one drop a week to ultimately control this chronic inflammatory disease manifesting as a keratitis or an iritis,” Dr. Margolis said.

The three systemic antivirals are equally effective, but dosing can be confusing: 800 mg five times daily for acyclovir; 1 gram three times daily for valacyclovir; and 500 mg three times daily for famciclovir.

Dr. Margolis said topical antivirals have “no efficacy in acute disease” according to randomized clinical trials.

Chronic and recurrent herpes zoster due to active viral replication can occur, but the incidence and prevalence have not been clearly elucidated in population-based studies.

“Mucous plaque keratopathy, which is infectious epithelial disease, occurs in about 13% of patients; recurrent iritis, which also has active viral replication, occurs in about 7.5% of patients; and recurrent keratitis where you can find DNA and antigen in the cornea in about 7% of patients,” Dr. Margolis said.

Dr. Margolis likens VZV neurotrophic keratopathy to “the diabetic foot ulcer of the eye,” that occurs in part from exposure and in part from iatrogenic insults.

Prevention is the key, he said—test all patients who have had zoster and if they’re neurotrophic educate them about proper drop delivery and the benefits of shielding their eyes at night.

Don’t discount tarsorrhaphy; a temporary tarsorrhaphy can be done with Breathe Right medical strips or medical tape, he said.

Also remind patients there is an approved vaccine for zoster that has been shown to reduce the incidence by 51% to 67%. The Shingrix vaccine (GSK) was just approved in 2017; phase III data found a 91% efficacy rate, Dr. Margolis said.

CMV Iritis and Endothelitis

Presentation may include small keratic precipitate (KP) and KP corrals, iris atrophy, low-grade anterior chamber inflammation, and cytomegalovirus in the aqueous. While patients may not be systemically immunocompromised, they are probably locally immunocompromised.

“We don’t yet understand what that ‘hole’ is in their immunity; we can get the virus under control with antivirals, but we rarely eliminate the chronic infection,” he said. There currently is no “best way” to manage this disease.
Cataract patients may benefit from new drug-delivery methods

Approaches aim to improve compliance for efficacy, while reducing medication burden

By Laird Harrison; Reviewed by Francis S. Mah, MD

NEW SYSTEMS for delivering antibiotic and anti-inflammatory drugs hold promise for cataract surgery, said Francis S. Mah, MD. Patients will benefit from not having to administer eye drops, explained Dr. Mah, director of cornea and external disease, Scripps Clinic, La Jolla, CA.

“One of the drivers for this is to improve compliance to improve efficacy and reduce problems with the medication,” he said.

Applying eye drops requires more knowledge and manual dexterity than most patients can muster. One recent study (J Cataract Refract Surg. 2014;40:1857–1861) showed that 93% of patients do not correctly apply eye drops they were prescribed after cataract surgery, even when carefully educated, Dr. Mah said.

“And that’s when they were in a study and educated in the proper methods,” he said. “Our patients are probably getting much less education.”

New devices might improve efficacy and reduce toxicity as well, he said.

“If we’re talking about drops in general something like less than 1% of the drop gets to the site of the target,” he said. Some of the eye drop drains through the lacrimal system, he said, and the cornea and epithelium also keep the drops from penetrating into the eye.

Pharmaceutical companies are also interested in developing drug-delivery systems that are unique so they can patent them, fending off competition from generic versions of their drugs, Dr. Mah said.

The devices may become even more important for glaucoma and retina diseases because the targets are inside the eye, he said.

For prevention of miosis and pain in cataract surgery, the FDA has approved some new drug delivery devices and others are in the pipeline. One approved drug is phenylephrine/ketorolac injection 1%/0.3% (Omidria, Omeros Corp.) One 4-ml single-use vial is added to a 500-ml container of irrigation solution. Preservative and bisulfate-free, the drug product is considered safe and well tolerated. Adverse reactions were similar to those of placebo in clinical trials.

It decreased pupil diameter by at least 2.5 mm in 27% in one phase III trial and 28% in another while reducing pain. Patients taking phenylephrine/ketorolac used fewer analgesics.

In one case review, phenylephrine/ketorolac caused fewer complications, less papillary dilating device dependence, improved best-corrected visual acuity on day one in select age groups, and decreased procedure times compared with intracameral epinephrine alone.

Some physicians are also administering compounded antibiotics, steroids, and non-steroidal anti-inflammatory drugs (NSAIDs) in the anterior chamber or through intravitreal or transzonular injection.

Examples include:

- TRi-MoXi
  Imprimis’ proprietary injectable formulation of triamcinolone acetonide and moxifloxacin hydrochloride, and vancomycin.

- TRI-MoXi-Vanc
  Imprimis’ proprietary injectable formulation of triamcinolone acetonide, moxifloxacin hydrochloride, and vancomycin.

- DEX-MOx
  Ocular Science’s clear formulation of dexamethasone and moxifloxacin hydrochloride.

- PRED-MOxI
  A combination of prednisolone acetate or prednisolone sodium phosphate with moxifloxacin hydrochloride.

- PRED-Ketor
  A combination of prednisolone acetate or sodium phosphate with ketorolac tromethamine.

- PRED-Moxy-Ketor
  A combination of prednisolone acetate or sodium phosphate with moxifloxacin hydrochloride and ketorolac tromethamine.

- PRED-Levo
  A combination of prednisolone sodium phosphate and levofloxacin.

A compounded combination of topical drops may reduce the number of prescriptions and cut the number of surgical drops up to 75% Dr. Mah said.

Fewer bottles are needed; compliance is better; costs are lower; fulfillment of the medication is guaranteed, and there are fewer calls back. The overall healthcare system may save, as long as the compounded medications are safe and efficacious, he noted.

In his own practice, Dr. Mah uses compounded intracameral moxifloxacin-dexamethasone for routine cataract procedures, along with topical diltiaprednate 0.05% (off-label) and nepafenac 0.3% or bromfenac 0.075% (off-label) for 4 weeks (off-label).

In a study published by Dr. Mah, he showed that antibiotic and/or anti-inflammatory drugs can also be combined with hydrogel sealants used to prevent leakage from corneal incisions.

Alternatively, Sun Pharmaceutical’s BromSite, which recently received FDA approval, delivers 0.075% bromfenac in a synthetic polymer of crosslinked polyacrylic acid developed as DuraSite by InSite Vision. DuraSite is also the vehicle for Bausch + Lomb’s besifloxacin.
LEADING-EDGE RESEARCH IN ANTIBIOTIC & ANTI-INFLAMMATORY DRUGS

ophthalmic suspension (Besivance) and Akorn’s azithromycin ophthalmic solution (AzaSite).

The formulation improves solubility, absorption, bioavailability and residence time compared to other topical therapies, Dr. Mah said. In phase III trials, 38% to 57% of patients were free of inflammation at day 15 compared with 19% to 22% who received the vehicle alone.

And at day one, 76.8% to 82.1% were pain-free compared with 48.2% to 62.4% of those on the vehicle alone.

Another route of administration is Ocular Therapeutix’s dexamethasone depot, which is placed in the canaliculus of the eyelid. According to the company, 36.2% of patients implanted with the depot had no anterior chamber cells at day 14, compared with 22.7% of patients implanted with a placebo depot.

Icon Biosciences conducted a phase III clinical trial of a bioabsorbable vehicle for 342 μg or 517 μg dexamethasone, which maintains therapeutic levels of the drug for 21 days. In a study the company presented at ASCRS 2015, 63.1% of patients on the low dose and 66% of patients on the high dose were clear of anterior chamber cells at day 8. This device has recently been FDA approved and acquired by EyePoint Pharmaceuticals.

More is in the pipeline, Dr. Mah said, including:

- **KALA PHARMACEUTICALS**
  - phase III trial of KPI-121 loteprednol delivered through mucus-penetrating particle (MPP) technology.

- **ENVISIA THERAPEUTICS**
  - (which recently licensed its proprietary drug-delivery device to Aerie Pharmaceuticals) phase I trial of ENV905 difluprednate delivered through particle replication in non-wetting templates (PRINT), a technology platform used to create a pipeline of small- and large-molecule, particle-based ocular therapeutics.

- **MATI THERAPEUTICS**
  - phase I trial of EVOLUTE steroids and NSAIDs through a punctual plug.

Even when these drugs earn approval, reimbursement can prove challenging, Dr. Mah said.

“In cataract surgery, if I were to use a medication in the operating room, I cannot have the patient nor the insurance buy it separately,” he explained. “However, if I write a prescription, the patient picks it up before or after surgery and the insurance company, or the patient, covers the cost.”

Advocates for these drugs are working on legislation to improve reimbursement.

“It’s not unusual for cataract patients to put in 12 drops a day—4 drops of 3 medications—in addition to having to go to the pharmacy and buy the medications, which might be hundreds of dollars, even for generics,” said Dr. Mah, adding that patients would welcome not needing to take eye drops.

References:
3. Aashish Anand, MD, Carlos Gustavo De Moraes, MD, Christopher C Teng, MD, Celso Tello, MD, Jeffrey M Liebmann, MD, Robert Ritch, MD. Lower Corneal Hysteresis Predicts Laterality in Asymmetric Open Angle Glaucoma, IOVS Papers in Press. Published on June 23, 2010 as Manuscript iovs.10-5580. CPT is registered trademark of the American Medical Association.
Range of surgical options growing for infectious keratitis patients

Medical therapy may not always be adequate, particularly for fungal keratitis

By Laird Harrison; Reviewed by Jennifer R. Rose-Nussbaumer, MD

EARLY SURGICAL intervention may effectively treat cases of infectious keratitis that do not yield to medicine, according to Jennifer R. Rose-Nussbaumer, MD.

“Medical therapy doesn’t always seem to be adequate at this time, particularly for fungal keratitis,” she said.

Dr. Rose-Nussbaumer gave an overview of surgical interventions for infectious keratitis.

Infectious keratitis is “a big problem in tropical countries,” she said. Even in Florida, up to half of infectious keratitis may be fungal, she said. “People are having devastating outcomes even though we are giving them everything we know how to do medically.”

Medical treatments still work fairly well for bacteria, she said. She cited the example of a recent patient with a Pseudomonas corneal ulcer who improved from 20/1200 to 20/25 vision in 12 months as infiltrates and scars cleared.

Natamycin is the most effective antifungal available for infectious keratitis, Dr. Rose-Nussbaumer said.

But it doesn’t penetrate the cornea, and only prevents perforations or the need for a therapeutic keratoplasty about half the time in severe cases.

Oral voriconazole has proved disappointing, she noted. In the randomized controlled mycotic ulcer treatment trial II, Dr. Rose-Nussbaumer and her colleagues found that adding oral voriconazole to topical treatments did not reduce the risk of corneal perforation or the need for a therapeutic keratoplasty. The risk of perforation or need for therapeutic penetrating keratoplasty was about 50% in both groups.

In a secondary analysis of this data, they found that the risk doubled if the patients had a hypopyon at baseline, if the infection involved the posterior third or if the infiltrate was greater than 6.5 mm. Almost all the patients with these risk factors had a perforation or needed a therapeutic keratoplasty, Dr. Rose-Nussbaumer said.

They found that those with positive 6-day cultures had much worse visual acuity and larger scar sizes at 3 months, and were 7 times more likely to perforate or need therapeutic penetrating keratoplasty, she said.

The researchers graded infiltrate depth as 1) no infiltrate, 2) infiltrate involving the anterior one-third of the stroma, 3) infiltrate involving two-thirds of the stroma and 4) infiltrate involving the deepest third of the cornea.

For each step increase in the infiltrate depth as measured at baseline, there was 1.69 times the odds of the patient developing a full-thickness corneal perforation and/or needing a therapeutic penetrating keratoplasty.

At baseline, visual acuity was generally poor. The median was logMAR 1.7. For every line of worsening in baseline visual acuity, the odds of a perforation increased 1.06 times, but this was not statistically significant.

Epithelial defect size, baseline culture positivity, type of filamentous fungal organism, and duration of symptoms were not statistically significant predictors of progression, nor were demographic factors such as age, sex, and occupation.

The researchers noted that all the participants in the study were from Southeast Asia and it is possible that organisms in this area have different characteristics than those in other regions.

When infections do not respond to antimicrobials, thinning progresses, or perforation occurs, surgery is indicated.

When infections do not respond to antimicrobials, thinning progresses, or perforation occurs, surgery is indicated.

Diving Deeper

Researchers are still looking for new options to treat infectious keratitis. Among those being tested are corneal collagen crosslinking and intrastromal injection of voriconazole, she said.

Crosslinking is an interesting alternative because the procedure can be anti-microbial, anti-inflammatory and anti-collagenase. It may overcome such problems as drug resistance, toxicity and non-compliance.

Dr. Rose-Nussbaumer and colleagues have enrolled 110 patients in a 4-arm trial comparing natamycin alone, natamycin plus crosslinking, amphotericin alone, and amphotericin plus crosslinking. They are expecting the study results soon.

Among other outcomes, they are measuring repeat culture at 24 hours, best-corrected visual acuity at three months, infiltrate or scar size, the rate of penetration, astigmatism, corneal thickness, and vision-related quality of life.

