THE FDA APPROVAL of topical cenegermin (Oxervate, Dompé Farmaceutici SpA) for the treatment of moderate-to-severe neurotrophic keratitis (NK) last month represents a breakthrough for management of a disease that has been a frustrating problem for clinicians and devastating condition for patients. Cenegermin, a recombinant form of human nerve growth factor (hNGF), was granted marketing authorization by the European Medicines Agency in July 2017. "Topical cenegermin may represent a paradigm shift in the treatment of neurotrophic keratitis, a sight-threatening condition that has been treated with a variety of non-validated therapies with varying success," said Stephen C. Pflugfelder, MD, an investigator in the cenegermin clinical trial. "The clinical trial results for topical cenegermin showed that it was associated with statistically significant and clinically meaningful healing of neurotrophic keratitis due to different etiologies," said Dr. Pflugfelder, professor and director of the ocular surface and the James and Margaret Elkins Chair, Department of Ophthalmology, Baylor College of Medicine, Houston. It is the first FDA-approved therapy for this condition, and the evidence suggests that it will improve treatment outcomes and reduce the need for corneal transplantation, which has a high failure rate in these eyes, he added.

"Neurotrophic keratitis has been a real treatment challenge," said Flavio Mantelli, MD, PhD, chief medical officer–biotech, Dompé Farmaceutici, Milan, Italy, and a trained cornea specialist.

NEURO SIGNS: WHEN AUTOIMMUNE AFFECTS THE EYES

WHEN OCULAR or orbital disease is detected in patients with autoimmune conditions, ophthalmologists should consider a differential diagnosis with the inflammatory state in mind. While the involvement of the uvea and cornea is usually more common than the posterior segment, ocular manifestations of autoimmune and inflammatory diseases may also present as neuroophthalmic signs, according to the authors of this month's "Neuro-Connection" column.
THE EHR SYSTEM SO ADVANCED, IT ACTUALLY LEARNS FROM YOU.

Imagine first logging into an EHR that immediately begins learning how you practice, diagnose and treat patients, customizing itself to give your practice greater efficiency. One built by ophthalmologists with specialty workflow in mind. With our all-in-one platform, that’s just simply part of what makes it the #1 ophthalmology-specific EHR system.*

SEE IT LIVE AT AAO 2018 BOOTH #1349

*2018 Black Book™ Research
The FDA approval of topical cenegermin (Oxervate, Dompé Farmaceutici SpA) for the treatment of moderate-to-severe neurotrophic keratitis (NK) last month represents a breakthrough for management of a disease that has been a frustrating problem for clinicians and devastating condition for patients.

Cenegermin, a recombinant form of human nerve growth factor (hNGF), was granted marketing authorization by the European Medicines Agency in July 2017. "Topical cenegermin may represent a paradigm shift in the treatment of neurotrophic keratitis, a sight-threatening condition that has been a frustrating problem for clinicians and devastating condition for patients," said Stephen C. Pflugfelder, MD, professor and director of the ocular surface and the James and Margaret Elkins Chair, Department of Ophthalmology, Baylor College of Medicine, Houston.

It is the first FDA-approved therapy for this condition, and the evidence suggests that it will improve treatment outcomes and reduce the need for corneal transplantation, which has a high failure rate in these eyes, he added.

"Neurotrophic keratitis has been a real treatment challenge," said Flavio Mantelli, MD, PhD, chief medical officer–biotech, Dompé Farmaceutici, Milan, Italy, and a trained cornea specialist. "The clinical trial results for topical cenegermin showed that it was associated with statistically significant and clinically meaningful healing of neurotrophic keratitis due to different etiologies," said Dr. Pflugfelder, who is a member of the cenegermin clinical trial. "Baseline inflammation decreased by week 8 in 80% of patients on cenegermin compared with 57% of patients on placebo."
INDICATION FOR USE.
The iStent inject® Trabecular Micro-Bypass System Model G2-M-IS is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma.

CONTRAINDICATIONS.
The iStent inject is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. WARNINGS. Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, Rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard.

MRI INFORMATION.
The iStent inject is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details.

PRECAUTIONS.
The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent inject have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoexfoliative, pigmentary or other secondary open-angle glaucomas, pseudoephelitic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents.

ADVERSE EVENTS.
Common postoperative adverse events reported in the randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent inject vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines at 3 months (2.6% vs. 4.2%). CAUTION: Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.


© 2018 Glaukos Corporation. Glaukos and iStent inject are registered trademarks of Glaukos Corporation. PM-US-0026
SEPTEMBER 1, 2018 :: Ophthalmology Times

Ophthalmology Times

Contents

Surgery

8 NOVEL TECHNOLOGIES: EARLY EXPERIENCES
How developing technologies in refractive surgery may increase patient satisfaction.

Drug Therapy

21 TWO DRUGS BETTER THAN ONE IN DME THERAPY?
Simultaneous combination of steroid and anti-VEGF treatments shows benefit at 6 months.

Practice Management

44 WHY PHYSICIANS SHOULD WATCH FOR THESE SCAMS
Does a payment plan sound too good to be true? Protect yourself against debt relief scams with skepticism and research.

In This Issue

4 EDITORIAL
39 FOCAL POINTS
42 MARKETPLACE

What’s Trending
See what the ophthalmic community is reading on OphthalmologyTimes.com

1 7 ways to hack your EHR
OphthalmologyTimes.com/EHRhacks

2 Novel treatment could minimize surgical infections
OphthalmologyTimes.com/Microspears

3 Hey, chocolate chip cookie fans!
OphthalmologyTimes.com/Cookies

4 IOP: An analysis using the IRIS Registry
ModernRetina.com/Atchison

Digital App

Introducing the Ophthalmology Times app for iPad and iPhone. Download it for free today at OphthalmologyTimes.com/OTapp.

Video

To watch a video of an IOL explantation, go to OphthalmologyTimes.com/explantation
(Video courtesy of Andrea Cantagalli, MD, FEBOphth)

eReport

Sign up for Ophthalmology Times’ weekly eReport at Ophthalmologytimes.com/eReport.

Facebook

Like Ophthalmology Times at Facebook.com/OphthalmologyTimes
Why the NEI is crucial

Advances in ophthalmic research wouldn’t be possible without it

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.

NEI’s creation by Congress represented the firing of a starter’s pistol when it came to making major investments in the study of eye disease. Federal funding for research has paid dividends to American taxpayers by improving our understanding of the pathogenesis of eye diseases.

These funds have resulted in better therapeutics or provided the scientific basis for industry to find drugs/devices to address the targets identified in federally funded research labs. In retinal diseases alone, think of the argon laser, anti-VEGFs, OCT, and more.

CREATION OF INSTITUTION

Rather, the event to which I refer is the creation of the National Eye Institute (NEI) within the National Institutes of Health.

At a time when members of Congress routinely worked across the aisle, our elected representatives became educated to the fact that although Americans feared loss of vision second only to cancer when it comes to health, very little federal research funding was being directed toward addressing eye disease.

The education of our elected representatives did not occur by accident. Rather it resulted from concerted efforts of leaders from academia, professional societies, industry, and charitable organizations who shared concerns over the increasing numbers of blind Americans and the lack of appropriate research to stop or reverse this trend.

Prior to the NEI’s formation, scientists wishing to study eye disease might apply to another one of the institutes within NIH, such as the National Institute of Neurological Diseases and Blindness. “After all,” went the thinking, “isn’t the eye part of the brain?”

Predictably, review panels composed of large numbers of neurologists or neuroscientists with no experience in eye disease did not consider eye research a priority in comparison with neurological diseases.

The only difference between death and taxes is that death doesn’t get worse every time Congress meets.” —Will Rogers

FIFTY YEARS AGO, an event occurred that led to dramatic improvement in our understanding of how the eye works and how to treat eye disease. No, that event was not my becoming an ophthalmology resident (but I understand how you might think I am that old). And no, the event was not my becoming chief medical editor of Ophthalmology Times (it only seems like forever that you have been forced to tolerate these columns of mine).

IMPORTANCE OF FUNDING

The track record of NEI-supported research is impressive. Still, polls of Americans rank fear of blindness as a top healthcare concern across all racial and ethnic groups.

The Alliance for Eye and Vision Research (AEVR) was founded 25 years ago to educate Americans about the importance of funding for research into eye disease. Privately funded by professional organizations, private foundations (such as Research to Prevent Blindness) and industry (you can guess the names), AEVR’s three founding members are the American Academy of Ophthalmology, ARVO and AUPO (the organization of ophthalmology department chairmen).

AEVR allows all of its member organizations to speak with one voice about the need for research that will lead to the improved drugs and devices that we ophthalmologists need to better care for our patients. (Full disclosure: Since 2013, yours truly has served as President of AEVR).

Surprisingly, a decade or so ago the proposal was raised of eliminating the separate NEI budget and folding it into a “Brain Institute.” Harkening back to the old days, researchers wanting to understand eye disease would have had their grants graded by neurologists and others with little to no knowledge of eye disease. Fortunately, this proposal did not gain traction. This step back in time failed, I believe, at least in part to the educational efforts of AEVR, which emphasized the potential loss of critical front-of-the-eye research.

Like Will Rogers, you might occasionally make fun of Congress. But the creation of the NEI augured a half century of stunning progress in understanding eye disease and better care for patients.
XIIDRA MAY INTERRUPT THE CYCLE OF INFLAMMATION CENTRAL TO DRY EYE DISEASE\(^1,2\)

The exact mechanism of action of Xiidra in Dry Eye Disease is not known.\(^1\)

Xiidra blocks the interaction of ICAM-1 and LFA-1, which is a key mediator of the inflammation central to Dry Eye Disease. In vitro studies have shown that Xiidra may inhibit the recruitment of previously activated T cells, the activation of newly recruited T cells, and the release of pro-inflammatory cytokines.\(^1\)

Indication
Xiidra\(^\circledast\) (lifitegrast ophthalmic solution) 5% is indicated for the treatment of signs and symptoms of dry eye disease (DED).

Important Safety Information
Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.

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.

Check out Xiidra-ECP.com

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

References:

©2018 Shire US Inc., Lexington, MA 02421. 1-800-828-2088. All rights reserved. SHIRE and the Shire Logo are trademarks or registered trademarks of Shire Pharmaceutical Holdings Ireland Limited or its affiliates. Marks designated \(\circledast\) and \(\text{TM}\) are owned by Shire or an affiliated company. 540448 07/18
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).

DOSSAGE AND ADMINISTRATION
Instil 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. 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.

Manufactured for: Shire US Inc., 300 Shire Way, Lexington, MA 02421. For more information, go to www.Xiidra.com or call 1-800-828-2088. Marks designated © and ™ are owned by Shire or an affiliated company. ©2018 Shire US Inc. SHIRE and the Shire Logo are trademarks or registered trademarks of Shire Pharmaceutical Holdings Ireland Limited or its affiliates. Patented: please see https://www.shire.com/legal-notice/product-patents Last Modified: 01/2018 533769
ophthalmologists, specifically refractive surgeons, along with their patients, have enjoyed huge success with ablative (corneal tissue removal) procedures over the 30 years since Marguerite McDonald, MD, performed the first PRK on a sighted eye in New Orleans on March 25, 1988.

How things have developed since then, with the advent of LASIK, LASEK, TE-PRK, femto-LASIK and SMILE—a plethora of tools that allow the refractive surgeon to select the most appropriate procedure for each patient. All these procedures modify the corneal shape by removing corneal tissue, thereby correcting the refractive error. LASIK has become the most studied and most successful elective procedure, with the highest patient satisfaction rating of any elective procedure.