Jennifer R. Rose-Nussbaumer, MD

This article was adapted from Dr. Rose-Nussbaumer’s presentation at Cornea Subspecialty Day during the 2017 meeting of the American Academy of Ophthalmology. Dr. Rose-Nussbaumer did not indicate any proprietary interest relevant to the subject matter.
Indications and Usage

BromSite® (bromfenac ophthalmic solution) 0.075% is a nonsteroidal anti-inflammatory drug (NSAID) indicated for the treatment of postoperative inflammation and prevention of ocular pain in patients undergoing cataract surgery.

Recommended Dosing

One drop of BromSite® should be applied to the affected eye twice daily (morning and evening) 1 day prior to surgery, the day of surgery, and 14 days postsurgery.

Important Safety Information

- Slow or Delayed Healing: All topical nonsteroidal anti-inflammatory drugs (NSAIDs), including BromSite®, 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 BromSite®. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.
- Increased Bleeding Time of Ocular Tissue: With some NSAIDs, including BromSite®, there exists the potential for increased bleeding time due to interference with platelet aggregation. There have been reports that ocularily applied NSAIDs may cause increased bleeding of ocular tissues (including hyphemas) in conjunction with cataract surgery. It is recommended that BromSite® be used with caution in patients with known bleeding tendencies or who are receiving other medications which may prolong bleeding time.
- Keratitis and Corneal Effects: Use of topical NSAIDs may result in keratitis. In some susceptible patients, continued use of topical NSAIDs may result in epithelial breakdown, corneal thinning, corneal erosion, corneal ulceration or corneal perforation. Patients with evidence of corneal epithelial breakdown should immediately discontinue use of topical NSAIDs, including BromSite®, and should be closely monitored for corneal health. 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 postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.
- Contact Lens Wear: BromSite® should not be administered while wearing contact lenses. The preservative in BromSite® benzalkonium chloride, may be absorbed by soft contact lenses.
- Adverse Reactions: The most commonly reported adverse reactions in 1% to 8% of patients were anterior chamber reactions in 1% to 8% of patients were anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain, and ocular hypertension.

Please see brief summary of Full Prescribing Information on the adjacent page.

References:

2. Hossein K, Hutchison J, Bowman L. Aqueous humor concentration of bromfenac 0.09% (Bromday™) compared with bromfenac in DuraSite® 0.075% (BromSite™) in cataract patients undergoing phacoemulsification after 3 days dosing. Poster presented at: ARVO Annual Meeting; May 9-13, 2013; Seattle, Washington.

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ADVERSE REACTIONS

All WARNINGs AND PRECAUTIONS

CONTRAINDICATIONS

INDICATIONS AND USAGE

BromSite® (bromfenac ophthalmic solution) 0.075%

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CONTRAINdications

None

WARNINGS AND PRECAUTIONS

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Potential for Cross-Sensitivity

There is the potential for cross-sensitivity to acetylsalicylic acid, phenylacetic acid derivatives, and other NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%. Therefore, caution should be used when treating individuals who have previously exhibited sensitivities to these drugs.

Increased Bleeding Time of Ocular Tissue

With some NSAIDs, including BromSite® (bromfenac ophthalmic solution) 0.075%, 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 BromSite® 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 BromSite® (bromfenac ophthalmic solution) 0.075%, 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 postsurgery may increase patient risk for the occurrence and severity of corneal adverse events.

Contact Lens Wear

BromSite® should not be administered while wearing contact lenses. The preservative in BromSite®, benzalkonium chloride, may be absorbed by soft contact lenses.

ADVERSE REACTIONS

The following serious adverse reactions are described elsewhere in the Brief Summary:

- Slow or Delayed Healing
- Potential for Cross-Sensitivity
- Increased Bleeding Time of Ocular Tissue
- Keratitis and Corneal Reactions
- Contact Lens Wear

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 in 1–8% of patients were: anterior chamber inflammation, headache, vitreous floaters, iritis, eye pain and ocular hypertension.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies in pregnant women to inform any drug associated risks. Treatment of pregnant rats and rabbits with oral bromfenac did not produce teratogenic effects at clinically relevant doses.

Clinical Considerations

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

Data

Animal Data

Treatment of rats with bromfenac at oral doses up to 0.9 mg/kg/day (195 times a unilateral daily human ophthalmic dose on a mg/m² basis, assuming 100% absorbed) and rabbits at oral doses up to 7.5 mg/kg/day (3243 times a unilateral daily dose on a mg/m² basis) produced no structural teratogenicity in reproduction studies. However, embryo-fetal lethality, neonatal mortality and reduced postnatal growth were produced in rats at 0.9 mg/kg/day, and embryo-fetal lethality was produced in rabbits at 7.5 mg/kg/day. 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.

Lactation

There are no data on the presence of bromfenac in human milk, the effects on the breastfed infant, or the effects on milk production; however, systemic exposure to bromfenac from ocular administration is low. The developmental and health benefits of breastfeeding should be considered along with the mother’s clinical need for bromfenac and any potential adverse effects on the breast-fed child from bromfenac or from the underlying maternal condition.

Pediatric Use

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

Geriatric Use

There is no evidence that the efficacy or safety profiles for BromSite® differ in patients 65 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 (129 times a unilateral daily dose assuming 100% absorbed, on a mg/m² basis) and 5 mg/kg/day (540 times a unilateral daily dose on a mg/m² basis), respectively revealed no significant increases in tumor incidence. Bromfenac did not show mutagenic potential in various mutagenicity studies, including the bacterial 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 (195 and 65 times a unilateral daily dose, respectively, on a mg/m² basis).

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SUN OPHTHALMICS
Diagnosis of fungal keratitis requires a deeper look—beyond the slit lamp

Natamycin an effective treatment, but some cases may require surgical intervention

By Vanessa Caceres; Reviewed by Eduardo C. Alfonso, MD

NATAMYCIN may be the drug of choice for filamentous keratitis, and intrastromal voriconazole is a potential option for recalcitrant fungal keratitis, according to Eduardo C. Alfonso, MD.

When physicians use only a slit lamp to potentially diagnose ulcerative keratitis, it can be easy to miss the diagnosis, said Dr. Alfonso, professor and chairman, Department of Ophthalmology; Kathleen and Stanley J. Glaser Chair in ophthalmology; and director, Bascom Palmer Eye Institute, University of Miami Miller School of Medicine, Miami.

“Clinical predictability is shown to be quite off when we talk specifically about keratitis. It can be wrongly diagnosed by slit lamp and history close to 55% of the time. I hope that makes you a little uncomfortable,” said Dr. Alfonso, citing a 2007 study from Dahlgren et al.1

“Certainly in today’s world in the United States, most patients come to us pre-treated. It was shown that when you are pre-treated, detecting at the slit lamp becomes even worse,” Dr. Alfonso said. “Unless we have artificial intelligence to analyze the clinical data, we won’t be doing a favor to our patients by using just a clinical diagnosis.”

GOLD STANDARD TESTING

The use of an ocular microbiology lab is a major boost to diagnose fungal keratitis.

Dr. Alfonso discussed the gold standard of using smear and cultures. Ninety-one percent of smears correlate with cultures, he said.

Other approaches to help diagnose fungal keratitis have proven to be useful, including molecular analyses, confocal microscopy, and anterior segment optical coherence tomography (OCT). Dr. Alfonso shared images from an anterior segment OCT in which a patient had fungal keratitis.

“Here we see fungal keratitis and the importance of OCT,” he said. “We can see how deep the infiltrate is.”

The availability of this technology helps ophthalmologists better plan their surgical strategy. With higher-resolution OCT, they may even be able to see the organism itself, he said.

Regarding treatment, Dr. Alfonso shared evidence that natamycin “continues to be the best drug for the bug,” he said.

“When we do a molecular analysis, natamycin seems to be better against Fusarium solani compared with voriconazole,” he said.

That said, intrastromal injections of voriconazole are a potentially good adjuvant therapy until the ulcer is controlled.

TREATMENT ROUTES

When Fusarium solani is present, it may have to be treated with surgery.

“It may not respond well to natamycin, especially in younger individuals who have this disease,” Dr. Alfonso said. “You may want to proceed with keratoplasty.”

Studies have found that early lamellar keratoplasty has been found to eradicate infection in 92.7% of patients, he said.

Corneal scrapings, crosslinking, and the use of photodynamic therapy are other treatments for fungal keratitis, Dr. Alfonso said.

He highlighted the case of a man with severe keratitis last year in whom photodynamic therapy was used. It prevented surgeons from having to perform a penetrating keratoplasty.

Reference

Postop endophthalmitis rates similar despite dissimilar practice patterns

Different studies show trend of decreasing risk of intraocular infections in recent years

By Cheryl Guttman Krader; Reviewed by Andrzej Grzybowski, MD, PhD, MBA

PRACTICE PATTERNS for the use of antibiotics to prevent endophthalmitis after cataract surgery vary around the world. However, the reported rate of postoperative endophthalmitis in different countries is similarly low regardless of the preferred route of administration, said Andrzej Grzybowski, MD, PhD, MBA.

Reviewing practice patterns for preventing endophthalmitis post-cataract surgery, he noted a study conducted by the European Society of Cataract and Refractive Surgeons (ESCRS) remains the only prospective, randomized, controlled trial investigating different approaches.

Its results showed use of intracameral cefturoxime reduced the risk of postoperative endophthalmitis by about five-fold compared with topical treatment and that there was no effect of preoperative topical antibiotic treatment with levofloxacin, said Dr. Grzybowski, professor and chairman, Department of Ophthalmology, University of Warmia and Mazury, Olsztyn, Poland.

“Adoption of intracameral antibiotics increased in some countries in Europe following publication of the ESCRs study results in 2007 and then after cefturoxime (Aprokam, Thea Pharmaceuticals) for intracameral use became commercially available in 2012,” he said. “Corresponding with this shift, there was a decline in preoperative use of topical antibiotics.

“Topical antibiotics are still being widely used postoperatively for 5 to 7 days, but practice patterns in different European countries still vary, and overuse and misuse of antibiotics remains a problem in different parts of the world,” Dr. Grzybowski said.

SURVEY DATA
A study published in 2013 examining endophthalmitis prophylaxis practices among European cataract surgeons found information on intracameral cefturoxime usage was lacking in some countries and varied significantly. In Sweden—where the idea of intracameral administration originated—about 90% of surgeons were using intracameral cefturoxime, but the rate was estimated to be ≤20% in Germany and Belgium.

A survey of ESCRs members conducted in 2012 found that 74% were using intracameral antibiotics routinely or usually. Similarly, a survey involving 33 centers in Poland found that in 2013-2014, about 70% of cataract surgeons were using intracameral antibiotics.

“In Sweden, Denmark, and France, current guidelines for cataract surgery endophthalmitis prophylaxis recommend intracameral antibiotics without use of preoperative topical antibiotics,” Dr. Grzybowski said.

Data from surveys conducted by the American Society of Cataract and Refractive Surgery show increasing use of intracameral antibiotic prophylaxis over time among surgeons in the United States, from 30% in 2007 to 50% in 2014. Over the same period, there was no change in preoperative or postoperative use of topical antibiotics.

Data on practice patterns in the United States were also included in a 2017 paper in which Dr. Grzybowski and colleagues examined practice patterns for endophthalmitis prophylaxis in cataract surgery among surgeons in a number of countries across different continents. It found that intracameral antibiotic usage was highest in Australia/New Zealand (78%) and the United States (50%), but it was adopted by only about 25% to 30% of surgeons in Canada, Argentina, and Russia and was being used even less frequently in Japan, China, India, and Mexico.

“Despite some evidence about its efficacy—especially in places where there is a relatively high rate of endophthalmitis—intracameral antibiotic use has not been universally adopted for postcataract surgery endophthalmitis prophylaxis. Moreover, different studies show a trend of decreasing risk of intraocular infections in recent years.

Continues on page 29: Endophthalmitis
**Thermoresponsive microspears may minimize surgical infections**

Technology at University of Pittsburgh may overcome antibiotic prophylaxis concerns

By Michelle Dalton, ELS

**ENDOPHTHALMITIS** may be a rare occurrence, but it can be a devastating one. Acute cases are known to be caused by gram-positive bacteria and usually present within 6 weeks post-surgery.

Chronic cases can occur beyond the 6-week timetable, but are often related to a previous surgery and the culprit is often a progressive infection (e.g., fungus). Acute cases should be treated as an emergency (and may result in treatment with vitrectomy if presenting vision is poor enough). If vision has not yet been adversely impacted, treatment may only require antibiotics or antifungal agents.

Preventing endophthalmitis, therefore, has often been the goal for surgeons, and patients are typically prescribed an antibiotic prophylaxis regimen prior to undergoing surgery.

But most antibiotic prophylaxis regimens are comprised of multiple doses, meaning “patient compliance is always a concern, especially for older patients who may have difficulty in instilling the drops,” said Eric Romanowski, MS (The Charles T. Campbell Ophthalmic Microbiology Laboratory, University of Pittsburgh).

To overcome that obstacle and eliminate the patient adherence issue, one potential solution has been to provide a noninvasive depot of antibiotic that can be released over time to replace the multiple doses of antibiotic.

At the University of Pittsburgh, however, engineers have developed a thermoresponsive, hydrolgel-controlled release drug containing microspheres, or SoliDrop.

**RABBIT STUDIES**

SoliDrop is liquid at room temperature, but “forms a comfortable, pliable, formfitting non-degradable hydrogel after exposure to body temperature in conjunctival cul-de-sac,” he said. The hydrogel material “is loaded with controlled-release microspheres capable of delivering a wide range of drugs for varying lengths.”

Preliminary rabbit studies using SoliDrop with glaucoma drug brimonidine demonstrated good efficacy over 28 days. The goals of the latest study were to evaluate the efficacy of the drug-delivery system and its ability to release moxifloxacin at a high concentration over a short period.

“We wanted to provide a proof of principle that the placement of a single drop of moxifloxacin controlled release hydrogel drop into the conjunctival cul-de-sac can provide effective prophylaxis against bacterial endophthalmitis in a rabbit model,” Romanowski said. Leaving Morgan V. Fedorchak, PhD (developer of the technology) to “do her magic,” Romanowski said she was able to develop microspheres that have “a quick burst release over 60 minutes, and while there were other microspheres that will allow a release over 7 days.”

There were eight rabbits in each of three groups: a moxifloxacin microsphere group, a blank hydrogel group, and a control group that was instilled with 10 drops of moxifloxacin over 24 hours; they then injected Staphylococcus aureus into the anterior chamber.

Researchers began instilling moxifloxacin starting an hour before inoculation, every 15 minutes, then again right before inoculation and once after inoculation, and four more times post-inoculation over 24 hours. The hydrogel depot was placed 60 minutes before inoculation.

At 24 hours post-injection, the researchers performed a slit lamp exam, and then cultured the aqueous and vitreous for bacterial strains.

Both the hydrogel implant and the control moxifloxacin eyes had no evidence of endophthalmitis. The blank hydrogel eyes, however, all developed endophthalmitis.

Further clinical studies are needed to confirm these initial results, Romanowski said.

**ENDOPHTHALMITIS**

(Continued from page 28)

usage was highest in Australia/New Zealand (78%) and the United States (50%), but it was adopted by only about 25% to 30% of surgeons in Canada, Argentina, and Russia and was being used even less frequently in Japan, China, India, and Mexico.

“Despite the wide variation in intracameral antibiotic use across these different countries, the rate of postoperative endophthalmitis was similar to that reported in European countries where intracameral antibiotics is standard practice,” he said. “A recent study from Japan, where intracameral antibiotics are rarely used, reported an endophthalmitis rate of about 0.02%, which is much lower than that reported by any studies of intracameral antibiotic use.”

Dr. Grzybowski noted the results from the ESCRS prospective randomized study are often incorrectly generalized, but it is important to keep in mind that every antibiotic is different.

“The ESCRS study only supports use of intracameral cefuroxime. It does not support the effectiveness of intracameral gentamicin, tobramycin, moxifloxacin, and vancomycin,” he said. “Thus, as long as we do not have any other randomized controlled studies of endophthalmitis prophylaxis, we have good scientific evidence for the intracameral use of only cefuroxime.”

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This article was adapted from Romanowski’s AAO 2017 presentation. He has no financial disclosures.

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This article was adapted from Dr. Grzybowski’s presentation at the 2017 meeting of the American Academy of Ophthalmology. Dr. Grzybowski is a speaker, consultant, and/or lecturer for companies that market antibiotics used for cataract surgery endophthalmitis prophylaxis.
SCUT trial delves into corticosteroid role for bacterial corneal ulcers

Randomized study gives guidance on when to use—and not use—this controversial treatment

By Cheryl Guttman Kreader | Reviewed by Thomas M. Lietman, MD

**THE PROSPECTIVE.** Randomized, placebo-controlled Steroids for Corneal Ulcer Trial (SCUT) was conducted to address the controversy over the role of topical corticosteroids in the management of bacterial corneal ulcers. The study’s main results showed that adding a topical corticosteroid to antibiotic treatment did not improve spectacle-corrected visual acuity (BSCVA) at 3 months nor lead to an increase in overall adverse events, said Thomas M. Lietman, MD.

“Based on these findings, ophthalmologists can feel comfortable using a topical corticosteroid in an eye with a culture-proven bacterial corneal ulcer whereas those who choose not to use a corticosteroid can also defend their decision,” said Dr. Lietman, director, Francis I. Proctor Foundation for Research in Ophthalmology, University of California, San Francisco (UCSF).

“However, findings from some analyses of secondary outcomes pointed to situations where corticosteroids might be preferred or avoided and suggested that when a corticosteroid is used, it is better to start the treatment earlier than later,” he said.

Patients who were randomly assigned to treatment in SCUT were carefully selected, meaning they all had a culture-proven bacterial infection without evidence of fungal, *Acanthamoeba*, or herpetic keratitis, he noted.

**SCUT OUTCOMES**

Sponsored by the National Eye Institute, SCUT enrolled patients at three centers—Aravind Eye Care System in India, Dartmouth Medical School, Lebanon, New Hampshire, and UCSF, although the greatest number of participants were enrolled in India. All patients were started on topical moxifloxacin, and after at least 48 hours, those with a culture-proven bacterial infection began adjunctive treatment with topical prednisolone phosphate, 1% or placebo with tapering of the dose over 3 weeks.

A total of 500 patients were randomly assigned to treatment. The most common isolates were *Streptococcus pneumoniae* (~50%), *Pseudomonas aeruginosa* (~25%), and *Nocardia* spp (~10%), although the latter organism was predominantly isolated in India and is rarely seen as a cause of keratitis in the United States, Dr. Lietman observed.

The primary endpoint analysis of BSCVA at 3 months showed no significant difference between treatment groups. The safety review found no significant differences in rates of most adverse events with two exceptions. The proportion of eyes without healing of the epithelial defect by day 21 was higher in the corticosteroid group compared with the controls, 17.6% versus 10.8%.

More significantly, the safety review showed a significant difference in rate of perforation between the two groups. “Final scar size and frequency of perforation were also not different between arms,” he said.

The other difference was in the rate of IOP spikes (>25 mm Hg and <35 mm Hg), but these events occurred significantly less often in the corticosteroid-treated eyes than among the controls.

“It may be that decreasing the inflammation with corticosteroid treatment has a protective effect on IOP,” he said.

**EPITHELIAL HEALING**

“This difference was also seen in the pilot trial, and so it seems to be a true finding that epithelial healing takes longer with corticosteroid use,” he said. “Final scar size and frequency of perforation were also not different between arms.”

The other difference was in the rate of IOP spikes (>25 mm Hg and <35 mm Hg), but these events occurred significantly less often in the corticosteroid-treated eyes than among the controls.

“Although the difference between groups was not statistically significant, the benefit favoring corticosteroid treatment was actually greatest in eyes with *Pseudomonas* infection than with any other pathogen,” he said. “Prior to SCUT, we would not have used a corticosteroid in an eye with a central *Pseudomonas* ulcer. It was encouraging to see, therefore, that eyes with *Pseudomonas* did not do worse when treated with a corticosteroid.”

Among eyes with a *Nocardia* corneal ulcer, however, BSCVA at 3 months was significantly worse in the corticosteroid group. The difference compared with controls was about 1 line, and an analysis of BSCVA outcomes at 1 year showed a significant difference favoring corticosteroid treatment when eyes with *Nocardia* were excluded.

**RESULTS**

“Results of the SCUT trial show that adjunctive topical corticosteroid therapy in eyes with bacterial corneal ulcers is safe, might be particularly useful in eyes with severe ulcers or *Pseudomonas* infection, and is more beneficial when started earlier than later, and should be avoided when *Nocardia* is the causative pathogen.”

**OBSERVATIONS**

“The message here is do not use corticosteroids to treat a corneal ulcer caused by *Nocardia*. In fact, the data suggests that perhaps *Nocardia* ulcers should have been excluded from SCUT,” he said.

Other secondary outcome analyses compared BSCVA outcomes of the corticosteroid and placebo treatment groups in eyes with baseline BSCVA <20/400 or central ulcers. For these subgroups with the “worst” ulcers, mean BSCVA at 3 months was significantly better in the corticosteroid group compared with controls.

Another secondary outcome analysis examined whether the timing of corticosteroid initiation affected functional outcomes. Its results showed a 1.1-line greater improvement in BSCVA among eyes that received corticosteroid treatment within 2 to 3 days versus those where there was a longer delay, and the benefit of earlier treatment was statistically significant.

“This finding was somewhat surprising because it was previously thought that it was better to try to eliminate the bacteria before adding the corticosteroid,” he said.

**CONCLUSIONS**

The SCUT trial adds yet another piece to the puzzle of the role of corticosteroids in the management of bacterial corneal ulcers. It supports findings from previous studies that corticosteroids might be preferred or avoided in the management of bacterial corneal ulcers.

**About the Author**

**Thomas M. Lietman, MD**

This article was adapted from Dr. Lietman’s presentation during Cornea Subspecialty Day at the 2017 meeting of the American Academy of Ophthalmology. Dr. Lietman has no relevant financial interests to disclose.
Dendritic cells migrate to regions of retinal stress to mediate neurodegeneration

Presence and activity of these cells may have implications for novel therapeutics

By Peter H. Tang, MD, PhD; Special to Ophthalmology Times

**EDITOR'S NOTE**

- Ophthalmology Times is pleased to announce Peter H. Tang, MD, PhD, vitreoretinal surgery fellow, Stanford University Byers Eye Institute, Palo Alto, CA, as the second-place honoree of the inaugural Ophthalmology Times Research Scholar Honoree Program. Dr. Tang’s abstract is featured here.

The Ophthalmology Times Research Scholar Honoree Program is dedicated to the education of retina fellows and residents by providing a unique opportunity for fellows/residents to share notable research and challenging cases with their peers and mentors. The program is supported by unrestricted grants from Regeneron Pharmaceuticals and Carl Zeiss Meditec Inc.

Elizabeth Atchison, MD, senior fellow, Rush University and Illinois Retina Associates Chicago, is the first-place honoree of the Ophthalmology Times Research Scholar Honoree Program. Her abstract is featured at ModernRetina.com/Atchison

Look for more case study honorees in future issues.

**BACKGROUND**

RPE65 protein dysfunction disrupts retinal metabolism of vitamin A leading to Leber congenital amaurosis (LCA), a congenital retinal dystrophy characterized by early-onset cone death and progressive vision loss. Human LCA is recapitulated in the RPE65 gene knockout (RPE65^-/-) mice. Previous studies of mice with genetically engineered dendritic cells (DCs) expressing green fluorescent protein (GFP) show that these cells were attracted to retinal injury.

In our study, we asked if apoptotic photoreceptor cell death in RPE65^-/- mice induced a retinal response that involved these DCs.

**METHODS**

RPE65^-/- mice with DC expressing GFP were generated through cross-breeding and analyzed by immunohistochemistry, confocal microscopy, fluorescence funduscopy, and flow cytometry. Tamoxifen was used to deplete DC in separate sensitive RPE65^-/- mice to investigate the potential role of DC in LCA.

Continues on page 32 : Research scholar

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**Morphology**

Left: Cone death recruits DC to outer retina (4 weeks). Right: DC recruited to the OPL (3 weeks).
RESEARCH SCHOLAR

Continued from page 31

RESULTS

DCs were found to concentrate in the photoreceptor cell layers coinciding with the peak of cone death at 2 to 3 weeks of age. Elevated numbers of DC remained in RPE65+/− retinas after the first month of age, suggesting that other factors, possibly rod degeneration, may play roles in recruiting and retaining DC cells in the outer retina.

Sustained tamoxifen-mediated depletion of DC in the RPE65−/− mice from day 7 to 41 of age accelerated cone death.

CONCLUSION

Our results show that DCs are recruited to the sites of retinal injury and stress. DC in an animal model of LCA show migration to the outer retina by cone death due to disruption of intrinsic retinoid metabolism.

The presence and activity of these cells may have implications for novel therapeutics involving immune cells in the treatment for congenital retinal dystrophies.

The presence and activity of these cells may have implications for novel therapeutics involving immune cells in the treatment for congenital retinal dystrophies.

Flow cytometry

Dendritic cells recruited to retina (age 2 weeks).

Elevated numbers of DC remained in RPE65−/− retinas after the first month of age, suggesting that other factors, possibly rod degeneration, may play roles in recruiting and retaining DC cells in the outer retina.

(Images courtesy of Peter H. Tang, MD, PhD)
L ow capture rate. One of the most overlooked revenue-generating areas of your practice may be “right under your nose,” as the saying goes. It has to do with the way you (or your physicians) conclude a comprehensive eye examination.

For purposes of this article, the question is: Why do so many ophthalmology practices have a low capture rate?

One of the primary reasons is lack of physician involvement. This generally manifests as the physician failing to recommend appropriate eyewear.

Continues on page 34: Hand off
HAND OFF

(Continued from page 33)

and then not channeling patients into the dispensary. In dispensary terms, this channeling is known as a “hand-off.” Put another way, there is a direct correlation between the hand-off and the practice’s capture rate.

Capture rate is defined as the number of prescriptions generated daily divided by your daily refractions expressed as percentage. The capture rate is the principle financial driver which creates the revenue stream produced in your optical dispensary. Many practices that track this metric discover that capture rate may initially fall between 25% to 35%. This is significantly lower than an ideal goal of 60% of all patients who are refracted.

How do you go about improving the patient hand-off from physician to the optical dispensary and thus improve your capture rate? Let’s start with some marketing theory.

PATH TO PURCHASE

If you are familiar with the marketing concept of the Path to Purchase, you know there are moments along that decision-making path when shoppers are open to receiving information that can help them decide what to purchase and where to purchase it. These are known as Moments of Maximum Impact (MMI).