So why are we looking for even more options?

There are several reasons, most of them related to shortcomings of the ablative procedures. All procedures that remove corneal tissue reduce the corneal biomechanical strength to some extent. At one extreme is a thick-flap microkeratome LASIK and at the other are PRK and SMILE, which maintain more biomechanical strength.

Dry eyes are less of an issue today thanks to heightened awareness and the tools that we have at our disposal to treat dry eye prior to surgery.

There are some refractive errors that simply don’t do particularly well with ablative techniques; for example, high hyperopia and conditions like keratoconus. Presbyopia remains the last refractive challenge, and potentially represents the biggest market.

Besides monovision/blended vision, there are no widely adopted corneal ablative refractive procedures to treat presbyopia.

Also, market research indicates that some people steer away from the ablative techniques as they feel they are too permanent and non-reversible. Some might think a permanent outcome would be a bonus but not all patients agree.

**CORNEAL TISSUE ADDITION**

Enter the corneal tissue addition and permanent biological contact lens company, Allotex. Instead of removing tissue to change the corneal shape, the company adds tissue to achieve the same result.

The human corneal tissue can be added intrastromally under a flap (an inlay) or as an onlay, on top of Bowman’s membrane but under the epithelium. Addition as an onlay is reversible, addressing some patient concerns. An onlay should have very minimal dry eye side effects and no biomechanical side effects.

An inlay, under a thin LASIK flap, would also have fewer dry eye effects as there is no excimer ablation of corneal nerves and no further removal of corneal tissue from the stromal bed.

For example, consider a 32-year-old high hyperope (+6.00 D) with a flat cornea (40 D) and insufficient anterior chamber depth to consider a phakic IOL. This patient would be deemed untreatable by most surgeons, being too young for refractive lens exchange, having no space for an iris claw lens and being too hyperopic for most surgeons to consider LASIK.

With Allotex, a +6.00 lenticule—fashioned by the excimer laser to have appropriate characteristics for the particular eye—placed under a flap may provide an excellent outcome. And if it doesn’t work out as intended, the lenticule can simply be removed and you’re back where you started.

Synthetic materials must be placed deeply to avoid the immunologically active part of the anterior cornea, but this is not the case.
with allografts. Given that no immunologic response is anticipated, the effect of the lenticule can therefore be varied by changing not only its shape and thickness but also the depth at which it is placed. The more anterior the lenticule, the more effect it will have.

Furthermore, the lenticule can be customized to meet the exact refractive needs, including higher-order aberration needs. Imagine the application for keratoconus. Placing the exact shape required to regularize the cornea and improve the vision, while thickening the cornea. For presbyopia, instead of having a one-size-fits-all approach (for instance, Raindrop inlay), there are more options.

Further innovation is brought to the allograft space with improved storage techniques including a much longer shelf life (2 years).

**MONITORING VISUAL BEHAVIOR**

A second technology of interest is the vision behavior monitor (VBM) (Vivior), a wearable device that attaches to a pair of spectacles and seamlessly gathers visual behavior information about the patient (Figure 1).

It’s not a camera but it records working distances, ambient lighting conditions and the head positions used while performing different tasks, allowing you to “sit on the shoulder” of your patient and observe their every move for a few days. Of course, you don’t really accompany them at home and work! But you could have just as well.

This is the first time that patients and I have had the opportunity to discuss their visual needs and the best solution using their own personal, objective data. The conversation is elevated to a different level, as understanding increases on both sides. The whole issue of compromise is better understood.

Prior to surgery many patients have a dream of great, natural distance vision and don’t truly understand the impact of losing near vision (if they were myopic and presbyopic). After wearing the VBM, the limitations of perfect distance vision are very easily understood. They now comprehend that perfect distance vision is going to translate to a light reading add for the computer and reading glasses for near, and they know what percentage of each day they spend looking at the PC and how much time they spend doing close work.

I have seen a significant upsurge in the number of patients requesting multifocal, trifocal and EDOF IOLs, depending on where their greatest needs are. Any early side effects from these IOLs are more readily tolerated because the patient is more aware of the problems that the selected IOL is solving.

Instead of choosing an IOL based on a conversation or questionnaire, the choice is now based on objective data. For example, while a 6’5” man has a different reading distance from a 5’4” woman, both describe this activity as “reading” in a questionnaire. The VBM changes the information from subjective to objective and thereby provides a greater chance of delivering a solution fit for the patient’s needs.

I have a question for readers: Figure 2 shows the data from when I wore the VBM for a 3-hour period during the day. What do you think I was doing? ■

**LENSTAR INC.** has announced global healthcare senior executive Gary Winer has joined the company’s board of directors, effective immediately.

“LENSTAR’s impressive growth in the global market will be well served by Gary’s significant international experience and we look forward to his insights to build on our momentum,” said Nicholas Curtis, chief executive officer of LENSTAR Inc. “The refractive cataract market is poised for explosive growth and working with Gary and the rest of the board we can continue to leverage the opportunities for our technology and surgeons.”

With more than 20 years in leadership positions in the healthcare and pharmaceutical industries, Winer has been tapped by Fortune 100 companies to manage blockbuster product lines and introductions in the United States, Latin America, Asia, and Japan. Specifically, Winer has contributed his leadership and market skills to companies including AbbVie, Abbott Laboratories, and Pfizer, helping launch and promote such notable brands as Humira and Celebrex. ■

---

**ARTHUR CUMMINGS, MD, FRCSED**

e: ABC@WellingtonEyeClinic.com

Dr. Cummings is based at Wellington Eye Clinic, Dublin, Ireland. He is an investigator for Allotex but has no financial interest in the company, and is on the medical advisory board of Vivior.
Case study: Challenge of presbyopic patient who refuses spectacles

Clear lens exchange with implantation of a trifocal IOL may be best option

By Cyres Keiki Mehta, MS(Ophth), MCH(Ophth)

AFTER THE AGE of 40, most people develop presbyopia. A person aged around 37 or 38 years who is mildly (+0.50–0.75 D) hyperopic for distance simply accommodates and does not need to wear glasses.

However, by the time that person turns 40, near work is hindered by bouts of blurring, accommodative asthenopia and headaches. A person who has never worn spectacles before is now faced with needing them for both distance and near vision. This problem gets worse with time as the presbyopia increases and residual accommodation decreases.

CASE HISTORY

A 60-year-old woman, a former Bollywood movie star, presented with recurrent headaches. On examination, she had spectacle prescription of OD +1.00 D for distance, +3.5 D for near, and OS +1.25 D for distance and +3.75 D for near.

After a thorough diagnostics workup, including optical coherence tomography (OCT) (AngioVue Imaging System, Optovue), biometry (IOL Master 700, Carl Zeiss Meditec) and slit-lamp examination (BQ 900, Haag-Streit), I identified the problem. The patient did not want to wear spectacles and had actually never worn them, even though she owned a pair.

She claimed not to be an avid reader; however, I noticed that she used her smartphone frequently in the office, and she reported that she used her tablet quite often. After some observation and subsequent conversation, she admitted that she read on her smartphone all day and was a frequent user of social media and networking sites.

I explained that her persistent headache was due to slight hyperopia coupled with presbyopia, and that without correction and an adjustment of her current habits her headaches would not go away.

For this patient, I had to face the fact that she would never wear spectacles and had a high need for excellent near and intermediate vision. After patient counseling it became clear that she would accept a loss of contrast for distance. Additionally, because she did not drive, I had no concerns with night-time halos.

Considering these facts, I decided that the best solution for her was a clear lens exchange with implantation of a trifocal IOL.

THERAPEUTIC STRATEGY

I counseled the patient about the clear lens exchange technique and procedure, including risks as well as benefits. This included a pre-operative data assessment with a full-length OCT image (IOLMaster 700, Carl Zeiss) and a customized surgical plan.

I used the SRK/T formula to calculate the appropriate IOL power and decided to order trifocal IOLs (AT LISA tri 839MP, Carl Zeiss; right eye 22.5 D, left eye 23.0 D).

Because my clinic and operating facility are located at different venues, I perform computer-assisted (Callisto, Carl Zeiss) cataract surgery that allows for data transfer between various places. Before I started to use a computer-guided system, I used to pre-mark the eye of the patient in a sitting position using a digital marker (AXsys, ASICO). This was fairly accurate, but I considered the following drawbacks when adopting the change:

1. I could never be sure that the patient’s head was completely vertical;
2. Studies show that if the axis shifts 10 degrees, one-third of the toric IOL’s effect will be lost. If the axis shifts 20 degrees, two-thirds of the toric IOL’s effect is lost;*3. Using ink on the eye disturbs the epithelium, and the cornea is less clear the next day;
4. If the patient is apprehensive and suddenly moves, the cornea gets an epithelial scratch that might take a day or two to heal. During this time, the patient will experience dysphotopsia and a teary, uncomfortable eye. Although this is rare, I have witnessed it occur.

During surgery, I used a precision laser system (Catalys, Precision Lens) to create a precise central capsulorhexis, followed by phacoemulsification with a phacoemulsification and vitrectomy system (Visalis 500, Carl Zeiss). Conveniently, the trifocal IOL selected was a preloaded lens that was injectable through the main 2.2 mm tunnel.

Whenever I have a patient with more than 0.5 D cylinders preoperatively, I choose to implant a toric IOL. This is because, in a multifocal IOL, any cylinder more than 0.5 D blurs vision and decreases patient satisfaction.

My preferred toric IOL implantation technique is to put the leading haptics in the bag at the time of injection of the preloaded IOL, and then to rotate it to the desired meridian with the trailing haptics out of the bag. With this technique, there is limited if not zero stress on the capsular bag zonular mechanism.

When the toric IOL reaches the desired meridian, I simply deepen the chamber using the bimanual irrigation/aspiration hand piece (Geuder) and gently tap the lens into place. This ensures that the IOL remains on its desired meridian even after I have removed all viscoelastic.

The patient achieved −0.25 D in both eyes. Postoperatively, she was able to do her daily reading on her smartphone and tablet without the need to wear spectacles or to suffer any limitations.

CONCLUSION

I have been performing bilateral cataract surgery with multifocal IOLs for more than 15 years now, and I have implanted more than 35,000 IOLs.

It is important to remember that in cases with multifocal IOLs, the patient’s vision is the best when there is zero residual cylinder.
Let’s Focus on Dry Eye!

The Keratograph® 5M assists you in finding the cause of dry eye quickly and reliably. Summarize all data from your dry eye workup in the Crystal TEAR Report.

• Save time: The complete examination process can be delegated.
• Excel with your dry eye diagnosis: The complete course of treatment is recorded.
• Combine screening and patient education: Your patient receives an easy-to-grasp printout.

Try the software at booth #MS8053 during Vision Expo West.
Pneumatic vitreolysis considered ‘highly effective’ treatment for VMT

Technique achieving VMT release (86%) for focal VMT, macular hole closure rate of 62%

By Michelle Dalton, ELS

TREATING symptomatic vitreomacular traction (VMT) with pneumatic vitreolysis and limited face-down positioning “is a highly effective emerging technique for achieving VMT release (86%) for focal VMT, with a respectable macular hole closure rate of 62%,” said Calvin Mein, MD.

VMT is caused by an anomalous posterior vitreous separation with vitreous traction that distorts the foveal architecture. Newer technologies such as optical coherence tomography (OCT) have allowed clinicians to more readily and easily diagnose VMT, said Dr. Mein, of Retinal Consultants of San Antonio, TX.