The general principle that marketing experts agree on is that the most powerful MMI in ophthalmology is when the patient is sitting in the examination room chair and the doctor is giving them recommendations. From a dispensary standpoint, this is known as “prescribing from the chair.”

PRESCRIBING FROM THE CHAIR

Prescribing from the chair is the art of making appropriate recommendations to patients for specific eyewear. Those recommendations should be solidly based on patient responses to direct questions about how they use their eyes. Those questions should cover work, hobbies, or other visual task requirements.

Using the same techniques you would use to recommend cataract surgery or any procedure, inform patients of their options and suggest they visit your dispensary for more information.

THREE OPTIONS

As mentioned above, moving the patient from the examination room to the dispensary is known as the hand-off. A proper patient hand-off is the key to improving your practice’s capture rate and hence your dispensary’s revenue. So, how do you improve the hand-off? The answers vary by practice but there are several methods that work.

1 PHYSICIAN ESCORTS. The first hand-off option is for you, the doctor, to escort the patient to the dispensary. Introduce them to the optician, then instruct the optician about the specific frame and lens recommendations you have made for that patient. This is by far the most effective hand-off method. The reason given most often for not using it is that many doctors feel they do not have the time for it.

2 TECH ESCORTS. The second hand-off option is to transfer your eyewear recommendations to your tech or scribe and have them escort the patient to the dispensary. This is an area that is well worth the time to look into.

3 PRINT PRESCRIPTIONS IN DISPENSARY. Those practices that use an electronic health record (EHR) system can often arrange for the patient’s eyeglass prescription to be printed in the dispensary. In this case, the patient is instructed to go to the dispensary to obtain the prescription. Some practices use their EHR system that contains an array of recommendation check boxes. The physician reviews his specific recommendations with the patient, checks the appropriate boxes in the EHR system, and then directs the patient to pick up their printed prescription at the dispensary. The optician then reviews the physician recommendations with the patient. This method has the advantage of requiring 100% of the patients to present at the dispensary.

4 CALL THE OPTICIAN. Some practices use systems (lights, buzzers, etc.) that alert the optician when a patient has completed their examination. The optician is then called back, so to speak, introduced to the patient and given the physician’s frame and lens recommendations. The optician then escorts the patient to the dispensary and demonstrates the recommended products.

BOTTOM LINE

The bottom line is that with a little physician engagement and a little reworking of some basic processes, your practice’s capture rate can improve—in some cases, dramatically.

Considering that the inverse of your capture rate is the number of patients who chose to leave your practice with their unfilled prescription in their hand, I would say this is an area that is well worth the time to look into.
Dry eye is one of the most frequent causes of patient visits to eye care practitioners, affecting an estimated 30 million people in the US. As many as 1 in 3 ophthalmic patients report experiencing at least one symptom of dry eye. Yet this condition may be missed by eye care providers, in part because of the wide variability in its clinical presentation. Not all patients present with the classic symptoms such as irritation and burning. Many may seek help for what they describe as fluctuating vision, eye fatigue, among other atypical symptoms.

In addition to prompt recognition, an understanding of the mechanisms leading to dry eye is key to its management. In July 2017, the Tear Film and Ocular Surface Society published the second Dry Eye Workshop (DEWS II) findings which emphasize that the tear film should be thought of as 2-layered, with a lipid layer overlaying a muco-aqueous phase. It is likely that interactions of the whole tear film, including lipids, mucins, proteins, and salts, maintain tear film homeostasis, and thus a lubricant that addresses all layers of the tear film is needed.

Restoration of tear homeostasis is indeed the focus in the management of dry eye. In aqueous-deficient dry eye, lacrimal secretion is reduced. In evaporative dry eye, patients experience excessive evaporation from insufficient production of protective lipids as seen in cases of meibomian gland dysfunction (MGD).

In my clinical practice it is rare to see a patient with purely aqueous-deficient dry eye. In fact, an overlap of both types of dry eye can be seen in 30-70% of patients according to the DEWS II report. If only one of these dry eye types is addressed, patients may not be able to derive maximal relief. A simple way to help patients is to recommend a drop designed for all major types of dry eye, such as SYSTANE® Complete. This innovative formulation supplements all the layers of the tear film, which helps to restore the tear structure and protect from evaporation. SYSTANE® Complete is designed to minimize blur on instillation due to its nano-droplet formulation. The new formulation of SYSTANE® Complete with the nano-droplet technology resulted in increased moisture retention based on pre-clinical studies in comparison to SYSTANE® Balance lubricant eye drops.

Dry eye is complex and can have a real impact on a patient’s quality of life. SYSTANE® Complete is designed to provide symptom relief for every major type of dry eye.
Ophthalmologists can choose from a range of devices for measuring IOP, each with its own strengths and weaknesses, according to Yvonne Buys, MD.

Though new technology continues to emerge, nothing has yet to replace the Goldmann applanation tonometer, said Dr. Buys, who gave an overview of tonometer technology.

“The Goldmann remains the gold standard,” said Dr. Buys, professor, Department of Ophthalmology and Vision Sciences, University of Toronto, Canada. “But you need to have another device to measure IOP when you can’t use the Goldmann.”

Multiple limitations have spurred researchers to develop alternatives. Variations in the cornea—such as corneal thickness, curvature, elasticity or rigidity, and hydration—can influence Goldmann readings.

**LIMITATIONS OF GOLDMANN**

The Goldmann tonometry also cannot accommodate patients unable to sit at a slit lamp because they are bedridden, in wheelchairs, have severe neck problems, or certain body types. In addition, the Goldmann requires sterilization and calibration.

Because patients must visit their practitioners for Goldmann tonometry, it only provides IOP at a single point in time, typically during normal office hours.

“It only allows you to get a snapshot measurement,” Dr. Buys said. “We do know that eye pressure varies throughout the day. With tonometry, it is also important to know the range of variability and specifically how high it’s going.”

Since the advent of the Goldmann tonometer in 1954, at least nine other approaches have emerged, seven of them in the past 15 years, said Dr. Buys.

Released in 2003, the Pascal Dynamic Contour Tonometer works by the principle of contour matching rather than applanation. This eliminates the influence of corneal thickness, rigidity, curvature, and elastic properties. It is not a variable-force tonometer, and it provides the ocular pulse amplitude.

On the other hand, it takes a mean of 6 seconds to obtain a reading.

“In a busy clinic this can be a limitation,” added Dr. Buys.

The Diaton is a transpalpebral, transcleral tonometer that may have had use in patients with keratoprostheses, a challenge none of the other devices have surmounted.

“Unfortunately, it’s more like a random number generator because its values are really not comparable to Goldmann tonometry,” said Dr. Buys.

The Icare Rebound tonometer directs a disposable magnetized probe to the cornea. It converts the deceleration time of this contact to IOP. Because it is fast, it doesn’t require anesthesia, but for the same reason, it is influenced by short-term variations in pressure, so a mean of about six measurements are needed for a final reading.

The Icare HOME, a hand-held device, can be used by the patient at home, so it is not limited to office hours. It also doesn’t require anesthesia.

It recognizes the difference between the left and right eyes, and it stores its results for viewing on a personal computer. However, it cannot be used lying down.

About 75% to 100% of patients were able to use the Icare Home successfully in various studies. Industry standards call for a variation from Goldmann readings of ± 5 mm Hg.

When patients, who were excluded from correlations studies, were added, about 50%-100% of readings fell within that margin. The Icare Home tends to underestimate at lower pressures and overestimate at higher pressures, Dr. Buys said.

Continues on page 37: IOP measure
How to find the right EHR point person

Appoint an in-office ‘superuser’ who knows the ins, outs of EHRs to minimize frustration

By Mary K. Pratt

**PHYSICIANS** have had a long list of frustrations with their electronic health record (EHR) systems for years.

However, they may minimize or even eliminate much of their frustration by dedicating a “superuser” in their practice.

“Everyone has different workflows, different processes, and they meet federal requirements in different ways, so you want someone who really understands how the software works with the processes in your office,” said Randi Terry, MBA, director of information services at Munson Healthcare, a regional nonprofit medical system in Traverse City, MI.

A superuser is someone who has a superior knowledge of the software and how it can be best utilized.

**SCAN YOUR STAFF**

Terry notes that physicians themselves shouldn’t take this on. She said some very tech-minded doctors do indeed work well in this role but most don’t have the time, or inclination, to focus on software.

Physicians could train a current employee to do the job; larger practices could consider hiring someone for the position. Employees who like challenges and are skilled at problem-solving and multitasking are good candidates, according to Terry.

The ideal EHR point person should understand every aspect of the office so they can make the software work for the practice.

This staff member needs to receive advanced training in the EHR—something that vendors generally offer either at the practice, at their own facilities, or electronically via webinars. Additionally, this employee should understand how the front and back office work, how the clinical side operates and how regulatory requirements fit in, “so they can make that software work for the practice,” Terry said.

She emphasizes that this position is not the same as bringing in a consultant.

“They might give a best practice, and it might really be a best practice, but it might not work in that practice,” she said.

**SUPERUSER BENEFITS**

Help everyone in the office maximize their use of the EHR for clinical, regulatory and operational requirements.

Instruct colleagues on how to better utilize the system and help train new workers on its use. Guide physicians and other staff through upgrades as features.

Find opportunities to use the EHR to streamline processes and become more efficient and effective.

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**Editor’s Note:** This article originally appeared in sister publication Medical Economics.

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**IOP MEASURE**

(Continued from page 36)

**TRIGGERFISH LENS**

The Sensimed Triggerfish is a soft disposable silicone contact lens embedding a micro-sensor that captures spontaneous circumferential changes at the corneoscleral area. These changes are presumed to be influenced by IOP, but the manufacturer assumes the changes are linear.

“I can’t imagine the corneal curvature change is the same when you go from 7 mm Hg to 8 mm Hg as it is from 59 mm Hg to 60 mm Hg,” said Dr. Buys.

The Triggerfish does offer a robust number of measurements, and its software cleans up erroneous values, she said.

In their own research, Dr. Buys and colleagues found that readings with the Triggerfish tend to drift upward over time, and other researchers have corroborated this finding.

It is not clear whether this is some statistical artifact, whether the tight-fitting Triggerfish contact lens is affecting pressure, or whether this is an actual phenomenon. However, Dr. Buys and colleagues did not find a similar increase in pressure when comparing measurements with the Goldmann immediately before and after using the Triggerfish.

Another limitation of the Triggerfish is that it measures in arbitrary units rather than mm Hg, the standard unit of measure for eye pressure, said Dr. Buys.

**NEW DEVICE CHALLENGES**

In general, poor correlations with Goldmann values has posed a challenge with the newer devices, she said—with the Pascal overestimating; the Reichert, Corvis, and Icare over- and under-estimating; and the Diaton correlating so poorly that no comparison can be made.

For this reason, Dr. Buys recommended against changing techniques while following an individual patient.

Dr. Buys concluded that while the Goldmann remains the gold standard, all these devices can indicate high pressures, and each has some advantages that might make it worthwhile for a particular patient. This highlights the importance of an individualized approach to tonometry.

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**YVONNE BUYS, MD**

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This article was adapted from Dr. Buys’ presentation during Glaucoma Subspecialty Day at the 2017 meeting of the American Academy of Ophthalmology.

Dr. Buys receives grant support from Sensimed.
How to ‘hack’ your EHR for the best customized alerts

Clinical-decision support includes ticklers, medical evidence relevant to ophthalmic practices

By Nancy Groves; Reviewed by Kelly E. Chung, MD

THE ROLE OF ELECTRONIC health record (EHR) systems in improving the quality and safety of care may be undervalued in practices that have not customized the generic alerts and forms in their EHR system to make them more relevant to the needs of ophthalmology patients, according to Kelly D. Chung, MD.

Many physicians may have become jaded about EHR alerts—also known as clinical-decision support—since a flagged drug-drug interaction may have no relevance to the medications commonly used in their particular specialty, resulting in a high frequency of false positives, said Dr. Chung, who is in private practice with Oregon Eye Specialists, Portland, and a member of the American Academy of Ophthalmology Medical Information Technology Committee.

However, both medication alerts and other support functions of EHRs can be modified to make them more pertinent, she said.

“If you can implement some focused support tools for your practice, it can help you move beyond just using your EHR for documentation and billing to using it for improving the quality of your patient care,” she explained.

“Clinical-decision support is the use of computer functionality to make us better doctors by selectively presenting information when we need it,” Dr. Chung said. “And when we need it is the key point—the last thing we need to do is click on more information that isn’t relevant; a lot of the things that have been built into these big systems are pretty generic but can be modified to be more relevant to a specific practice setting and specialty.”

Types of alerts—some of which can be customized without special assistance from your vendor and some that might require coding—include immediate alerts, such as warnings and critiques; event-driven alerts and reminders; order sets, care plans, and protocols; parameter guidance; smart document forms; relevant data summaries; predictive and retrospective analytics; filtered reference and information; and the expert work-up advisor.

PATIENT SERVICE

“Studies in the realm of clinical-decision support have demonstrated their ability to improve the quality and safety of our care,” Dr. Chung said.

As a case in point, a study on the effectiveness of documentation forms and decision support tools for hydroxychloroquine screening showed a definite improvement in the appropriateness of screening (from 46% to 75%) and a decrease in inappropriate screening from 25% to 2% (Ophthalmology. November 2016).

SOME EXAMPLES

Instances of clinical-decision support specific for ophthalmology medical alerts include:

- A graph shows that a glaucoma patient’s IOP is above the target pressure.
- Clicking an advisory icon for ethambutol, a rarely encountered drug, shows the recommended screening for ocular toxicity.
- The system highlights that a patient is taking certain systemic medications such as beta-blockers or alpha adrenergic agonists (e.g., Flomax).
- Systemic medications that have ocular side effects can be highlighted or flagged, and clicking the drug name for further information reveals what those are. For example, docetaxel (Taxotere) could cause a host of ocular side effects.
- An intake form for patients on hydroxychloroquine will prompt the user to record relevant information including height, weight, and medication history. Further, the latest dosage guidelines can be incorporated into a standard letter to be sent to the referring rheumatologist to help disseminate preferred practice guidelines.

TAKE-HOME

- Practices can get more out of their EHR system than billing and documentation. Systems can be customized to provide many forms of clinical-decision support including alerts and medical evidence relevant to ophthalmology practices.

ASK FOR HELP

Dr. Chung’s suggestion for practices: If you aren’t aware of all the decision-support capabilities of your system or need help with modifications, speak with your vendor and appoint a physician or technician champion in your office to lead this process from within your organization.

“We are far from using the power that these systems could give us to enhance rather than just document care,” Dr. Chung said.

“EHR companies have been so focused on other priorities that making clinical-decision support enhancements has taken a back seat to regulatory considerations,” she said. “Make your clinical-decision support work. Customize it to your needs, and implement best medical evidence into clinical workflows.”

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This article was adapted from Dr. Chung’s presentation at the 2017 meeting of the American Academy of Ophthalmology. She has no relevant financial disclosures.
INDICATION

VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

IMPORTANT SAFETY INFORMATION

• Increased pigmentation of the iris and periorbital tissue (eyelid) can occur. Iris pigmentation is likely to be permanent.
• Gradual changes to eyelashes, including increased length, increased thickness, and number of eyelashes, may occur. These changes are usually reversible upon treatment discontinuation.
• Use with caution in patients with a history of intraocular inflammation (iritis/uveitis). VYZULTA should generally not be used in patients with active intraocular inflammation.
• Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. Use with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

VYZULTA DELIVERS A DUAL MECHANISM OF ACTION FOR THE REDUCTION OF IOP IN GLAUCOMA PATIENTS

ONE MOLECULE. TWO OUTFLOW PATHWAYS. PROVEN IOP REDUCTION

‘In studies up to 12 months’ duration, the IOP-lowering effect was up to 7.5 to 9.1 mmHg, in patients with an average baseline IOP of 26.7 mmHg

IMPORTANT SAFETY INFORMATION (CONTINUED)

• There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products that were inadvertently contaminated by patients.
• Contact lenses should be removed prior to the administration of VYZULTA and may be reinserted 15 minutes after administration.
• Most common ocular adverse reactions with incidence ≥2% are conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%).

For more information, please see Brief Summary of Prescribing Information on next page.

References:
2. Weinreb RN, Sforzolini BS, Vittitow J, Liebmann J. Latanoprostene bunod 0.024% versus timolol maleate 0.5% in subjects with open-angle glaucoma or ocular hypertension: the APOLO study. Ophthalmology. 2016;123(5):965-973.

For more information about VYZULTA and how it works, visit vyzultanow.com
BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all the information needed to use VYZULTA safely and effectively. See full Prescribing Information for VYZULTA.

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024%, for topical ophthalmic use.

Initial U.S. Approval: 2017

1 INDICATIONS AND USAGE

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% is indicated for the reduction of intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Pigmentation

VYZULTA™ (latanoprostene bunod ophthalmic solution) 0.024% may cause changes to pigmented tissues. The most frequently reported changes with prostaglandin analogs have been increased pigmentation of the iris and peribulbar tissue (eyelid).

Pigmentation is expected to increase as long as latanoprostene bunod ophthalmic solution is administered. The pigmentation change is due to increased melanin content in the melanocytes rather than an increase in the number of melanocytes. After discontinuation of VYZULTA, pigmentation of the iris is likely to be permanent, while pigmentation of the peribulbar tissue and eyelash changes are likely to be reversible in most patients. Patients who receive prostaglandin analogs, including VYZULTA, should be informed of the possibility of increased pigmentation, including permanent changes. The long-term effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with VYZULTA™ (latanoprostene bunod ophthalmic solution), 0.024% can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly [see Patient Counseling Information (17) in full Prescribing Information].

5.2 Eyelash Changes

VYZULTA may gradually change eyelashes and vellus hair in the treated eye. These changes include increased length, thickness, and the number of lashes or hairs. Eyelash changes are usually reversible upon discontinuation of treatment.

5.3 Intraocular Inflammation

VYZULTA should be used with caution in patients with a history of intraocular inflammation (iritis) and should generally not be used in patients with active intraocular inflammation as it may exacerbate this condition.

5.4 Macular Edema

Macular edema, including cystoid macular edema, has been reported during treatment with prostaglandin analogs. VYZULTA should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

5.5 Bacterial Keratitis

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

5.6 Use with Contact Lens

Contact lenses should be removed prior to the administration of VYZULTA because this product contains benzalkonium chloride. Lenses may be reinserted 15 minutes after administration.

6 ADVERSE REACTIONS

The following adverse reactions are described in the Warnings and Precautions section: pigmentation (5.1), eyelash changes (5.2), intraocular inflammation (5.3), macular edema (5.4), bacterial keratitis (5.5), use with contact lens (5.6).

6.1 Clinical Trials Experience

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

VYZULTA was evaluated in 811 patients in 2 controlled clinical trials of up to 12 months duration. The most common ocular adverse reactions observed in patients treated with latanoprostene bunod were: conjunctival hyperemia (6%), eye irritation (4%), eye pain (3%), and instillation site pain (2%). Approximately 0.6% of patients discontinued therapy due to ocular adverse reactions including conjunctival hyperemia, conjunctival irritation, eye irritation, eye pain, conjunctival edema, vision blurred, punctate keratitis and foreign body sensation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no available human data for the use of VYZULTA during pregnancy to inform any drug associated risks.

Latanoprostene bunod has caused miscarriages, abortion, and fetal harm in rabbits. Latanoprostene bunod was shown to be abortifacient and teratogenic when administered intravenously (i.v.) to pregnant rabbits at exposures ≥ 0.28 times the clinical dose.

Doses ≥ 20 μg/kg/day (23 times the clinical dose) produced 100% embryofetal lethality. Structural abnormalities observed in rabbit fetuses included anomalies of the great vessels and atrioventricular septum, heart, aorta, and ventricular septal defect anomalies, limb hypertelorism and malrotation, abdominal distension and edema. Latanoprostene bunod was not teratogenic in the rat when administered i.v at 150 mcg/kg/day (87 times the clinical dose) [see Data].

The background risk of major birth defects and miscarriage for the indicated population is unknown. However, the background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data

Animal Data

Embryofetal studies were conducted in pregnant rabbits administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 19, to target the period of organogenesis. The doses administered ranged from 0.24 to 80 mcg/kg/day. Abortion occurred at doses ≥ 0.24 mcg/kg/day latanoprostene bunod (0.28 times the clinical dose). When body surface area is used, assuming 100% absorption, Embryofetal lethality (resorption) was increased in latanoprostene bunod treatment groups, as evidenced by increases in early resorptions at doses ≥ 0.24 mcg/kg/day and late resorptions at doses ≥ 6 mcg/kg/day (approximately 7 times the clinical dose). No fetuses survived in any rabbit pregnancy at doses of 25 mcg/kg/day (23 times the clinical dose) or greater. Latanoprostene bunod produced structural abnormalities at doses ≥ 0.24 mcg/kg/day (0.28 times the clinical dose). Malformations included anomalies of sternal, coarctation of the aorta with pulmonary trunk dilation, retroesophageal subclavian artery with absent brachiocephalic artery, domed head, forepaw hypoplasia and hindlimb malrotation, abdominal distension/edema, and missing/fused caudal vertebra.

An embryofetal study was conducted in pregnant rats administered latanoprostene bunod daily by intravenous injection on gestation days 7 through 17, to target the period of organogenesis. The doses administered ranged from 150 to 1500 mcg/kg/day. Maternal toxicity was produced at 1500 mcg/kg/day (870 times the clinical dose). Malignant tumors in adrenal, ovary, and liver were observed at doses ≥ 300 mcg/kg/day (174 times the clinical dose). Malformations included anomalies of the sternum, domed head, forepaw hypoplasia and hindlimb malrotation, vertebral anomalies and delayed ossification of distal limb bones. A no observed adverse effect level (NOAEL) was established at 150 mcg/kg/day (67 times the clinical dose) in this study.

8.2 Lactation

Risk Summary

There are no data on the presence of VYZULTA in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother’s clinical need for VYZULTA, and any potential adverse effects on the breastfed infant from VYZULTA.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Latanoprostene bunod was not mutagenic in bacteria and did not induce micronuclei formation in the in vivo rat bone marrow micronucleus assay. Chromosomal aberrations were observed in vitro with human lymphocytes in the absence of metabolic activation.

Latanoprostene bunod has not been tested for carcinogenic activity in long-term animal studies. Latanoprost acid is a main metabolite of latanoprostene bunod. Exposure of rats and mice to latanoprost acid, resulting from oral dosing with latanoprost in lifetime rodent bioassays, was not carcinogenic.

Fertility studies have not been conducted with latanoprostene bunod. The potential to impact fertility can be partially characterized by exposure to latanoprost acid, a common metabolite of both latanoprostene bunod and latanoprost. Latanoprost acid has not been found to have any effect on male or female fertility in animal studies.

13.2 Animal Toxicology and/or Pharmacology

A 9-month toxicity study administered topical ocular doses of latanoprostene bunod to one eye of cynomolgus monkeys: control (vehicle only), one drop of 0.024% bid, one drop of 0.048% bid and two drops of 0.048% per dose, bid. The systemic exposures were equivalent to 4.2-fold, 7.9-fold, and 13.5-fold the clinical dose, respectively, on a body surface area basis (assuming 100% absorption). Microscopic evaluation of the lungs after 9 months observed pleural/subpleural chronic fibrosis/inflammation in the 0.04% dose male groups, with increasing incidence and severity compared to controls. Lung toxicity was not observed at the 0.024% dose.

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Bridgewater, NJ 08807 USA

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How EHR harmony can enhance intra-office communication

Cohesive, uniform terminology can also improve practice reimbursement percentages

By Nancy Groves; Reviewed by Edward L. Colloton, MD

HARMONIZING documentation from your electronic health record (EHR) system can improve both intra-office communication and the documentation and reporting of quality metrics, according to Edward L. Colloton, MD, an ophthalmologist in private practice in Bloomington, IL.

Several years ago, the four-person practice embarked on an effort to get all the “alpha types” in the anterior segment specialty group to agree on terminology used in documentation and reporting and used the reporting from the American Academy of Ophthalmology’s IRIS Registry (Intelligent Research in Sight) to motivate physicians to be more consistent with their language.

It is common for the clinicians in a group to have strong opinions on how to do things, Dr. Colloton said.

“Everybody knows that the way they do it is the right way to do it,” he said. “It’s very difficult to get those personality types to agree.”

However, common sense dictates that agreements must be reached on some key issues, and that achieving a consensus is not a trivial issue.

TERMINOLOGY ISSUES
Dr. Colloton recommends that practices acknowledge that while there is often more than one way to say the same thing, everyone must agree on an accepted usage.

For example, a particular change on the optic nerve head could be called a circumpapillary change, peripapillary atrophy, a scleral crescent, a myopic crescent, or several other terms. To avoid confusion, particularly for technicians and transcriptionists, choose a term and stick with it.

Terminology can also make a difference in reporting and reimbursement. When his practice began participating in the IRIS Registry, Dr. Colloton discovered that for the second quarter their rate for documentation of presence or absence of macular edema and level of severity of retinopathy was 62.65%, which was below the benchmark registry average of 65% despite insistence from the doctors and scribes that they were documenting this data.

A closer look showed that doctors weren’t getting credit in the numerator because mild background diabetic retinopathy wasn’t being accurately described.

“You and I might agree that a few microaneurysms with extraretinal exudates and rare dot hemorrhage is mild background diabetic retinopathy, but our software didn’t know that until we told the software that what we had just described is mild background diabetic retinopathy,” Dr. Colloton said. “We specifically had to add that language to the dropdown.”

A year after making that change, the rate of documentation in the practice had increased to 82.33%, and by the second quarter of 2017 it had reached 99.33%.

“This is a concrete example of how by agreeing to change and changing our culture we were able to achieve measurable improvement,” he said.

In other example involving the IRIS Registry, the practice’s performance for optic nerve evaluation in primary open-angle glaucoma was 45.97% when first calculated, compared with the registry average of 72.32%. The blame was pointed at the software—“it must be a glitch”—since the scribes and physicians were certain data were being correctly documented.

DATA MISFIRES
Motivated by their seeming “failure” at performing so far below average, the physicians began to investigate. They found that their EHR system did not recognize their documentation of an optic nerve evaluation, for purposes of the IRIS Registry, when the cup-to-disc ratio had not been entered following an exam performed with optical coherence tomography. Despite all the other data from the analysis, lack of that number meant no credit in the numerator. Now that this omission has been corrected, the practice has a 78.64% score for optic nerve evaluation.