Under specific circumstances, tractional forces associated with progression of VMT may lead to the development of a full-thickness macular hole and further vision loss. Management for symptomatic VMT includes observation, vitrectomy, and intravitreal injection of ocriplasmin.

Concerns about the use of ocriplasmin and its potential side effects have led to pneumatic vitreolysis being suggested as an alternative.

Pneumatic vitreolysis is an intravitreal injection of a small quantity of expansile gas for the purpose of achieving focal VMT release, or for inducing VMT release and the close of a macular defect for eyes with a small stage-2 macular hole, Dr. Mein said.

“We performed a retrospective study on patients with focal VMT who underwent PVL in 2 centers from 2010-2017. Patients were required to avoid supine position after receiving 0.3 mL C3F8 gas injection until gas resolution,” he said.

Patients with macular hole were asked to maintain face-down positioning for at least 4 days. Best-spectacle corrected visual acuity (BSCVA) was performed at baseline and at each follow-up visit, Dr. Mein said.

The surgical technique is an in-office procedure using subconjunctival anesthesia. Dr. Mein creates an anterior chamber paracentesis, injects 0.3 cc of C3F8 at 12 o’clock. If the patient has a macular hole, they must stay face down for 45 minutes every hours for the first 3 days postop.

“These have to be motivated patients,” he said. “Pneumatic vitreolysis has a CPT code—67025—almost as much as vitrectomy.”

STUDY RESULTS

Sixty-nine consecutive eyes in 68 patients with VMT (47 women; mean age of 70.7 [range: 48-85]) underwent pneumatic vitreolysis; 42 of these patients had VMT only and 20 patients had small macular holes.

Overall VMT release was achieved in 59 eyes (85.5%) within a mean time to release of 2.9 weeks. Subgroup analysis showed VMT release in 79.2% of VMT-only eyes.

“That’s why it’s important to use C3F8 in these patients, because SF6 goes away sooner,” he said, adding that SF6 “only works about half the time.”

In eyes with macular holes, 61.9% of eyes closed with just using a gas bubble, Dr. Mein said. All eyes with macular holes that failed to close with pneumatic vitreolysis were closed with surgery—pars plana vitrectomy, membrane-ectomy, gas-fluid exchange, he said.

Median baseline and final BSCVA was 0.3979 ±0.213 and 0.24 ± 0.173 (20/50 and 20/35), respectively (p < 0.0001). For eyes with macular holes, baseline vision was 20/64, which improved to a final BSCVA of 20/33 (p = 0.001).

There were several characteristics predictive of success, Dr. Mein said, including a younger age, VMT size less than 1 disc diameter, and a lack of diabetes (although this was a small number). There was a trend toward cellophane maculopathy as a predictive characteristic, but it was not yet statistically significant (p = 0.077) and again, there were small numbers of patients.

The technique is not without complications, Dr. Mein said. These included retinal tears in 2 eyes, retinal detachment in 2 eyes, and VMT progressing to macular hole in one eye; all responded to treatment.

Future studies will include the Diabetic Retinopathy Clinical Research (DRCR) Network’s Protocol AG, a randomized clinical trial for VMT. The DRCR’s Protocol AH will be a single arm study investigating pneumatic vitreolysis for small macular holes.

Reference


PRESBYOPIC

(Continued from page 10)

and the residual sphere is under 0.25 D. Any more than this, particularly if there is any residual cylinder, will decrease the patient’s satisfaction.
YOUR PARTNERS IN ANTERIOR SURGERY OUTCOMES

AL-SCAN OPTICAL BIOMETER
- 6 measurements in 10 seconds (K, AL, PS, WTW, CCT, ACD)
- Easy to use: 3-D auto tracking and auto shot for all measurements
- Toric Assist function

CEM-530 SPECULAR MICROSCOPE
- Easy to Use: 3-D auto tracking / auto shot / auto analysis
- Paracentral and Peripheral imaging for overall endothelial cell health of the cornea
- Manual Analysis function

NIDEK Inc.
47651 Westinghouse Drive
Fremont, California 94539-7474 USA
Telephone: 1-800-223-9044 • Fax: 1-510-226-5750

Caution: U.S. Federal Law restricts this device to sale, distribution, and use by or on the order of a physician or other licensed eye care practitioner. Specifications may vary depending on circumstances in each country. Specifications and design are subject to change without notice.

LEARN MORE: info@nidek.com
or usa.nidek.com

March 10, 2017
17-0014
THOUGH I AM primarily a cataract and refractive surgeon, I treat a lot of patients with glaucoma. Taking an interventional approach to glaucoma therapy fits perfectly with the goal in my practice to identify technologies that allow out-patients to lower IOP and reduce medications—without a major procedure that requires a lot of perioperative and postoperative management. We are well positioned to treat glaucoma before it reaches the severity level for major surgery.

Cataract surgery alone brings down the pressure, so we cataract and refractive surgeons are accustomed to moving the needle for our patients with glaucoma, but the shift to actively treating glaucoma is a major change.

I’ve always known that about 15% of my cataract patients were on some type of glaucoma medication, and cataract surgery might help reduce the burden somewhat. Now we have the technology to bring down pressure significantly during cataract surgery, or even as a standalone procedure.

The most exciting part of this, from an interventional glaucoma perspective, is that this is an entirely different threshold for glaucoma surgery than we saw in the past. Well short of the need for trabeculectomy or tube shunt, patients can have minimally invasive, low-risk therapies that lower pressure and reduce the burden of medication. It’s a major blow against compliance problems and disease progression. And several procedures can take place during cataract surgery, with no additional risk.

Many cataract surgeons will expand into the MIGS space because the patient base is already in our exam rooms.

Whether surgeons adopt cataract surgery-paired MIGS implants or a broader range of interventional therapies, our practices will change because we are so well positioned to meet patients’ urgent need for glaucoma therapy beyond eye drops.

THERAPIES PATIENTS NEED

Interventional glaucoma therapies have been part of my practice since 2002, when I started with endocyclophotocoagulation (ECP, Endo Optiks). Today, I use CyPass (Alcon Laboratories) or iStent (Glaukos) during cataract surgery, as well as standalone procedures such as the Kahook Dual Blade (New World Medical), Visco 360 (Sight Sciences) and XEN Gel Stent (Allergan).

I am also trained in performing trabeculectomy and tube shunt surgery, but a lot goes into managing those cases. Newer procedures have much lower risk of complications, making them suitable for the majority of patients.

While we’re already working inside the eye for cataract surgery, iStent and CyPass procedures help lower pressure and get patients off their medications. What’s more, these procedures do not add significant complexity to the management of cataract patients, nor do they close any doors to future treatments. Not surprisingly, my patients are very receptive to getting one of these MIGS devices; about 95% say “Yes.”

Standalone procedures fit into my practice as well. When patients are using drops or SLT to buy time until they can get a combined cataract-MIGS surgery, but those therapies aren’t proving effective, a standalone procedure may make sense.

For example, we use gel stents (XEN) for patients with moderate to severe pseudophakic glaucoma, with results similar to trabeculectomy without the risks. Some patients whose surgeons recommend trabeculectomy or tube shunt come to our practice because they have read about these devices, and they want to try something less invasive first. It does not affect future cataract surgery or even future MIGS procedures.

It’s nice to have a variety of interventional glaucoma approaches that we can match to different types or severities of glaucoma. For example, stents and other procedures can be combined to address different mechanisms of
outflow and aqueous production, at the same time or in sequential fashion.

**HOW THIS CHANGES YOUR PRACTICE**

There is no major investment required to start using interventional glaucoma therapies. Neither is there a perceptible difference in preoperative time. When patients are referred to me with both cataracts and glaucoma, I need to assess the baseline pressure to document the severity of the disease and the efficacy of current treatments.

Postoperative care for combined cataract-MIGS procedures is similar to cataract alone. Following cataract surgery, we see patients at 1 day and 1 month, and for MIGS patients, we add a visit at 1 week to check the pressure and adjust glaucoma medications.

Postoperative care varies for standalone procedures, but it is not burdensome and does not carry the risk and worry of traditional surgeries.

We have found that interventional glaucoma procedures do not affect patient flow. We schedule cataract and cataract-MIGS surgeries the same, without any dedicated time of day. Standalone procedures (such as Khook Dual Blade, Visco 360 and XEN) are usually scheduled at the end of our cataract surgery schedule but can be intermixed with little disruption to the schedule.

The learning curve for these procedures is not steep, but it does require that cataract and refractive surgeons get comfortable using a gonio lens, which many of us do not do often. Insurance carriers vary widely in what they are willing to cover, despite the long-term benefits of reducing reliance on patients’ compliance with drops to preserve vision and avoid major surgery. Some insurers only cover MIGS during cataract surgery or only approve standalone surgery for severe glaucoma.

Thankfully, in a situation where coverage can dictate our choices, we usually have several options that will work well for any given patient. If you’re concerned about reimbursement, you might choose to start with Medicare patients because most MIGS are covered. When we want to perform a new procedure, we do so if we find it has a Medicare T code and set rate. If not, we choose a different procedure.

We have to be careful about coding for cataract-MIGS combinations when optometrists refer patients for that procedure. If we code MIGS as the primary procedure, then the referring optometrist will get a reduced comanagement fee for the cataract procedure and no fee for the MIGS procedure.

We need to bill cataract surgery as the primary procedure and the MIGS treatment as the secondary procedure so the referring doctor receives the full comanagement fee for the cataract and still none on the MIGS procedure.

As long as insurance companies make interventional treatment of glaucoma financially viable for cataract and refractive surgeons, surgeons will gravitate toward this approach. These procedures will continue to increase our ability to intervene early and effectively to treat glaucoma, reducing the number of cases where poor compliance with drops leads to vision loss and the need for more advanced surgery.

Farrell "Toby" Tyson, MD, is medical director, Tyson Eye, Cape Coral, Fl. He was an investigator for the Glaukos iStent inject.
While the targets and mechanisms of systemic inflammatory diseases are variable, many of these diseases share similar manifestations in the eye. Therefore, through the course of these autoimmune conditions, it is imperative to keep in mind the potential ocular ramifications associated with these diseases.

Whether directly through immunologic mechanisms, or indirectly through the development of various pathologic states such as hypertension, hypercoagulability, arteritis, and mass effect, autoimmune diseases have significant potential to threaten patients’ vision.

When ocular or orbital disease is detected in patients with autoimmune conditions, ophthalmologists should consider a differential diagnosis with the inflammatory state in mind.

While the involvement of the uvea and cornea is usually more common than the posterior segment, ocular manifestations of autoimmune and inflammatory diseases may also present as neuro-ophthalmologic signs involving the optic nerve, retina, and cranial nerves. These pathologies can include, but are not limited to optic neuritis, a spectrum of ischemic optic neuropathies (arteritic anterior ischemic optic neuropathy, non-arteritic anterior ischemic optic neuropathy, posterior ischemic optic neuropathy), orbital inflammatory syndrome, retinal vasculitis, retinal vein occlusions, retinal artery occlusions, secondary pseudotumor cerebri, and symptoms such as amaurosis fugax.

Numerous reports of autoimmune diseases associated with these pathologies have been described (see Table 1).

The mechanisms through which autoimmune diseases exert neuro-ophthalmologic effects are numerous but may include immune-mediated demyelination, vasculitis, vasospasm, immune complex deposition, and hypercoagulability.

In recent studies, the mechanisms underlying hypercoagulability in autoimmune disease have been further elucidated. Systemic inflammation has been shown to increase thrombotic processes through the suppression of fibrinolysis, upregulation of fibrin production, and alteration of platelet function.