When the performance data for a practice is not up to the expected standard, another way to investigate the problem is by examining the data for provider variation, Dr. Colloton said.

If the data show that certain providers are performing well below average, it opens the door to conversations about how to deliver a higher level of care.

CHANGING EHR FOR BETTER
“We have been able to use the tools the IRIS Registry has given us to encourage our doctors to agree, and that can be a tricky thing to accomplish,” Dr. Colloton said. “The IRIS Registry serves as a tool to help us clarify our communication with our doctors and improve on an already positive office culture while demonstrating measurable improvement in performance.”

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This article was adapted from Dr. Colloton’s presentation at the 2017 meeting of the American Academy of Ophthalmology. He did not report any financial disclosures.
How Medicare Part D affects your glaucoma patients

When lack of coverage is a concern, discussion between physician and patient is key

By Nancy Groves; Reviewed by Miranda Gill, MSN, RN, and Savak “Sev” Teymoorian, MD, MBA

TWO NEW GLAUCOMA DRUGS

approved in late 2017 are not on the 2018 Medicare Part D formulary, creating quandaries for physicians who would like to prescribe them and for patients who may have to pay out of pocket.

While latanoprostene bunod (Vyzulta, Bausch + Lomb) and netarsudil ophthalmic solution 0.02% (Rhopressa, Aerie Pharmaceuticals) are the two latest examples, it is not uncommon for the timing and length of the approval process to lead to delays in coverage, but there are ways to address the situation.

Drug companies often try to mitigate the situation with payment-assistance plans or vouchers, but drug discount programs usually do not work with Medicare Part D, said Savak “Sev” Teymoorian, MD, MBA, Harvard Eye Associates, Laguna Hills, CA.

However, if patients make the personal choice to buy medications outside of their Medicare Part D prescription drug plan, the price could be lowered with a co-pay card, voucher, or bridge program, said Miranda Gill, MSN, RN, NEA-BC, director of clinical innovation, CoverMyMeds, Columbus, OH.

“To help patients get on and stay on the medications they need, medication adherence programs, patient assistance programs, and disease specific foundations are some forms of assistance that I would attempt to explore with my patients,” Gill said.

These organizations can be discovered through the Patient Access Network Foundation (https://panapply.org).

While it is drug- and disease-dependent, if assistance is identified, the amount of aid a patient receives can be significant, Gill said.

Physicians can also write a request to Medicare to ask for a coverage determination or an exception. There are three ways to go about this: call the patient’s plan, write a letter, or send a completed “Model Coverage Determination Request” form to ask for a coverage determination or exception.

Once a plan has received the standard request, it has 72 hours to notify the sender of its decision. (Forms and instructions can be found at https://www.cms.gov) When the lack of Medicare coverage for the two glaucoma drugs becomes a concern, the key to finding a solution is discussion between physician and patient.

“Our goal isn’t to dictate care, it’s to educate the patient,” Dr. Teymoorian said. “We can advise and recommend what we would do, and most patients take our recommendation if possible.”

“It is really important for providers and prescribers to involve the patient and be as transparent as possible with the information that they have available to them, discussing the unique clinical indicators that are prompting them to prescribe this particular medication and how it plays into their individual care plan,” Gill said.

SHARED DECISION MAKING

In this process of shared decision making, clinicians need to explain not only clinical indicators but also efficacy and side effects, as well as cost and accessibility, she added.

Continues on page 44: Coverage
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“However, most providers don’t have access to patient pay information, and the patient is often unaware of the out-of-pocket costs until they arrive at the pharmacy,” she said.

“Luckily, there are tools available that enable prescribers to view patient cost-share information while the patient is in the office,” Gill said. “RxBenefit Clarity, for example, is a tool that delivers the most accurate patient pay and real-time benefit information in the prescribing workflow, which can help prescribers have more informed conversations with their patients that can help drive adherence.”

It is also helpful to outline the process of drug approval and addition to Medicare formularies so that patients understand that decisions about coverage are made not by their doctors but by the government agency.

Though it is difficult to predict when (or if) a drug will be added to the formulary, patients who are likely to use a medication long-term may be reassured by the prospect that high out-of-pocket costs could be a temporary obstacle if a drug is added to the Medicare formulary within a matter of months.

The discussion also should explore include alternative medications to achieving treatment goals if no options exist to lower the cost of a drug and the patient is unable or unwilling to pay the full amount.

“The price is very important, because it comes into play, but we shouldn’t eliminate an option that we think is right for the patient strictly based on price. We need to at least present alternatives to the patient and let them decide what’s the best option.”

An alternative to latanoprostene bunod would be to prescribe one of the already approved prostaglandin analogs, which should achieve similar intraocular pressure reductions. But there is no drug similar to netarsudil ophthalmic solution, a rho kinase inhibitor that has a novel mechanism of action and has been placed in a new class of drugs. This distinction is important, since patients may more readily pay out of pocket for a drug that has no alternatives, especially if it seems to have an advantage, such as the use of netarsudil ophthalmic solution as a once-daily adjunct to a prostaglandin, Dr. Teymoorian said.

Even if patients are willing to pay for a drug that is not covered by Medicare Part D, it may take some negotiating with local pharmacies to ensure that they can fill the prescription.

Not all pharmacies are willing to stock these drugs because of lower demand, Dr. Teymoorian said, and physicians may need to identify those that carry or will order them and encourage patients to visit these locations.

**TAKE-HOME**

> With two new glaucoma drugs not on the Medicare Part D 2018 formulary, doctors and patients need to explore options to lower the cost and discuss alternative treatments.

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2. **Monitor patient engagement activity.** Enabling patients to engage in self-management and then tracking whether they are fulfilling the desired actions is a critical step to determine which interventions are most successful at an individual patient level.

3. **Schedule appointments.** To save time and make scheduling vastly more efficient, patients can be given the ability to schedule their own appointments online or via a mobile app.

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6. **Provide patient education.** Providing online education materials for patients to access and review at their convenience is another key aspect of the portal.

7. **Set up home device monitoring.** Wireless monitoring devices that automatically transmit data and store it in the patient portal can help patients better manage their chronic conditions, while helping clinicians manage their care plans, spot trends, and improve and sustain their clinical and financial outcome goals.

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BRIEF SUMMARY
Consult the Full Prescribing Information for complete product information.

INDICATIONS AND USAGE
RHOPRESSA® (netarsudil ophthalmic solution) 0.02% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

DOSEAGE AND ADMINISTRATION
The recommended dosage is one drop in the affected eye(s) once daily in the evening.

If one dose is missed, treatment should continue with the next dose in the evening. Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

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

Use with Contact Lenses
RHOPRESSA contains benzalkonium chloride, which may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of RHOPRESSA and may be reinserted 15 minutes following its administration.

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

The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA dosed once daily was conjunctival hyperemia which was reported in 53% of patients. Other common (approximately 20%) ocular adverse reactions reported were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

Corneal Verticillata
Corneal verticillata occurred in approximately 20% of the patients in controlled clinical studies. The corneal verticillata seen in RHOPRESSA-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes in patients. Most corneal verticillata resolved upon discontinuation of treatment.

USE IN SPECIFIC POPULATIONS
Pregnancy
There are no available data on RHOPRESSA use in pregnant women to inform any drug associated risk; however, systemic exposure to netarsudil from ocular administration is low. Intravenous administration of netarsudil to pregnant rats and rabbits during organogenesis did not produce adverse embryofetal effects at clinically relevant systemic exposures.

Animal Data
Netarsudil administered daily by intravenous injection to rats during organogenesis caused abortions and embryofetal lethality at doses ≥0.3 mg/kg/day (126-fold the plasma exposure at the recommended human ophthalmic dose [RHOD], based on $C_{\text{max}}$). The no-observed-adverse-effect-level (NOAEL) for embryofetal development toxicity was 0.1 mg/kg/day (40-fold the plasma exposure at the RHOD, based on $C_{\text{max}}$).

Netarsudil administered daily by intravenous injection to rabbits during organogenesis caused embryofetal lethality and decreased fetal weight at 5 mg/kg/day (1480-fold the plasma exposure at the RHOD, based on $C_{\text{max}}$). Malformations were observed at ≥3 mg/kg/day (1330-fold the plasma exposure at the RHOD, based on $C_{\text{max}}$), including thoracogastroschisis, umbilical hernia and absent intermediate lung lobe. The NOAEL for embryofetal development toxicity was 0.5 mg/kg/day (214-fold the plasma exposure at the RHOD, based on $C_{\text{max}}$).

Lactation
There are no data on the presence of RHOPRESSA in human milk, the effects on the breastfed infant, or the effects on milk production. However, systemic exposure to netarsudil following topical ocular administration is low, and it is not known whether measurable levels of netarsudil would be present in maternal milk following topical ocular administration. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for RHOPRESSA and any potential adverse effects on the breastfed child from RHOPRESSA.

Pediatric Use
Safety and effectiveness in pediatric patients below the age of 18 years have not been established.

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

NONCLINICAL TOXICOLOGY
Carcinogenesis, Mutagenesis, Impairment of Fertility
Long-term studies in animals have not been performed to evaluate the carcinogenic potential of netarsudil. Netarsudil was not mutagenic in the Ames test, in the mouse lymphoma test, or in the in vivo rat micronucleus test. Studies to evaluate the effects of netarsudil on male or female fertility in animals have not been performed.

Manufactured for: Aerie Pharmaceuticals, Inc., Irvine, CA 92614, U.S.A.

For more information, go to www.RHOPRESSA.com or call 1-855-AerieRx (1-855-237-4379).

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AE, adverse event; IOP, intraocular pressure; ROCK, rho-associated protein kinase.

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INDICATION
Rhopressa® (netarsudil ophthalmic solution) 0.02% is a Rho kinase inhibitor indicated for the reduction of elevated intraocular pressure in patients with open-angle glaucoma or ocular hypertension.

Dosage and Administration:
The recommended dosage is one drop in the affected eye(s) once daily in the evening.

IMPORTANT SAFETY INFORMATION

Dosage and Administration:
Twice a day dosing is not well tolerated and is not recommended. If RHOPRESSA® is to be used concomitantly with other topical ophthalmic drug products to lower IOP, administer each drug product at least 5 minutes apart.

Warnings and Precautions:

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

Adverse Reactions:
The most common ocular adverse reaction observed in controlled clinical studies with RHOPRESSA® dosed once daily was conjunctival hyperemia, reported in 53% of patients. Other common (approximately 20%) adverse reactions were: corneal verticillata, instillation site pain, and conjunctival hemorrhage. Instillation site erythema, corneal staining, blurred vision, increased lacrimation, erythema of eyelid, and reduced visual acuity were reported in 5-10% of patients.

The corneal verticillata seen in RHOPRESSA®-treated patients were first noted at 4 weeks of daily dosing. This reaction did not result in any apparent visual functional changes. Most corneal verticillata resolved upon discontinuation of treatment.

REFERENCES:

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INSIGHTS FROM PERFORMANCE-DRIVEN SURGEONS:
Practice Profiles and Experts’ Pearls
SCOTT LABORWIT, MD, is a solo practitioner with 2 offices in the Baltimore, Maryland, area, and is a volunteer faculty member at the Wilmer Eye Institute of the Johns Hopkins University School of Medicine. He specializes in cataract surgery and operates in 2 outpatient surgery centers. One of these centers is directly connected with an office, with the other being nearby his second office.

Dr. LaBorwit installed the LenSx® Laser 5½ years ago at what was then his only surgery center and purchased a LenSx® Laser for the second center when it opened 2 years later. He does about 30 cataract surgeries each week, of which almost 70% are femtosecond laser-assisted cataract surgery (FLACS) cases and 20% to 25% receive an advanced technology intraocular lens (IOL).

**Why did you decide that getting a femtosecond laser was a good fit for you as a performance-driven surgeon?**

I actually went out to a meeting in California expecting to hear information reinforcing my belief that I did not need the laser. Instead, I realized the laser could help me offer better options to patients.

**Why did you choose the LenSx® Laser?**

Three companies were marketing a laser, and because of the financial commitment involved, the manufacturer’s history was important. I chose the LenSx® Laser because Alcon had the highest market penetration, and I was always happy with Alcon’s record of service and innovation. I also liked that the LenSx® Laser did not have a fixed bed. We use chair stretchers in the surgery centers, and avoiding transfers has benefits for patient comfort and efficiency.

When I opened my second surgery center, I considered getting a different laser system so that I could do comparative studies. But when I thought about how satisfied I was with the LenSx® Laser and Alcon, it made no sense to switch. The technology itself and level of service and innovation had all exceeded my expectations.

**What was the learning curve like with the LenSx® Laser?**

Getting started was relatively easy. I had no problems with docking because I had done femto-LASIK, and with the current, smaller patient interface (SoftFit™ Patient Interface) (FIGURE 3), docking is even easier now.

I experienced a learning curve about 6 months after I got the laser, but that involved experimentation with modifying my technique in the operating room (OR). I started to bowl out the lens instead of creating a groove and to use more vacuum and less phaco. With those changes, I significantly reduced ultrasound energy use.

**Describe your surgical workflow**

I start the day by doing the laser treatment on 2 patients, and then go into the OR to complete the first case. When I am putting the implant in, the circulating nurse rings a wireless doorbell that will alert the laser room, which is down the hall, to insert the lid speculum and raise the stretcher. When I go into the laser room, anesthesia has another patient ready to go into the OR.