### (Table 1) Examples of neuro-ophthalmologic pathologies and associated autoimmune conditions

<table>
<thead>
<tr>
<th>NEURO-OPHTHALMOLOGIC PRESENTATION</th>
<th>ASSOCIATED INFLAMMATORY CONDITIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optic neuritis</td>
<td>SLE, sarcoidosis, IBD, APLS, Sjogren syndrome</td>
</tr>
<tr>
<td>Ischemic optic neuropathy</td>
<td>SLE, GCA, PAN, Takayasu arteritis, EGPA, Crohn’s disease</td>
</tr>
<tr>
<td>Retinal vasculitis</td>
<td>SLE, PAN, GCA, EGPA, Behcet’s disease, multiple sclerosis, sarcoidosis, GPA, IBD</td>
</tr>
<tr>
<td>Orbital inflammatory syndrome</td>
<td>SLE, GPA, GCA, Crohn’s disease, EGPA, scleroderma, sarcoidosis, dermatomyositis, rheumatoid arthritis</td>
</tr>
<tr>
<td>Vaso-occlusive retinopathies</td>
<td>SLE, sarcoidosis, APLS, Crohn’s disease, GPA, EGPA, PAN</td>
</tr>
<tr>
<td>Secondary pseudotumor cerebri</td>
<td>SLE, sarcoidosis, Behcet’s disease, APLS, IBD</td>
</tr>
<tr>
<td>Amaurosis fugax</td>
<td>SLE, GCA, Crohn’s disease, APLS, Takayasu arteritis</td>
</tr>
</tbody>
</table>

SLE = systemic lupus erythematosus; IBD = inflammatory bowel disease; APLS = antiphospholipid antibody syndrome; GCA = giant cell arteritis; PAN = polyarteritis nodosa; EGPA = eosinophilic granulomatosis with polyangiitis. (Table courtesy of Andrew G. Lee, MD)
‘Ocular manifestations of autoimmune and inflammatory diseases may also present as neuro-ophthalmologic signs involving the optic nerve, retina, and cranial nerves.’

of procoagulants, downregulation of anticoagulants, and genesis of pathogenic antibodies (e.g. lupus anticoagulant, anti-cardiolipin, and anti-B2 glycoprotein 1)5.

In light of these mechanisms, autoimmune disease may be considered a hypercoagulable state, thus explaining why numerous autoimmune diseases such as systemic lupus erythematosus, inflammatory bowel disease, and Behcet’s syndrome have been shown to confer a high risk of venous thromboembolism5.

Since thrombosis underlies many neuro-ophthalmologic conditions, in patients with symptoms concerning for these pathologies, autoimmunity should be considered as a culprit.

In conclusion, in patients with history of autoimmune disease that present with neuro-ophthalmologic signs and symptoms, after pertinent workup, treatment should focus on the underlying etiology behind these processes.

Patients with acute neuro-ophthalmic presentations who have active systemic autoimmune disease might require hospital admission, urgent neuroimaging and systemic evaluation, high-dose intravenous corticosteroids, or additional immunosuppressive or disease modifying rheumatologic drugs.

References

IYZA F. BAIG
es: iyza.baig@uth.tmc.edu
Baig is affiliated with the McGovern Medical School at The University of Texas Health Science Center in Houston (UTHealth), Houston.

AROUCHA VICKERS, DO
es: aroucha.vickers@gmail.com
Vickers is affiliated with the Department of Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital, Houston.

ANDREW G. LEE, MD
es: aglee@houstonmethodist.org
Dr. Lee is affiliated with the Department of Ophthalmology, Blanton Eye Institute, Houston Methodist Hospital; Baylor College of Medicine, Houston; Dr. Deepak Rao Chair in Ophthalmology and Neuro-Ophthalmology at the University of Texas Health Science Center at Houston; and the Department of Ophthalmology, University of Virginia, Charlottesville. He is a member of the editorial board of Ophthalmology and Neuro-Ophthalmology at the University of Texas Health Science Center at Houston; and the Department of Ophthalmology, University of Virginia, Charlottesville. He is a member of the editorial board of Ophthalmology and Neuro-Ophthalmology at the University of Texas Health Science Center at Houston; and the Department of Ophthalmology, University of Virginia, Charlottesville.
Telehealth program lowers unneeded diabetic retinopathy referrals

New approach cuts wait times for patient populations who need treatment

By Leah Lawrence

THE LOS ANGELES County Department of Health Services safety net clinics successfully implemented a primary care-based teleretinal diabetic retinopathy screening (TDRS) program, eliminating the need for more than 14,000 visits to specialty-care professionals, according to the results of a study published recently [JAMA Intern Med. 2017;177:642-649].

“We see an immense amount of preventable blindness from diabetic retinopathy in our Los Angeles County population and, as in most U.S. safety net populations, our screening rates for this disease were low,” said Lauren P. Daskivich, MD, MSHS, of the department’s Ophthalmology and Eye Health Programs. “While our goal was to implement an intervention to help address this, we also wanted to study what we implemented to ensure that it was truly meeting the needs of our patients and our healthcare system.”

Of screened patients, 19.6% were referred for treatment or monitoring of DR, 68.8% did not require referral for eye care, and 11.6% were referred for other eye conditions.

Dr. Daskivich said that an important aspect of this program is its integration into the primary-care clinics, allowing for patients to be screened within their primary-care medical homes, even at their initial point of contact with the healthcare system.

“This requires collaboration with our primary care and specialty care colleagues, an interaction integral to the overall care of persons with diabetes,” she said.

“Earlier screening for diabetic retinopathy in U.S. safety net populations, leading to earlier detection and treatment, could lead to a significant cost-savings to society in terms of blindness prevention,” Dr. Daskivich said. “Integration of the diabetic retinopathy screening process into primary-care clinics using certified medical assistant photographers could also provide a less costly option than performing these screenings in specialty-care clinics by eye-care providers.”

Dr. Daskivich and colleagues tested a primary care-based TDRS program in five of 15 Los Angeles County Department of Health Services safety net clinics between September 2013 and December 2015. The safety net program is a “nonvertically integrated system” that serves underinsured and uninsured patients.

The TDRS program was designed to move patients with normal retinal photographs out of line to be seen by specialty-care professionals, reducing wait times for patients who do require treatment.

In the program, 58 certified medical assistants and licensed vocational nurses were trained and certified as fundus photographers and existing medical assistants were trained to use the cameras in primary-care settings and to upload these digital images to a web-based screening software.

The study evaluated the annual rates of screening for diabetes retinopathy (DR) before and after implementation of the program and time to screening for DR in a random sample of 600 patients.

In all, 21,222 patients underwent screening through the program and the median time to screening for DR significantly decreased ($p < 0.001$).

“We increased our screening rate for diabetic retinopathy by 16.3% in the study clinics and the median time to DR screening decreased significantly from 158 days before the intervention to 17 days after implementation of the program (89.2%), while at the same time eliminating the need for over 14,000 specialty eye care visits overall,” Dr. Daskivich said.

Annual screening rates increased significantly from 40.6% (5,942 of 14,633 patients) to more than one-half (56.9%; 7,470 of 13,122 patients; OR = 1.9; 95% CI, 1.3–2.9; $p = 0.002$).

According to Dr. Daskivich, “these are visits that are then available for patients waiting to see eye care providers for other sight-threatening conditions.”

‘Earlier screening for diabetic retinopathy in U.S. safety net populations . . . could lead to a significant cost-savings to society in terms of blindness prevention.’

— Lauren P. Daskivich, MD, MSHS

Dr. Daskivich and colleagues tested a primary care-based TDRS program in five of 15 Los Angeles County Department of Health Services safety net clinics between September 2013 and December 2015. The safety net program is a “nonvertically integrated system” that serves underinsured and uninsured patients.

The TDRS program was designed to move patients with normal retinal photographs out of line to be seen by specialty-care professionals, reducing wait times for patients who do require treatment.

In the program, 58 certified medical assistants and licensed vocational nurses were trained and certified as fundus photographers and existing medical assistants were trained to use the cameras in primary-care settings and to upload these digital images to a web-based screening software.

The study evaluated the annual rates of screening for diabetes retinopathy (DR) before and after implementation of the program and time to screening for DR in a random sample of 600 patients.

In all, 21,222 patients underwent screening through the program and the median time to screening for DR significantly decreased ($p < 0.001$).

“We increased our screening rate for diabetic retinopathy by 16.3% in the study clinics and the median time to DR screening decreased significantly from 158 days before the intervention to 17 days after implementation of the program (89.2%), while at the same time eliminating the need for over 14,000 specialty eye care visits overall,” Dr. Daskivich said.

Annual screening rates increased significantly from 40.6% (5,942 of 14,633 patients) to more than one-half (56.9%; 7,470 of 13,122 patients; OR = 1.9; 95% CI, 1.3–2.9; $p = 0.002$).

According to Dr. Daskivich, “these are visits

\[ \text{TAKE-HOME} \]

\begin{itemize}
\item A diabetes retinopathy screening program in the Los Angeles County Department of Health Services eliminated the need for more than 14,000 visits to ophthalmologists by certifying medical assistants and nurses to take fundus photography in primary-care settings. The images were read by web-based screening software.
\end{itemize}
I AM MODERNIZING OPHTHALMOLOGY

WITH A SMARTER EHR

It’s so advanced, it actually learns from you. Modernizing Medicine®’s all-in-one platform was designed by practicing ophthalmologists to streamline treatment and improve outcomes. From the moment you first log in, it begins learning how you practice, diagnose and treat patients, customizing itself to give your practice greater efficiency.

So you can see more patients, while seeing more of your patients. It’s time to demand more from your EHR.

VIEW OUR 2-MINUTE DEMO
MODMEDOPHTH.COM

TOGETHER, WE ARE MODERNIZING MEDICINE.

©2018 Modernizing Medicine, Inc.
A short course of oral mifepristone may reduce or improve subretinal fluid and improve best-corrected visual acuity (BCVA) in patients with chronic or recurrent central serous chorioretinopathy (CSC), said Roger Goldberg, MD, MBA, with Bay Area Retina Associates.

There are numerous risk factors for CSC, including being Type A personality, systemic hypertension, Cushing syndrome, pregnancy, organ transplantation, allergic respiratory disease, or autoimmune disorders.

Mifepristone is a potent, glucocorticoid steroid antagonist and because CSC is associated with either excessive endogenous cortisol and epinephrine levels, or excessive exogenous cortisol that affects the autoregulation of choroidal circulation, mifepristone is a natural possibility to consider for treatment of CSC.

“It is thought that excess cortisol levels in predisposed individuals affects the choroidal circulation and autoregulation,” Dr. Goldberg said. “This suggests that if we can inhibit or block the effect of steroids, we might be able to offer a treatment to these patients.”

Mifepristone binds to cytosolic glucocorticoid receptors and prevents gene expression, but it is also a progesterone antagonist. The compound has a high oral bioavailability with an acceptable side effect profile, Dr. Goldberg said.

In the U.S., the compound has been approved for use in two separate indications, one as an abortifacient (RU-486) in a lower dose proved for use in two separate indications, one as an abortifacient (RU-486) in a lower dose, and the other for Cushing syndrome with a 300 mg dose.

**STOMP-CSC**

STOMP-CSC was a randomized, placebo-controlled, double-masked, multicenter, investigator-initiated study (ClinicalTrials.gov ID NCT02354170).

“There was no corporate oversight or data control,” Dr. Goldberg said, although Corcept did provide the study drug kits.