**How is your practice structured to provide counseling to patients about their surgical options?**

Clinics were designed to see just cataract evaluation patients, allowing streamlining of testing, resources, and information and creating a predictable experience for the patients. Patients are initially given an informational sheet that introduces the concept of laser technology and the different kinds of implants.

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* Dr. Scott LaBorwit, Dr. Parag Majmudar, Dr. Carlos Martinez, and Dr. Zarmeena Vendal are all paid consultants to Alcon.

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PERFORMANCE-DRIVEN CATARACT SURGEONS, by their own definitions, aim to optimize the surgical experience for their patients and strive to consistently achieve accurate refractive results. To do so, they take advantage of the benefits provided by cutting-edge techniques and technologies and continue to introduce refinements guided by the findings of outcomes monitoring.

This supplement profiles 4 performance-driven refractive cataract surgeons* and their experiences using the LenSx® Laser System (FIGURE 1) and ORA SYSTEM® Technology (FIGURE 2) to achieve surgical success and satisfied patients. They represent a diverse group geographically, with respect to practice type, and in terms of what technology they are using and how. Thus, the insights shared by these expert users should have relevance for all cataract surgeons.
When I see a patient, we determine together whether or not the surgery should be done. I offer the laser to patients who have more than 0.5 D of corneal astigmatism. I use it when patients choose a toric or multifocal IOL, because I think a laser-assisted procedure gives me the best chance of hitting the refractive target and therefore achieving the goal of giving them reduced dependence on glasses.

I explain that I offer traditional and laser surgery technology, and I discuss the risks and benefits of each. Then patients meet with the surgical counselor who goes over the different packages and their costs based on knowledge of the patient’s copay and deductible.

Has the adoption rate of the laser changed over time?
It has been steadily high, even after I bought the second laser and raised the price by about 20% to cover my increased expenses. A RAND study on price elasticity in healthcare showed that time spent with patient education can offset the negative effect of rising cost on outcomes. Therefore, benefits of access to intraoperative aberrometry and the femtosecond laser were also clear.

I began using ORA SYSTEM® Technology in its first iteration, and that was several years before the advent of femtosecond lasers for cataract surgery. Once the LenSx® Laser was approved, our private practice recognized its acquisition would be integral for driving growth in our premium IOL segment. Because the surgery center is used by other specialists, we came up with a creative way to set up ownership of the laser that reduced the burden for the surgery center. The laser was acquired as a joint venture in which half of the cost was paid for by the surgery center and the other half by a corporation formed by the 8 ophthalmologists who were routinely doing cataract surgery.

Both the surgery center and our surgeon corporation have recovered our initial cost for the laser and subsequently enjoyed a good revenue stream from it.

We were also very instrumental in getting our community hospital to purchase the LenSx® Laser. That acquisition happened about 2 years ago, but the laser has done well and its availability in the hospital has benefited a lot of patients who otherwise might not have had access to the technology.

Why did you decide that getting a femtosecond laser and intraoperative aberrometry were a good fit for you as a performance-driven surgeon?
In 1998, I became one of the first ophthalmologists to complete a dedicated refractive surgery fellowship, and I carried the mindset that I had from that training into the cataract surgery segment of my practice. It was obvious to me that access to technology preoperatively and intraoperatively was the fundamental driving force behind achieving good refractive outcomes. Therefore, benefits of access to intraoperative aberrometry and the femtosecond laser were also clear.

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We were also very instrumental in getting our community hospital to purchase the LenSx® Laser. That acquisition happened about 2 years ago, but the laser has done well and its availability in the hospital has benefited a lot of patients who otherwise might not have had access to the technology.

Why did you choose the LenSx® Laser?
It was the only viable option available at the time, but I have never had any regrets since. Alcon was first to market with femtosecond technology, and this has advantages and disadvantages. A possible disadvantage was turned into a powerful advantage moving forward as Alcon solicited input from early adopters and introduced multiple hardware and software upgrades during the first 2 years alone to keep pace with advances in technology and make adjustments based on real-world experiences. Most of these advances improved patient outcomes by making the procedure more reproducible.

I also particularly like that the LenSx® Laser can be used with any OR bed, because it allows us to maintain the pace and volume that are required to run an efficient and profitable surgery center.

What was the learning curve like with the LenSx® Laser and ORA SYSTEM® Technology?
The laser docking and programming steps were familiar to me because I was well-versed in femto-LASIK, but surgeons at our center without any prior laser experience found a relatively shallow learning curve with the LenSx® Laser. Platform advances for ORA SYSTEM® Technology have shortened the learning curve tremendously. As with any new technology, obtaining the best results with either device requires surgeons make a concerted and committed effort toward learning and achieving mastery of it. Alcon also spent an enormous amount of time providing training and support for our staff, which made adopting FLACS relatively smooth.

How is your practice structured for counseling patients about their surgical options?
We have surgical counsellors who educate...
patients about their technology options, including different IOLs, the LenSx® Laser, and ORA SYSTEM® Technology, and help them navigate the financial options we have available for patients. Patients also watch an educational video as part of the informed consent process, and we have various brochures and other videos, including materials provided by Alcon.

What types of packages do you offer with the LenSx® Laser and ORA SYSTEM® Technology?
We tried to simplify the choices to minimize confusion for patients and staff. For refractive cataract surgery, we offer 3 packages (TABLE 1): glasses package—patients need glasses for all distances; distance only correction—correction of astigmatism either with the LenSx® Laser limbal relaxing incisions or a toric IOL and FLACS; and distance and near correction—involving a multifocal or accommodating IOL, astigmatism correction with incisions created with the LenSx® Laser or toric IOL, and FLACS.

ORA SYSTEM® Technology is used in all toric IOL cases and when IOL power calculation may be challenging, such as in patients with a history of corneal refractive surgery, forme fruste keratoconus, or pellucid marginal degeneration.

Describe your surgical workflow
At all of our centers, the laser is located in a nonsurgical room that is close to the OR, and I alternate between laser and nonlaser cases. I perform the laser procedure for patient 1 while nonlaser patient 2 is being brought to OR 2.

<table>
<thead>
<tr>
<th>Table 1. Packages for cataract surgery patients</th>
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<tr>
<td>Package</td>
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<tr>
<td>Patient expectations</td>
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<td>Management of pre-existing astigmatism</td>
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While patient 1 is being wheeled into OR 1, I operate on patient 2, and then complete the procedure on patient 1. Then I do the laser treatment for patient 3, etc. I call this the “triangle” offense, with apologies to Phil Jackson, and it allows us to perform a high number of surgeries per hour in a very efficient manner.

Have ORA SYSTEM® Technology and the LenSx® Laser affected your outcomes?
There is no doubt that this technology has improved my outcomes for astigmatism management and that it translates to better functional outcomes with multifocal IOLs. Published reports show benefits of FLACS for improving refractive predictability and stability.1,2

I have taught astigmatism management at the American Academy of Ophthalmology meeting for 19 years, and I know that even in expert hands, manual incisions are not very precise or reproducible. In my opinion, the accuracy and consistency that is possible with the LenSx® Laser has made a huge difference in outcomes.

How do you educate and motivate your staff?
Making sure staff is well versed in the pros and cons of the technology is vital for delivering accurate information to patients and helping them make informed decisions.

Our staff receives regular training both internally and from Alcon practice development teams. I think they are motivated by example from our physicians who are dedicated to achieving the best outcomes and satisfied patients and by the feedback and gratitude of “20/happy” patients.

What would be your main message to colleagues who are considering adding a femtosecond laser and/or intraoperative aberrometry?
I would urge them to become performance-driven surgeons and be sure that they and the staff in their office and surgery center are 100% committed to consistently achieving the best outcomes possible.

Why did you decide that getting the LenSx® Laser and ORA SYSTEM® Technology was a good fit for you as a performance-driven surgeon?
I had thought that the laser was a marketing gimmick and something that I didn’t need because I already had very few complications and very happy patients. I even said that it was unethical for me to sell FLACS because I could do as good a job without it, and the patient would not have to pay.

As I came to understand more about the procedure and the science, I decided I needed to try it. I contracted with a company that has a roll-on/roll-off program, and I immediately realized how predictable the incisions were and how the laser could safely and reliably treat the lens. I thought that if I needed cataract surgery, I would want a laser-assisted procedure, and that led me to make the purchase.

I had similar ideas about not needing ORA SYSTEM® Technology, and I wondered what I would do if the intraoperative reading did not match my preoperative plan. But, as I learned more and understood it better, I ad-

Why did you choose the LenSx® Laser?
I did a lot of research, met with different physicists and marketing people from each company, and I talked with a mentor of mine who was the medical monitor for another laser company. I chose the LenSx® Laser because I was impressed by the variable beam technology, patient interface, and fast OCT (optical coherence tomography) imaging. The SoftFit™ patient interface was introduced soon after I got the laser, and that made for greater patient comfort and improved the reliability of complete capsulotomy.

What was the learning curve like with the LenSx® Laser and ORA SYSTEM® Technology?
I think surgeons can use the LenSx® Laser safely and reliably to benefit patients beginning on the first day, but I worked to improve the procedure over time with modifications. For example, the LenSx® Laser gives users options
Describe your surgical workflow

The LenSx® Laser is kept in a small room that is between 2 ORs. Typically, I start by doing the laser portion of the procedure on 2 consecutive patients, and then I alternate between doing the phaco and the laser portions. I find this approach is very efficient, but it is important that all of the surgical staff understand the workflow to avoid wasting time and also to have good scheduling.

At the return visit, a technician spends about an hour reviewing the options. The LenSx® Laser and ORA SYSTEM® Technology are included in all toric or presbyopia-correcting IOL packages.

How is your practice structured for counseling patients about their surgical options?

Early in my practice, I realized that as soon as I told patients they needed cataract surgery, they became anxious and stopped listening to me. Therefore, patients are first given some informational material to review and scheduled for another appointment during which they will be counseled about the different options.

At the return visit, a technician spends about an hour reviewing the options. The LenSx® Laser and ORA SYSTEM® Technology are included in all toric or presbyopia-correcting IOL packages.

Describe your surgical workflow

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Based on a time study we did, I allocate 3 minutes for the laser and 4.5 minutes for ORA SYSTEM® Technology, both of which are really in excess of what is needed. I think that the idea that these technologies add too much time to the case is not a legitimate objection. Their use has markedly decreased the amount of chair time and the need for enhancements, which has made me more efficient.

Have you seen a change in adoption of the premium procedures since you got these technologies?

It has grown over time, and part of that can be attributed to word-of-mouth referrals. Patients come in asking about FLACS, and some of those people complain they were not offered the option by another surgeon they had seen.

Have ORA SYSTEM® Technology and the LenSx® Laser affected your outcomes?

I track my outcomes using the AnalyzOR™ technology feature on ORA SYSTEM® Technology, and I found that my spherical equivalent and residual astigmatism outcomes (Figure 4) improved after I implemented the LenSx® Laser.

In addition, I found a wide distribution of the amount of astigmatism measured with the different instruments used in my office. In some cases, there would be a 2.2-D difference between my Pentacam®, VERION® Image Guided System, and IOLMaster® measurements (Figure 5). I also found lack of agreement between my preoperative toric IOL plan and the ORA SYSTEM® Technology recommendation in about a third of cases. By using AnalyzOR™, I was able to understand the shortcomings of the preoperative data we use to do the IOL calculations and therefore why it is unreasonable to expect consistently accurate refractive outcomes relying on those data. ORA SYSTEM® Technology tells me exactly what power to choose and how to align toric IOLs. It takes into account posterior cornea astigmatism, surgically induced astigmatism, and the patient’s individual keratometric index.

How do you educate and motivate your staff?

We have an educational meeting for our technicians every 2 weeks during which we discuss news from industry and in the literature. This keeps the staff up to date, but it also inspires them and generates enthusiasm, because it lets them know that our practice is committed to improving patient outcomes.
to delivering state-of-the-art care in an ethical and responsible way.

What would be your main message to colleagues who are considering adding a femtosecond laser and intraoperative aberrometry?

Some surgeons are held back by not wanting to go outside their comfort zone or are just very conservative when it comes to making significant expenditures. Speaking from experience, I would tell them to put their concerns aside and give the LenSx® Laser and ORA SYSTEM® Technology a try, because I think they will quickly see the benefits.

Why did you decide that getting a femtosecond laser and intraoperative aberrometry were a good fit for you as a performance-driven surgeon?

Our practice mission has been to make state-of-the-art technology available for patients, and I think we have a reputation in our community for delivering cutting-edge care. In addition, our urban practice serves a significant population of people who are younger, very technology oriented, and who have active lifestyles. Providing FLACS with intraoperative aberrometry addresses their interests and seems consistent with supporting our goal of offering multiple surgical options, especially considering these patients would frequently opt for premium IOL technology.

Why did you choose the LenSx® Laser?

The LenSx® Laser was the first laser approved for cataract surgery, and we felt it was the most advanced in terms of updates and improvements that were built partly on troubleshooting. In addition, we believed that the LenSx® Laser was superior to other platforms with regard to corneal incision capabilities at the time of our purchase. We also had confidence in Alcon’s customer service. Alcon has the largest ophthalmic service organization in the industry, and their turnaround time has been second to none.

What was the learning curve like with the LenSx® Laser and ORA SYSTEM® Technology?