The study enrolled 30 patients, who were randomly assigned to mifepristone 300 mg daily, mifepristone 900 mg daily, or placebo. Patients were dosed for 4 weeks, and then observed for an additional 4-week washout period. At baseline, 4 weeks, and 8 weeks, optical coherence tomography (OCT) angiography was used to assess treatment outcomes.

The investigators thought it imperative to include a true placebo arm as this disease has a known waxing and waning nature, and these predisposed patients may show a true placebo effect, he said.

The primary outcome was the change in central retinal thickness (CRT) on OCT. Key secondary outcomes were the change in BCVA as measured on the Early Treatment Diabetic Retinopathy Study, safety, and tolerability.

Key exclusion criteria included women who were breastfeeding, pregnant, or actively trying to conceive; patients with active intraocular inflammation; and patients who required concomitant treatment with systemic corticosteroids for serious medical conditions (i.e., immunosuppression after organ transplant).

**Take-Home**

- A small study found a significant reduction in subretinal fluid in patients with central serous chorioretinopathy who were treated with mifepristone.

**STUDY RESULTS**

Thirty patients enrolled, but one was excluded from the efficacy analysis after OCT revealed no subretinal fluid on central subfield. The average age of enrolled subjects was 54 years, and there were 25 men/5 women enrolled. The patients had an average duration of CSC of 5.3 years.

“Did mifepristone affect the central retinal thickness? Well, it certainly seemed to,” Dr. Goldberg said. “Patients who were treated with active treatment, either 300 mg or 900 mg, had a statistically significant reduction in their subretinal fluid.”

The mifepristone groups had a baseline CRT of about 351 μg that decreased to about 340 μg (p = 0.045).

The comparison between the active and placebo arms did not reach statistical significance (p = 0.15) but Dr. Goldberg attributed that to the small number of patients enrolled.

“The VA results correlated very nicely to the CRT outcomes,” he said. “Patients in the mifepristone arms gained 3.6 letters (p < 0.05) compared to the placebo group that gained 0.7 letters (p = 0.64).” Between group comparisons did not reach statistical significance (p = 0.19).

At baseline, 83% of patients had a baseline BCVA ≥20/40, which “may have produced a ceiling effect on the change in BCVA,” Dr. Goldberg said.

The drug was well tolerated, with nausea/dizziness the most common adverse event reported in the mifepristone arm (n = 4; 20%), followed by back pain and headache (n = 3 each; 15%), but these were mild and transient, Dr. Goldberg said.

“There are certainly some limitations and key learning points,” he said.

For example, the study had a small sample size, which may have resulted in a true placebo effect. After enrollment, the researchers identified one patient with choroidal neovascularization membrane on OCT, which should become an exclusionary factor in the future.

“This really speaks to our need for other functional endpoints beyond BCVA,” he said. “These patients are highly symptomatic and many of them have a ceiling effect because the baseline vision was so good. Or there was a basement effect—they had such severe disease that despite the anatomic improvement, it was impossible to show visual improvement.”

**Roger Goldberg, MD, MBA**

**E:** info@bayarearetina.com

This article was adapted from Dr. Goldberg’s presentation at the 2018 meeting of the American Society of Retina Specialists. Dr. Goldberg is an investigator for Concept Therapeutics.
Two drugs better than one in DME?
Combination steroid, anti-VEGF therapy given simultaneously showing benefit at 6 months

By Michelle Dalton, ELS; Reviewed by Charles C. Wykoff, MD, PhD

A PHASE II clinical trial evaluating suprachoroidal CLS-TA used with intravitreally administered aflibercept in patients with diabetic macular edema (DME) over a 6-month evaluation period (known as Tybee) has met both primary and secondary endpoints of vision and anatomic improvement, according to Clearside Biomedical in a prepared statement.

Suprachoroidal CLS-TA is a proprietary preservative-free, suspension of triamcinolone acetonide formulated for administration to the back of the eye via the suprachoroidal space. Clearside has said that the suprachoroidal treatment approach is designed “to enable rapid dispersion of a high amount of medicine” to the posterior segment.

Whereas most studies investigate one drug in each arm, “this approach is unique,” said Charles C. Wykoff, MD, PhD, of Retina Consultants of Houston. “It’s using combination therapy in DME patients to determine if we can do better from both an efficacy and durability perspective compared with monotherapy alone.”

On their own, both anti-vascular endothelial growth factor (VEGF) agents and steroids manage exudative retinal diseases, but “a core challenge is that most patients require repeated anti-VEGF injections over long-periods to achieve optimal outcomes,” adding substantially to the treatment burden. The study enrolled 71 treatment-naïve DME patients with baseline best-corrected visual acuity (BCVA) of 20/40–20/200 and center-involved macular edema of more than 300 μm.

The trial met its primary endpoint of mean improvement in BCVA from baseline over 6 months. Patients in the combination arm gained an average of 12.3 ETDRS letters compared to 13.5 ETDRS letters in the aflibercept alone control arm (p = 0.664).

In this multicenter, randomized, masked, controlled phase II trial, patients were randomly assigned 1:1 to receive quarterly treatments of suprachoroidal CLS-TA together with intravitreal aflibercept (months 0 and 3; the combination arm) or 4 monthly treatments of intravitreal aflibercept plus a sham suprachoroidal procedure (months 0, 1, 2, and 3; the control arm), with patients in both arms receiving intravitreal aflibercept treatment at months 4 and 5 as needed.

The trial used a direct head-to-head comparison for similarity between the arms, with a 90% confidence interval for the evaluation. The study also met secondary endpoints, with a mean reduction from baseline of 208 μm in central subfield thickness (CST) at 6 months in the combination arm, compared with a 177 μm mean reduction in the control arm (p = 0.156).

Further, 93% of patients in the combination arm had a greater than 50% reduction in excess CST at 6 months, compared with 73% of patients in the control arm.

There were no treatment-related serious adverse events reported through the 24-week evaluation period. Elevated IOP adverse events were reported for 8.3% of patients in the combination arm, compared with 2.9% of patients in the control arm.

About 5.6% of patients in the combination arm and 2.9% of patients in the control arm developed or showed progression of cataracts.

‘It’s using combination therapy in DME patients to determine if we can do better from both an efficacy and durability perspective compared with monotherapy alone.’ — Charles C. Wykoff, MD, PhD

TAKE-HOME

» The Tybee study of suprachoroidal CLS-TA used with aflibercept in DME patients met its primary and secondary endpoints.

DIVING DEEPER

Tybee investigators hoped to show that delivering 2 mg of aflibercept on the same day as 4 mg CLS-TA would achieve maximal outcomes while substantially decreasing treatment burden. The study enrolled 71 DME patients with baseline best-corrected visual acuity (BCVA) of 20/40–20/200 and center-involved macular edema of more than 300 μm.

The trial met its primary endpoint of mean improvement in BCVA from baseline over 6 months. Patients in the combination arm gained

Continues on page 23:: DME therapy
Because affected patients lack corneal sensitivity, they cannot feel if their condition is worsening, and so they need frequent follow-up visits with their ophthalmologist,” said Dr. Mantelli, adjunct associate professor of biology, Temple University School of Medicine, Philadelphia. “Furthermore, the only intervention that could be offered to these patients were measures to protect the cornea and try to delay the course of this progressive condition.”

In refractory cases and advanced disease stages, interventions include tarsorraphy, amniotic membrane transplantation, and creation of a conjunctival flap, but these measures are not very acceptable to patients because they are invasive and disfiguring, he said.

“Results from two randomized, masked controlled clinical trials show that cenegermin is safe, well-tolerated, and significantly more effective than vehicle for restoring corneal epithelial integrity in eyes with stage 2 (moderate, persistent epithelial defect) or stage 3 (severe, corneal ulcer) NK. We believe evidence shows that cenegermin is significantly more effective than vehicle for restoring corneal epithelial integrity. However, there was no objective evidence of improvement in the lesion size in the prior 2 weeks, and had decreased corneal sensitivity (<40 mm by Cochet-Bonnet aesthesiometer) within and in at least one corneal quadrant outside the area of the lesion.

The dose-ranging phase II study randomly assigned 156 patients 1:1 to treatment with cenegermin 20 mcg/mL, cenegermin 10 mcg/mL, or vehicle. Study treatment was used 6 times daily for 8 weeks. Patients in the vehicle group who experienced treatment failure during the 8-week controlled treatment period (i.e., their condition had worsened, not healed, or recurred) were eligible for an additional, uncontrolled treatment course with cenegermin 10 or 20 mcg/mL (a second randomization performed at baseline) for 8 weeks. All patients were followed for 48 weeks after completing treatment.

The primary endpoint was percentage of eyes achieving corneal healing at 4 weeks (defined as <0.5 mm maximum diameter of corneal fluorescein staining in the area of the defect). The study results showed a highly statistically significant difference favoring both cenegermin 10 mcg/mL and 20 mcg/mL over vehicle (54.9% and 58.0% versus 19.6%; p < 0.001 for both comparisons). The active treatments also maintained their superiority over vehicle in analysis of the prespecified secondary endpoint, corneal healing rate at 8 weeks, when nearly three-fourths of eyes treated with either 10 mcg/mL or 20 mcg/mL cenegermin had healed compared with just 43% of eyes in the control group (p < 0.002).

In a post hoc analysis using a more stringent definition of healing (0 mm staining in the lesion area and no persistent staining elsewhere), 49% of eyes treated with cenegermin 10 mcg/mL, 58% of eyes in the 20 mcg/mL group and 13.7% of controls had achieved corneal healing (p < 0.001 versus placebo for both groups). Evaluations at the end of the study showed the treatment benefit was maintained in the long term; 96% of patients whose defect healed with cenegermin remained healed at 48 weeks.

Other secondary and exploratory endpoints included measurement of corneal lesion size, time to corneal healing or onset of healing, best-corrected distance visual acuity, corneal sensitivity, and reflex tearing. Overall, the results from those assessments favored cenegermin versus vehicle, although the differences between groups were not always statistically significant at all time points, likely due to insufficient statistical power of the patient sample.

“The sample size for REPARO was chosen to demonstrate efficacy for the primary endpoint (corneal healing) and may not have been adequate to demonstrate statistically significant differences in the secondary and exploratory endpoints,” Dr. Mantelli said.

There were no clinically significant ocular or systemic adverse events during the treatment or follow-up periods. Eye pain and other similar complaints (e.g., abnormal sensation in the eye, excessive lacrimation, photophobia, eyelid pain, eye or eyelid irritation) were the most common treatment-related adverse events associated with cenegermin, but they could be interpreted as a sign of efficacy because they may reflect restoration of corneal innervation, corneal sensitivity, and reflex tearing.

A confirmatory trial conducted in the United States, NFG0214, enrolled 48 patients and compared cenegermin 20 mcg/mL with vehicle. It used the same enrollment criteria, treatment protocol, and endpoints as REPARO except that only NFG0214 allowed enrollment of patients with bilateral NK. Upon agreement with the FDA, patients were followed to just 6 months.

“In REPARO, the 10 and 20 mcg/mL cenegermin formulations had similar safety but the higher dose was more effective, and so it was chosen as the dose we wanted to pursue for commercialization,” Dr. Mantelli said. “The shorter follow-up in the confirmatory trial aimed to allow cenegermin to become commercially available sooner, and the healing responses observed in the confirmatory trial were strikingly similar to those seen in the first phase II study.”

Details regarding patient access will be announced prior to that time.

Cenegermin will be made available by Dompé in the United States by early 2019.

STEPHEN C. PFLUGFELDER, MD
stevenp@bcm.edu
Dr. Pflugfelder was an investigator in the Oxervate clinical trial and is consultant for Allergan and Shire.
Cenegermin will be made available by Dompé in the United States by early 2019.
Details regarding patient access will be announced prior to that time.
tional aflibercept injections during the PRN phase of the trial also showed a significant difference, with the control arm needing an additional 23 injections compared to 10 injections needed in the combination arm ($p = 0.03$).

From a safety perspective, “as with any steroid trial, we need to look at IOP elevations,” Dr. Wykoff said. One patient in the control arm and three who received suprachoroidal CLS-TA every 12 weeks gained at least 15 letters in BCVA from baseline at week 24, compared with 16% of patients who underwent a sham procedure.

The mean improvement from baseline was maintained throughout the evaluation period, with 9.6 letters gained at week 4 and 13.8 letters at week 24 in the active arm, compared in the combination arm (2.9% versus 8.3%, respectively) had elevated IOP.

“The phase II Tybee study met its primary endpoint and the secondary analyses all point toward an anatomic benefit beyond anti-VEGF monotherapy,” Dr. Wykoff said. “These signals support continued evaluation for a potential pivotal phase III program.”

**OTHER INDICATIONS**

CLS-TA also is under evaluation for the treatment of retinal vein occlusion (RVO) and non-infectious uveitis (NIU).

In RVO, the phase II Tanzanite study showed the combination arm provided better vision, faster onset of action, and a longer duration of action than treatment with intravitreal aflibercept alone.1 Clearside just finished enrollment in the phase II Sapphire study, which is evaluating CLS-TA with aflibercept for the potential treatment of RVO.

In the Peachtree trial for NIU patients with macular edema, 47% of patients with 1.2 letters at week 4 and 3.0 letters at week 24 in the control arm, respectively.

The company said it plans to file a New Drug Application with the FDA for CLS-TA as monotherapy for the treatment of macular edema associated with NIU.

**Reference**

Aflibercept Injected
Week 0
Ranibizumab Injected
Week 4
20/25
20/25
20/25
20/25
W1
W2
W4

OCT B Inferior Section (Greenline)

Patient in 1 week after their first anti-vascular endothelial growth factor (VEGF) injection to undergo OCT can provide insights about the membrane and its likelihood to respond.

“The decision to start treatment, switch to another, or stop treatment altogether is sometimes arbitrary and capricious,” he said. “We really don’t know before starting treatment that this anti-VEGF drug works best for this specific neovascular membrane.”

Using OCTEarlier

An 80-year-old Caucasian male complained of a new scotoma and distorted vision nasal to fixation in the right eye. Visual acuity was 20/25.

He had been treated with “all well-known treatment modalities for exudative macular degeneration,” Dr. Tornambe said—including 13 injections of bevacizumab, 13 of ranibizumab, five of aflibercept, two treatments of reduced fluence photodynamic therapy (PDT), and two intravitreal triamcinolone acetate injections—over the last decade and went into a remission for 18 months. The patient’s disease re-activated in Feb. 2017, where he was placed on a treat-and-extend every 2-3 months regimen. On August 19, 2017, he received PDT/aflibercept.

Dr. Tornambe said treatment was initiated after an OCT with an injection of aflibercept; the patient then had weekly OCTs for 3 weeks. The protocol was repeated every 4 weeks using ranibizumab and then bevacizumab. The patient agreed to monthly injections of a different VEGF inhibitor drug and weekly OCT A and B scans performed with an Optovue unit.

At week 1, OCT showed a “prompt effect of aflibercept on the temporal portion of the membrane and an almost complete resolution of subretinal fluid,” Dr. Tornambe said. By week 2, the neovascular membrane reperfused, but there was still no subretinal fluid. At week 4, visual acuity remained at 20/25. But OCT showed the temporal net had reperfused and subretinal fluid accumulated.

Reperfusion frequently develops before sub-

OCTA MAY BE HARBINGER OF ANTI-VEGF EFFICACY

Though may help customize drug to specific membrane, clinicians must temper initial enthusiasm with test of time

By Michelle Dalton, ELS; Reviewed by Paul Tornambe, MD

S

ometimes a single case example can provide food for thought and act as a springboard for future clinical studies. That’s exactly what Paul Tornambe, MD, of San Diego, hopes will happen from his findings on optical coherence tomography angiography (OCTA), choroidal neovascular membranes (CNVM), and treatment recommendations.

His case study results were presented at this year’s American Society of Retina Surgeons conference, and suggested bringing a
retinal fluid accumulates, and the “very early effect of the drug at one week” is readily seen on OCT.

“This case clearly shows a neovascular membrane’s response to VEGF-inhibitors is not homogeneous, occurs very early after the injections, and that only a portion of the membrane may be VEGF-inhibitor responsive,” he said. (See Figures 1 and 2.)

When the patient then underwent treatment with ranibizumab, the OCT showed the membrane to be the same as it was before the aflibercept injection. At week 1, there was less perfusion of the temporal complex, “but there was also persistent subretinal fluid,” Dr. Tornambe said. Weeks 2 and 4 showed approximately the same as when the patient had been given aflibercept.

“There appears to be no difference between these two drugs for this particular case,” Dr. Tornambe said. When the patient was injected with bevacizumab, however, there “appeared to be little to no effect on the neovascular complex for this specific case. Visual acuity did not change.”

In typical clinical settings, however, OCTs are often performed only at baseline at month 1/week 4, “So in this instance, there were no discernible difference between bevacizumab and ranibizumab, even though there was a significant ranibizumab effect at week 1,” Dr. Tornambe said.

Saying that OCTA may be a way to customize a drug to a specific membrane, “we must always temper initial enthusiasm with the test of time,” he said.

**CLINICAL RELEVANCE**

“Mature membranes don’t respond to VEGF Inhibitors, just those that are growing and those that are immature. And that’s really important because it makes no sense to keep injecting a VEGF inhibitor if the membrane’s mature,” Dr. Tornambe said.

Further, there is only one way to tell which membranes are mature, and that is with an OCT in the first post-injection week.

The greatest drug effect can be seen consistently during the first week following an anti-VEGF injection, “and reperfusion may develop prior to subretinal fluid accumulation, possibly signaling the need for another injection, thus a possible marker to treat sooner.”

**WEEK 1 IS KEY**

If there had been no OCT at week 1, “we would never have known there was any effect,” he said. “That is a very, very important finding because Centers for Medicare & Medicaid Services only pays for OCTs one month apart. Yet we’ve shown the 1-week time point is most clinically relevant.”

Dr. Tornambe’s group has now performed a case series and findings are mimicking this first case. If the 1-week OCT shows no effect on the membrane, it might suggest switching to another treatment or stopping injection treatments with close follow-up studies to search for recurrences elsewhere, he said.

“This methodology may prove to be the most patient-centered, customized, cost effective and rational way to determine drug selection, follow-up, and switching or stopping treatment for a specific neovascular membrane in a specific macular degeneration eye,” he said.

In the ongoing push towards treat-and-extend, “we are always looking for earlier markers for re-treatment,” he said. “In some of these cases, reperfusion has already occurred at week 3, and then 2-3 weeks later fluid returns. That’s what we’re trying to avoid.”

His advice is to take an OCT after week 1 (and if there is no change on OCT, change to a different anti-VEGF), and retreat when the vessel becomes reperfused, not when fluid returns.

Until there is a way to measure VEGF levels non-invasively, Dr. Tornambe believes early OCTs are the most effective way to measure treatment efficacy. He did caution that “we absolutely cannot generalize from this single case that bevacizumab is an inferior drug—it just did not work well on this particular CNVM. We must also ensure the OCT slices through the same area of the CNV complex, otherwise changes noted in the CNV perfusion may be due to an artifact.”

**OCTA EFFICACY**

(Continued from page 29)

Say that OCTA may be a way to customize a drug to a specific membrane, “we must always temper initial enthusiasm with the test of time,” he said.
Discerning between high astigmatism, subclinical keratoconus is problematic

Results suggest possible need for better diagnostic tools for subgroup of patients

By Cheryl Guttman Krader; Reviewed by Maria A. Henriquez, MD, MSc, PhD

CURRENTLY available keratoconus screening indices found on two commercially available Scheimpflug devices show a lack of predictability for accurately discriminating between subclinical keratoconus and normal eyes with high astigmatism, according to findings of a retrospective study conducted by Maria A. Henriquez, MD, MSc, PhD, and colleagues.

“The screening indices found on existing topography or tomography systems perform well for discriminating between normal eyes and eyes with keratoconus. However, discriminating between low ametropia and clear keratoconus is a different situation than discriminating between eyes with high ametropia versus subclinical keratoconus,” said Dr. Henriquez, director, Research Department, Oftalmosalud Instituto de Ojos, Lima, Peru, and professor of ophthalmology, Post GCRST Harvard Medical School, Boston.

“Our results show that eyes with high astigmatism are very often falsely diagnosed as having subclinical keratoconus using the keratoconus screening indices,” Dr. Henriquez said. “This creates a problem for surgeons because they are faced with trying to decide whether to operate on a patient whose parameters fit within the abnormal values or, because of the doubt raised by the machine’s results, to not operate on a patient whose eye may be normal.”

The study included 67 eyes of 67 patients who were evaluated with two Scheimpflug imaging devices (Pentacam, Oculus; Galilei, Ziemer) prior to undergoing LASIK. All eyes had >1.5 D of astigmatism in the subjective refraction and anterior cornea astigmatism and had been followed for at least 12 months after LASIK without evidence of developing ectasia.

The accuracy of 10 preoperative keratoconus screening indices found on each device and/or suggested by previous studies for diagnosing both keratoconus and subclinical keratoconus was evaluated by analyzing its rate of false positives in the sample size (i.e., eyes that were wrongly identified as having keratoconus or subclinical keratoconus).

“The indices and cutoff point we used represented those that had been suggested by previous studies as having the highest predictive value for identifying keratoconus and subclinical keratoconus from normal eyes,” Dr. Henriquez explained.

In the analysis of diagnostic performance for correctly identifying keratoconus, the false positive rates for all of the Pentacam screening indices except for one index fell within the previously suggested range. However, with the Galilei, only 2 of the 10 indices, had a false positive rate that did not exceed the previously reported maximum.

For diagnosing subclinical keratoconus, 6 of the 10 Pentacam screening indices and 7 of the 10 Galilei indices were associated with false positive rates that exceeded the values suggested as acceptable in previous studies or by the manufacturers.

Subgroup analyses were performed to determine the false positive rates for diagnosing keratoconus and subclinical keratoconus with eyes categorized by type of astigmatism (myopic, hyperopic, mixed, or simple). Overall the results showed that false positive rates were highest in the hyperopic astigmatism and mixed astigmatism groups, which leads us to think that there is still a need for better diagnostic tools for this subgroup of patients.

OCULUS debuts perimeter for central, peripheral visual field

OCULUS announced the release of its Smartfield perimeter, expanding its unique portfolio of compact visual field testing devices. The new device has been optimized specifically for examinations for functional impairment of the central visual field, but is also suited for peripheral measurements.

The device performs standard automated perimetry using an ultra-high luminance LCD display. Its short measurement times make it excellently suited for standard screening methods. In addition, the control software offers a wide array of state-of-the-art measurement procedures for diagnostic and follow-up examinations.

Thanks to its compact design this new perimeter requires only little set-up space. It can be operated in rooms with normal lighting conditions, saving the need for a darkroom.