I had been doing femto-LASIK, and so there was not a significant learning curve for using the laser. In addition, we had a really good foundation for getting started because of the level of clinical support and staff training provided by Alcon. After about 2 months, staff were comfortable with the new procedures and workflow, and we were back to normal surgical times.

The learning curve is a little longer with ORA SYSTEM® Technology, because there are interpretative aspects in addition to the technical component. The user has to consider the reading and decide how to apply it intraoperatively, and then also analyze the postoperative outcomes. You have to wait until patients are at least 1 month out to get the postoperative data, and then use AnalyzOR™ to understand how ORA SYSTEM® Technology was helpful and learn from the findings so that you can refine surgical decisions in the future.

Describe your surgical workflow

Patients go from the preoperative area into a surgical bay for the laser treatment and from there into the OR. Because almost all of the patients where we have the LenSx® Laser have FLACS, we didn’t face the need to identify a certain flow scheme for integrating them into the schedule. Instead, achieving efficiency with operation and flow was about educating the staff, so that everyone was knowledgeable and comfortable with what they needed to be doing. This led to extremely quick turnaround times.

What types of packages do you offer with

**Figure 5.** Astigmatism measurements for 26 patients undergoing phacoemulsification with AcrySof® IQ Toric IOL implantation. Notice the variability of the measurements for some individuals. (Data: Carlos Martinez, MD)
the LenSx® Laser and ORA SYSTEM® Technology?
We have astigmatism correction packages that include the laser with a monofocal IOL or the laser with a toric IOL and presbyopia-correcting packages with FLACS plus a multifocal or multifocal toric IOL. ORA SYSTEM® Technology is used in all FLACS cases.

How is your practice structured for counseling patients about their surgical options?
We start the education process using informational apps that show the difference between conventional and laser surgery. We firmly believe that meaningful, one-on-one counseling with the surgeon is critical. After that, we have very experienced surgery coordinators who review the various packages in greater detail.

Have ORA SYSTEM® Technology and the LenSx® Laser affected your outcomes?
Using AnalyzOR™ technology to analyze our refractive outcomes, we see an increase in the percentage of eyes within 0.5 D of target whether looking at patients with monofocal or premium IOLs. We also feel that using these technologies further solidifies our reputation as a premium service practice. It is our overall impression that patients are well educated and extremely happy and satisfied.

How has the adoption of FLACS evolved over time?
It built up fairly steadily over the first 2 years. I was a firm believer in FLACS being a useful tool, which was important for getting the staff behind it, and then we were very proactive and comfortable discussing the procedure with patients who were appropriate candidates. Adoption of the laser was successful because a large segment of our patients is very technology focused. By year 1, about 25% of my cataract surgery volume involved FLACS. As our population of post-FLACS patients grew, word about our practice spread in the community. At 3 years after getting the LenSx® Laser, FLACS accounted for about 70% of my cases, and it has been steady at that level for the past 2 years.

How do you educate and motivate your staff?
Our staff watches procedures when we introduce new technology, because we think that witnessing it firsthand is the best way to appreciate what it is about and to get behind it. We also do regular in-service programs on topics of interest, and our staff get more formal education by attending professional meetings. I think they are really motivated by the philosophies, vision, and professionalism of the doctors in our practice.

What would be your main message to colleagues who are considering adding a femtosecond laser and/or intraoperative aberrometry?
I would say you cannot decide whether or not this technology has benefits in your practice unless you actually use it. FLACS has been available for quite some time, and surgeons should feel comfortable taking time to assess its benefits. If in fact you give it a fair trial, you will likely experience an “Aha!” moment when you become truly convinced that the technology adds value to your practice.

REFERENCE

LENSES® LASER IMPORTANT PRODUCT INFORMATION
Caution
Federal Law restricts this device to sale and use by or on the order of a physician or licensed eye care practitioner.

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

Restrictions
• Patients must be able to lie flat and motionless in a supine position.
• Patient must be able to understand and give an informed consent.
• Patients must be able to tolerate local or topical anesthesia.
• Patients with elevated IOP should use topical steroids only under close medical supervision.

Contraindications
• Corneal disease that precludes application of the cornea or transmission of laser light at 1030 nm wavelength
• Descemetocle with impending corneal rupture
• Presence of blood or other material in the anterior chamber
• Poorly dilating pupil, such as the iris is not peripheral to the intended diameter for the capsulotomy
• Conditions which would cause inadequate clearance between the intended capsulotomy depth and the endothelium (applicable to capsulotomy only)
• Previous corneal incisions that might provide a potential space into which the gas produced by the procedure can escape
• Corneal thickness requirements that are beyond the range of the system
• Corneal opacity that would interfere with the laser beam
• Hypotony or the presence of a corneal implant
• Residual, recurrent, active ocular or eyelid disease, including any corneal abnormality (for example, recurrent corneal erosion, severe baseline membrane disease)
• History of lens or zonular instability
• Any contraindication to cataract or keratoplasty
• This device is not intended for use in pediatric surgery.

Warnings
The LenSx® Laser System should only be operated by a physician trained in its use. The LenSx® Laser delivery system employs one sterile disposable Patient Interface consisting of an applanation lens and suction ring. The Patient Interface is intended for single use only. The disposables used in conjunction with Alcon® instrument products constitute a complete surgical system. Use of disposables other than those manufactured by Alcon may affect system performance and create potential hazards.

The physician should base patient selection criteria on professional experience, published literature, and educational courses. Adult patients should be scheduled to undergo cataract extraction.

Precautions
• Do not use cell phones or pagers of any kind in the same room as the LenSx® Laser.
• Discard used Patient Interfaces as medical waste.

Complications
• Capsulotomy, phacofragmentation, or cut or incision decentration
• Incomplete or interrupted capsulotomy, fragmentation, or corneal incision procedure
• Capsular tear
• Corneal abrasion or defect
• Pain
• Infection
• Bleeding
• Damage to intraocular structures
• Anterior chamber fluid leakage, anterior chamber collapse
• Elevated pressure to the eye

Attention
Refer to the LenSx® Laser Operator’s Manual for a complete listing of indications, warnings and precautions.
**ORASYSTEM® TECHNOLOGY – IMPORTANT PRODUCT INFORMATION**

**FOR HEALTHCARE PROFESSIONALS**

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

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

**INTENDED USE:** The ORASYSTEM® technology utilizes wavefront aberrometry data to measure and analyze the refractive power of the eye (i.e. sphere, cylinder, and axis measurements) to support cataract surgical procedures.

**WARNINGS AND PRECAUTIONS:** The following conditions may make it difficult to obtain accurate readings using the ORASYSTEM® technology:
- Patients having progressive retinal pathology such as diabetic retinopathy, macular degeneration, or any other pathology that the physician deems would interfere with patient fixation;
- Patients having corneal pathology such as Fuchs’, EBMD, keratoconus, advanced pterygium impairing the cornea, or any other pathology that the physician deems would interfere with the measurement process;
- Patients for which the preoperative regimen includes residual viscous substances left on the corneal surface such as lidocaine gel or viscoelastic;
- Visually significant media opacity, such as prominent flotators or asteroid hyalosis, will either limit or prohibit the measurement process; or
- Patients having received retro or peri bulbar block or any other treatment that impairs their ability to visualize the fixation light.

**In addition:**
- Significant central corneal irregularities resulting in higher order aberrations might yield inaccurate refractive measurements.
- Post refractive keratotomy eyes might yield inaccurate refractive measurement.
- The safety and effectiveness of using the data from the ORASYSTEM® have not been established for determining treatments involving higher order aberrations of the eye such as coma and spherical aberrations.
- ORASYSTEM® technology is intended for use by qualified health personnel only.
- Improper use of this device may result in exposure to dangerous voltage or hazardous laser-like radiation exposure. DO NOT OPERATE the ORASYSTEM® in the presence of flammable anesthetics or volatile solvents such as alcohol or benzene, or in locations that present an explosion hazard.

**ATTENTION:** Refer to the ORASYSTEM® Operator’s Manual for a complete description of proper use and maintenance, as well as a complete list of contraindications, warnings and precautions.

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**VERION® IMAGE GUIDED SYSTEM – IMPORTANT PRODUCT INFORMATION**

**VERION® REFERENCE UNIT AND VERION® DIGITAL MARKER**

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

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

**INTENDED USES:** The VERION® Reference Unit is a preoperative measurement device that captures and utilizes a high-resolution reference image of a patient’s eye. In addition, the VERION® Reference Unit provides pre-operative surgical planning functions to assist the surgeon with planning cataract surgical procedures. The VERION® Reference Unit also supports the export of the reference image, preoperative measurement data, and surgical plans for use with the VERION® Digital Marker and other compatible devices through the use of a USB memory stick. The VERION® Digital Marker links to compatible surgical microscopes to display concurrently the reference and microscope images, allowing the surgeon to account for lateral and rotational eye movements. In addition, details from the VERION® Reference Unit surgical plan can be overlaid on a computer screen or the physician’s microscope view.

**CONTRAINDICATIONS:** The following conditions may affect the accuracy of surgical plans prepared with the VERION® Reference Unit: a pseudophakic eye, eye fixation problems, a non-intact cornea, or an irregular cornea. In addition, patients should refrain from wearing contact lenses during the reference measurement as this may interfere with the accuracy of the measurements. The following conditions may affect the proper functioning of the VERION® Digital Marker: changes in a patient’s eye between pre-operative measurement and surgery, an irregular elliptic limbus (e.g., due to eye fixation during surgery, and bleeding or bloated conjunctiva due to anesthesia). In addition, the use of eye drops that constrict sclera vessels before or during surgery should be avoided.

**WARNINGS:**
- Only properly trained personnel should operate the VERION® Reference Unit and VERION® Digital Marker. Use only the provided medical power supplies and data communication cable. Power supplies for the VERION® Reference Unit and the VERION® Digital Marker must be uninteruptible. Do not use these devices in combination with an extension cord. Do not cover any of the component devices while turned on. The VERION® Reference Unit uses infrared light. Unless necessary, medical personnel and patients should avoid direct eye exposure to the emitted or reflected beam.

**PRECAUTIONS:** To ensure the accuracy of VERION® Reference Unit measurements, device calibration and the reference measurement should be conducted in dimmed ambient light conditions. Only use the VERION® Digital Marker in conjunction with compatible surgical microscopes.

**ATTENTION:** Refer to the user manuals for the VERION® Reference Unit and the VERION® Digital Marker for a complete description of proper use and maintenance of these devices, as well as a complete list of contraindications, warnings and precautions.

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**ACRYSOF® FAMILY OF SINGLE-PIECE IOLs IMPORTANT PRODUCT INFORMATION**

**CAUTION:** Federal law restricts these devices to sale by or on the order of a physician.

**INDICATION:** The family of AcrySof® single-piece intracapsular lenses (IOLs) includes AcrySof® UV-absorbing IOLs (“AcrySof® UV”), AcrySof® IQ Toric and AcrySof® IQ ReStOR® and AcrySof® IQ ReStOR® Toric IOLs. Each of these IOLs is indicated for visual correction of aphakia in adult patients following cataract surgery. In addition, the AcrySof Toric IOLs are indicated to correct pre-existing corneal astigmatism at the time of cataract surgery. The AcrySof® ReStOR IOLs are for cataract patients with or without presbyopia, who desire increased spectacle independence with a multifocal vision. All of these IOLs are intended for placement in the capsular bag.

**WARNINGS/PRECAUTIONS:**
General cautions for all AcrySof® and AcrySof® UV IOLs:
- Careful preoperative evaluation and sound clinical judgment should be used by the surgeon to decide the risk/benefit ratio before implanting any IOL in a patient with any of the conditions described in the Directions for Use that accompany each IOL. Caution should be used prior to lens encapsulation to avoid lens decentration or dislocation. Viscoelastic should be removed from the eye at the close of surgery.

**Additional Cautions associated with AcrySof® IQ ReStOR® IOLs:**
- Some patients may experience visual disturbances and/or discomfort due to multifocality, especially under dim light conditions. A reduction in contrast sensitivity may occur in low light conditions. Visual symptoms may be significant enough that the patient will request explant of the multifocal IOL. Spectacle independence rates vary with all multifocal IOLs; as such, some patients may need glasses when reading small print or looking at small objects. Clinical studies indicate that posterior capsule opacification (PCO), when present, may develop earlier into clinically significant PCO with multifocal IOLs.

**Additional Cautions associated with AcrySof® IQ Toric, AcrySof® UV Toric and ReStOR® Toric IOLs:**
- Optical theory suggests that, high astigmatic patients (i.e., > 2.5 D) may experience spatial distortions. Possible IOL related factors may include residual cylindrical error or axis misalignment. Toric IOLs should not be implanted if the posterior capsule is ruptured, if the zonules are damaged, or if a primary posterior capsulotomy is planned. Rotation can reduce astigmatic correction; if necessary lens repositioning should occur as early as possible prior to lens encapsulation.

**Prior to surgery, physicians should provide prospective patients with a copy of the appropriate Patient Information Brochure available from Alcon informing them of possible risks and benefits associated with the AcrySof® Toric, AcrySof® IQ ReStOR® and AcrySof® IQ ReStOR® Toric IOLs.**

**ATTENTION:** Do not resterilize. Do not store at temperatures over 45°C. Use only sterile irrigating solutions to rinse or soak IOLs.

**ATTENTION:** Refer to the Directions for Use labeling for the specific IOL for a complete list of indications, warnings and precautions.