The new device comes with translucent lateral eye shields, also eliminating the need for an eyepatch and saving time in preparation for the examination. Another time saver is that patients with presbyopia require no refractive correction prior to testing.

Since the new device works entirely without moving parts, customers also enjoy the advantages of reduced maintenance costs and a longer service life. The practical carrying handle makes the perimeter convenient for portable use.
Light induced visual-response as objective, functional vision testing

Getting past perceived complexity of electrophysiology reveals applications in routine eye disease

By Steven M. Silverstein, MD, FACS; Special to Ophthalmology Times

LIGHT INDUCED visual (LIV)-response (the use of light to stimulate electrical responses from cells within the eye) has recently emerged as a better way to describe visual electrophysiology testing.

There is an old perception that electrophysiology is mostly used to detect esoteric eye disease and for monitoring subtle changes in rare pathologies in the institutional setting. In reality, modern LIV tests can help guide clinical decision making in pathologies that we see on a routine basis by using streamlined protocols and platforms which fit into the practice setting.

Modern LIV platforms do not require a PhD level of technical understanding. The reports generated by my in-office platform use green-yellow-red color-coding to note healthy, caution, and likelihood of pathology, respectively (Diopsys). The testing is comfortable for patients, does not require a contact lens, and is more patient-friendly than a visual field.

Additionally, using LIV has not negatively impacted our efficiency. We have a designated technician who performs all necessary testing, including OCT, visual fields, and LIV. At the same time, the platform we use has a template for running the chosen test that integrates with our electronic records systems for generating reports, patient follow up, scheduling future tests, and integration into coding and billing.

Studies have long supported the use of these types of objective, functional tests for common ocular pathologies, and now modern devices make the technology accessible to the practice.

DIABETIC RETINOPATHY

Flicker electroretinography (ERG) is a type of LIV that uses a fast flashing light to stimulate cone cells. Flicker ERG can help stage patients with diabetic retinopathy (DR), and with the recent availability of anti-VEGF therapy for treatment of DR, it adds additional clinical relevance.

Treatment of DR in the absence of diabetic macular edema (DME) is discretionary; serial LIV testing to objectively monitor the function of the retina may indicate decline before progression is evident on other imaging (including OCT and angiography). Certain clinical features, such as cotton wool spots, exudate, dot and blot hemorrhages, microaneurysms, and early IRMA, indicate a risk for DR progression. Closely monitoring patients with these signs using flicker ERG is beneficial for deciding when to start intravitreous anti-VEGF injections. Over time, flicker ERG output helps time the treatment intervals and may suggest a possibility of stopping therapy once stable disease has been achieved.

Flicker ERG can simplify the approach to patients with DR by stratifying patients with mild, moderate, or severe nonproliferative DR, and thereby use this objective information regarding the function of the retina to determine treatment in the first two categories of patients.

AMD

Similar to DR, clinical features will indicate a role for performing ERG in patients with age-re-
TRAVEL TO TRANSFORM WITH
PASSION TO HEAL™

PROVIDE OPHTHALMOLOGY CARE TO COMMUNITIES IN KENYA
Leverage your professional expertise and skills by making a difference in the world. Travel on a fully funded ME to WE Trip to rural Kenya to help transform eye care for thousands of adults and children in our charity partner’s communities. In collaboration with ME to WE Trips, the Passion to Heal™ initiative funds the cost of these medical volunteer trips, supported by Valeant Pharmaceuticals NA LLC (VPNA).

KENYA September 15 - 24, 2018

APPLY NOW FOR YOUR FULLY FUNDED TRIP!

PASSIONTOHEAL.COM
Evaluating corneal epithelium thickness imaged by HD-OCT

Corneal abnormalities detected with OCT can catch ocular warning signs earlier

By Nancy Groves; Reviewed by Hugo Y. Hsu, MD

A STUDY conducted at Doheny Eye Center, University of California, Los Angeles (UCLA), contributes to the literature suggesting that anterior segment OCT can assist clinicians with clinical assessments of diseased corneas and guide the treatment plan, said Hugo Y. Hsu, MD, professor of ophthalmology, Doheny Eye Center, Department of Ophthalmology, David Geffen School of Medicine, UCLA.

Dr. Hsu was senior author of a study using the high-definition optical coherence tomography (HD-OCT) (Cirrus, Carl Zeiss Meditec) to evaluate corneal epithelium thickness (CET) in healthy eyes. He noted that while technology such as OCT has become ubiquitous in retina, it currently plays a much smaller role in cornea.

“For the cornea, we have not been able to leverage all these new imaging modalities to understand the anatomy of the cornea and as a result determine if pathologic states are present,” Dr. Hsu said. “Imaging of the cornea has lagged significantly behind that of the retina. But the OCT technology exists; it’s just a matter of using different adaptive lenses to shift the focal point so that it can measure the cornea and also using software to interpret the information. We can then reconstruct the cornea shape to let us know what is normal versus abnormal.”

CORNEAL THICKNESS

Despite its suspected importance in disease states such as dry eye, keratoconus, and limbal stem cell deficiency, the corneal epithelium has been “elusive” in terms of the ability to obtain accurate measurements, Dr. Hsu said. Alterations in the corneal epithelial thickness may be early clues to disease as well as a parameter that could be followed to evaluate the effects of treatment.

Particularly with corneal cross-linking now an approved therapeutic approach for keratoconus, it behooves clinicians to diagnose this condition at a preclinical stage, Dr. Hsu said. Yet, while changes in CET are a likely harbinger of keratoconus, its measurement remains a challenge.

“We know that in general the corneal thickness increases from the center to the periphery, but investigators using various other techniques to try to measure the epithelium have reported variable results,” Dr. Hsu said. However, in this study, by using HD-OCT and special adaptive lenses specifically made for corneal imaging, investigators discovered that while corneal thickness increases from the center to the periphery, the corneal epithelium does the opposite.

Dr. Hsu and colleagues imaged 31 healthy eyes of 16 subjects by HD-OCT pachymetry scan, measuring CET in three separate corneal zones as well as its correlated characteristics. Zonal values for 0.20 mm, 2.0-5.0 mm, and 5.0-7.0 mm were obtained for both corneal thickness (CT) and CET. At least two measurements for each parameter were averaged and analyzed using ANOVA test.

Results of the analysis showed that CET was 48.3 ± 2.8 μm, 47.2 ± 2.5 μm, and 46.3 ± 2.2 μm in the 0-2.0 mm, 2.0-6.0 mm, and 5.0-7.0 zones, respectively (p < 0.05). Corneal thickness measured 535 ± 28.5 μm, 553 ± 29.0 μm, and 582 ± 29.4 μm in the three zones (p < 0.05). No statistically significant correlation was found between CET and CT in any of the three zones. While investigators found a statistically significant difference in CT based on gender, with males having thicker corneas in all three zones (p < 0.05), there was no significant gender-based difference in CET in any zone (p > 0.05), which differs from other reports.

“We’d like to think that this study has use in terms of establishing a device, the Zeiss Cirrus HD-OCT, that is readily available and that clinicians can use to measure the corneal epithelial thickness, as a way to monitor the onset of disease and disease progression and the use of therapeutic modalities that may help,” Dr. Hsu said.

A recent, small study adds to the growing body of literature indicating that optical coherence tomography can be adapted to evaluation of the cornea, arming physicians with more data on normal and abnormal anatomy and helping them detect early warning signs of ocular disease as well as monitor the progress of patients undergoing treatment.

Special Report | NEW WAVE OF DIAGNOSTIC TECHNOLOGY

HUGO Y. HSU, MD

This article was adapted from a poster presentation at the 2018 meeting of the American Society of Cataract and Refractive Surgery. Dr. Hsu did not report any financial relationships relevant to this study.
LIV TESTING

(Continued from page 32)

LIV testing, commonly known as Pattern ERG (electroretinographic), provides an index of ganglion cell viability. Pattern ERG is a type of LIV test which uses a pattern stimulus to induce an electrical response from retinal ganglion cells. While monitoring patients with ocular hypertension or suspect glaucoma, pattern ERG provides the earliest indication that ganglion cell viability is compromised relative to visual field and OCT. Pattern ERG can also be additive in diagnosing progression. For example, in a patient with suspicious disc, initially elevated pressures to the low or mid 20s, and no visual field changes, serial pattern ERG testing may be useful as a diagnostic tie breaker. Any change from the individual’s initial results may indicate an opportunity to intervene, even before a visual field deficit has been seen. Just as important, the pattern ERG signal can improve after treatment. At a biologic level, this is an indication that treatment started when the ganglion cells became unhealthy, but before they died. LIV results can show our patients we are not just preventing further damage, but we intervened early enough to help improve function.

CONCLUSION

LIV is a proven diagnostic tool that has been around for several decades. Modern devices now provide the technical capacity to offer LIV testing to more patients with no tech-learning curve, and easy clinician interpretation.

References


GVS partners with 20/20NOW to provide mobile eye care center

GENERAL VISION SERVICES (GVS), a leading vision benefits provider, and 20/20NOW, inventor of ocular telehealth eye exams, are partnering to create the first mobile eye care center featuring ocular telehealth. Commencing last month, the center will provide on-site eyecare and wearables services at GVS client locations. Members of GVS clients will be able to take care of all their optical needs while at work.

According to Maureen Flaherty, VP of network operations for GVS, “After reviewing the available tele-health options GVS selected 20/20NOW because of their standard of care and experience within the ocular tele-health space. “This new digital healthcare technology will enable us to provide our members with convenient access to eyecare services while at the same time lowering costs,” Flaherty said. “Oftentimes members don’t receive regular eye exams because they have to take time off work to see the doctor. With ocular telehealth, members are now able to receive comprehensive eyecare in a very convenient and cost-efficient manner.”

This is another example how telehealth can improve access to state-of-the-art equipment and digital comprehensive eye exams, added Chuck Scott, 20/20NOW CEO and telehealth industry veteran. “We look forward to partnering with GVS to improve the customer experience.”

GVS also shared that it recently contracted with Black Car Services, including Uber, Lyft and others to provide vision benefits to their qualified drivers in the greater NY metro region and that the new mobile eye care center, in conjunction with its PPO Network, will be used to provide eyecare services to the drivers.

“We are thrilled to provide such an innovative employee vision benefit to Black Car Service drivers,” according to Tony Rosario, Executive VP of GVS.
‘These findings may lead to customized treatment selections and better outcomes.’

— Pallak Kusumgar, MS

FINDINGS OF A STUDY associating the preoperative gene expression of certain molecular factors in corneal epithelial tissue and tears of keratoconus (KCN) patients with outcomes of corneal crosslinking (CXL) point to the possibility of developing an assay for predicting CXL response and complications.

“Our study suggests that the outcome of CXL may be determined by the levels of basal inflammation, collagen, and cellular components,” said Pallak Kusumgar, MS, Cornea, Cataract, and Refractive surgery fellow, Narayana Nethralaya Eye Hospital, Bangalore, India.

“Now our aim is to apply the results from this study and ongoing research to develop a rapid point-of-care kit for detecting predictive biomarkers in preoperative tears,” Kusumgar said.

“Such an assay could provide evidence-based prognostication and customized treatment selection for improved patient outcomes.”

To investigate associations between molecular markers and CXL outcomes, Kusumgar and colleagues undertook a prospective study enrolling patients with progressive keratoconus.

Eligible eyes had grade 1 or 2 keratoconus with >1 D increase in keratometry in the previous 6 months, corneal thickness ≥400 μm at the thinnest location, and contact lens intolerance, Kusumgar noted.

Patients with active allergic eye disease or ocular inflammation, central or paracentral scarring, or other ocular comorbidities were excluded.

Samples from the corneal epithelium over the ectatic cone area and the corneal periphery were obtained pre-operatively from KC patients when performing accelerated CXL. The tissue samples were analyzed for total mRNA levels of lysyl oxidase (LOX), matrix metalloproteinase 9 (MMP 9), bone morphogenic protein 7 (BMP7), tissue inhibitor of metalloproteinase 1 (TIMP1), and two collagens [collagen type I, alpha 1 (COL 1A1 and collagen type IV, alpha 1 (COLIV1)].

Patients were followed for at least 6 months and categorized as achieving an optimal or suboptimal response defined by whether or not they had a ≥0.5 D decrease from the preCXL maximum keratometry (Kmax).

Of 37 evaluable patients, 26 (70%) had an optimal outcome; they had a mean Kmax change from baseline of 1.4 D.

The mRNA analyses showed a statistically significant difference in expression levels between groups for LOX expression, with the ratio of cone:periphery expression being significantly higher in the optimal versus suboptimal group (0.66 versus 0.25; p = 0.001).

Patients who underwent bilateral CXL developed a unilateral sterile infiltrate. Analyses of a number of inflammatory cytokines in their preoperative tear samples showed that in both patients, the levels of these cytokines were >1.5-fold higher in the eye with the sterile infiltrate compared with the fellow eye that did not develop a complication.

“This finding suggests that detecting and managing increased inflammation of the ocular surface prior to CXL might help to mitigate the risk of developing a sterile infiltrate,” Kusumgar said.

Compared with the suboptimal group, there were trends for the optimal response group to have a higher cone:periphery ratio of BMP7, COL IV A1, and TIMP1 and a lower cone:periphery ratio of MMP9.

Two patients who underwent bilateral CXL developed a unilateral sterile infiltrate. Analyses of a number of inflammatory cytokines in their preoperative tear samples showed that...
Angiography boosts OCT in glaucoma

Researchers using it to look closely at macula, nerve, peripapillary areas

By Laird Harrison; Reviewed by Robert Stamper, MD

OPTICAL coherence tomography (OCT) angiography could yield important insights into glaucoma, according to Robert Stamper, MD. The new imaging technique shows significant loss of blood vessels around the optic nerve in patients with glaucoma, said Dr. Stamper, professor of ophthalmology, University of California, San Francisco.

OCT tomography scanners can create about 70,000 images of the back of the eye in 3 seconds. Using artificial intelligence, they apply corrections for blinking and microsaccades, said Dr. Stamper.

“If you have a constant background—the retina—and something is moving across it, and you know how quickly you’ve taken the photos, and the distance, you can sort out the movement that’s occurred from the stable background,” he explained. “That’s basically what OCT angiography depends upon.”

This analysis produces pictures of blood vessels—capillaries, as well as the arterioles and venules in the retina. Its in-depth scans can distinguish vascular layers.

“Motion correction is applied to get rid of saccades, so you get very nice pictures of both the capillary density and sometimes the structure of the capillaries,” said Dr. Stamper.

The pictures produced resemble a flat preparation of the whole retina. For that reason, retinal specialists have been the first ophthalmologists to begin using the new technology. They are using it to analyze macular degeneration.

“I don’t think you need to be an expert to pick up holes,” Dr. Stamper said.

Vascular anomalies show up in OCT angiography of eyes with diabetic retinopathy as well, he said.

In glaucoma, researchers are using the new tool to look more closely at the macula, nerve areas, and peripapillary areas. Comparing an image of a normal eye to an image of a glaucomatous eye, Dr. Stamper showed the absence of the capillary bed in the inferotemporal region. The loss of capillaries coincided with the area where the nerve fiber had degenerated, he pointed out.

“The big question is, ‘Does the capillary layer lose the nerve fiber layer loss, or does the nerve fiber layer loss precede the loss of capillary?’ I don’t have an answer to that.”

In another glaucoma image, he showed that the peripapillary region was reduced in its density. OCT angiography showing radial peripapillary capillaries lost at the level of the nerve confirm similar findings from a study on hundreds of specimens from eye banks conducted about 35 years ago, Dr. Stamper said.

“Just as the axons go into the optic nerve, that layer is reduced in glaucoma,” he said.

“It’s not new information, it’s been around for a long time.”

Particularly in the superficial circulation around the optic nerve, there is a decrease in the capillary density, he pointed out. “The deep layers don’t seem to be affected.”

The newer versions of OCT angiography software use color to compare the capillary density, distinguishing between areas where the capillaries are merely reduced and areas where they are completely missing.

“We actually can get numbers, so we can start to quantify,” Dr. Stamper said. “It’s a very, very interesting new technology.”

Already studies with OCT angiography have shown that the repeatability of vascular density measurements is reasonable.

“The pictures you would get are similar to indocyanine green angiography, but of course this is completely noninvasive.”

The technology can even capture changes that come with early ocular hypertension, he said. Another important finding: reducing IOP with a successful trabeculectomy does not bring back the vascular supply. “It looks like once the vessels go, they stay gone. So that’s a little bit disturbing.”

The new images correlate well with regular OCT and visual fields. “The question is, are we going to learn anything new that we don’t already know from this technology?” he said.

Hoping for an answer in the affirmative, researchers are starting to use quantitative measures and trends over time to search for clues about the pathophysiology of glaucoma. Among the questions this approach might help answer:

■ Does the loss of circulation occur gradually or episodically?
■ How well does the macular capillary density compare to the peripapillary capillary density?
■ Are there some patients in whom the vascular capillary density goes first, and then the nerve fiber layer seems to atrophy? In those particular patients, will it tell clinicians to focus more on the vascular issues?

Such studies could lead to individualization of glaucoma understanding and treatments, he said.

“We don’t have answers to those questions, and we certainly don’t even know if OCT angiography gives us additional information over and above the standard OCT,” said Dr. Stamper.

“But we think it’s a fascinating technology. And I have a feeling in my gut—backed up by no science whatsoever, so therefore I can speak with great passion about it—that it will offer us some insight.”

Robert Stamper, MD
415/514-6920
This article was adapted from Dr. Stamper’s presentation at the 2018 meeting of Glaucoma 360. He did not indicate any proprietary interest in the subject matter.

We actually can get numbers, so we can start to quantify. – Robert Stamper, MD
NEW WAVE OF DIAGNOSTIC TECHNOLOGY

Using SD-OCT to detect scotomas

Small case series has shown additional uses for spectral-domain OCT

By Michelle Dalton, ELS; Reviewed by Inder P. Singh, MD

SPECTRAL-DOMAIN optical coherence tomography (SD-OCT) can potentially be used to document the presence of symptomatic vitreous opacities by documenting the shadows they cause in the macula, said Inder P. Singh, MD, of the Eye Centers of Racine & Kenosha (Wisconsin).

“SD-OCT now has become somewhat ubiquitous in ophthalmology,” Dr. Singh said. “Even though we think about its primary use as a posterior segment retina issue, anterior segment surgeons are using this technology to screen patients for a variety of conditions, including premium lens candidates for cataract surgery. We’re looking at quality of vision issues, and SD-OCT is helping us better understand why a patient’s vision is not as good as it should be.”

Dr. Singh presented his retrospective analysis on six patients who were referred into his center for unexplained scotomas at this year’s American Society of Cataract and Refractive Surgery, and described how SD-OCT was used to diagnose the cause of the scotoma.

A fairly common complaint from patients is floaters, he said, but “we’re not trained very well (historically) to image floaters. We do not tend to look for floaters,” but instead are looking for cataracts, or some anomaly in the cornea or retina as a cause of decreased vision.

In his practice, Dr. Singh has used SD-OCT to determine for a “significant number” of patients whether or not a floater was the cause of the visual impact.

WHAT THE STUDY SAYS

Dr. Singh’s retrospective case series on six patients who were seen for a complaint of a central scotoma, documented on Amsler grid, and found to have an vitreous floater in the middle of the vitreous, over the macula, with no other pathology to explain the scotoma. Some patients had previously undergone MRIs and/or fluorescein angiography “but no one could figure out the cause.” These cases were unique in that the floater itself caused the scotoma.

What he found after SD-OCT can only be described as “amazing,” Dr. Singh said. “On SD-OCT, there were very obvious large black appearing opacities, which were the floaters, but also the shadow the shadow they were casting on the retina.”

SD-OCT “very clearly identified the shadow is what was causing the scotoma,” he said.

For these patients, Dr. Singh treated with YAG laser, and post-laser OCT showed complete resolution of the shadow and the black cloud in four patients, and a reduction in the size of the vitreous opacity and corresponding macular shadow in the remaining two patients.

Although these floaters were large amorphous clouds over the macula, Dr. Singh cautioned that SD-OCT would not find these floaters or clouds if they are in the periphery or if they were smaller in size.

ULTRAWIDE FIELD OR SD-OCT?

In these particular cases, the SD-OCT showed the actual shadow casted on the retina and was able to provide a cross-section view to confirm the shadow was caused by the floater, Dr. Singh explained.

“Ultrasound field OCT doesn’t always give you the ability to see that shadow being cast on the retina,” he said, adding that SD-OCT will allow clinicians to document the area in which the macula has been affected whereas ultrawide field may not be as obvious. Ultra-widefield would be beneficial to identify peripheral floaters, but in these specific cases, SD-OCT was crucial.

WHAT TO ANALYZE

When patients present with floaters that may or may not be causing scotomas or an actual visual complaint from the patient, Dr. Singh recommends erring on the side of caution and “definitely consider performing an OCT. They’re quick and easy to perform and do not take much additional time. If the floater is large enough, you’ll see it on OCT and can document it,” he said.

He also recommends SD-OCT for patients with unexplained scotomas.

“Don’t forget to look in the black area of the OCT—the vitreous—as we tend to only look at the retina,” he said. “In these cases, if you look just above the retina, you’ll be surprised at how many floaters are clumped in the vitreous, and sometimes you’ll see shadows.”

He cautioned against presuming those shadows are artifact. Floaters in the vitreous “is actually much more common than we think, but we often don’t look for it,” Dr. Singh said.

OCT is “a great option to make sure you’re not missing any macular pathology.”

When the floaters are in a good position (not too close to the lens or retina), are causing difficulty with daily tasks, and patients do have posterior vitreous detachment already, Dr. Singh does not hesitate to perform vitreolysis.

“If you’re uncomfortable performing vitreolysis (and not every YAG laser is optimized for floater treatment), refer your patient to someone who does these procedures or to a retina specialist to consider vitrectomy,” Dr. Singh said.

Patients’ quality of vision can be adversely affected by these specific kinds of floaters found in the middle of the vitreous and in the center of the visual axis, he said.

“Even if you don’t treat them, which is understandable, we need to identify them so we can explain to the patient what might be the cause of their diminished vision,” Dr. Singh said.

‘On SD-OCT, there were very obvious large black appearing opacities, which were the floaters, but also the shadow the shadow they were casting on the retina.’

—Inder P. Singh, MD
More than 120 ophthalmologists and other eye-care professionals voluntarily visited Cambodia in 2017 at close-to-weekly intervals in an initiative that was facilitated by the Khmer Sight Foundation (KSF). Most were from the United Kingdom but there were also volunteers from Germany, Austria, Italy, Singapore, and India.

The goal was to screen 20,000 Cambodians in need of eye care and perform up to 10,000 cataract and pterygium surgeries. This year, the need is still pressing, and the KSF continues to welcome new volunteers.

Where ophthalmology is concerned, there is a significant unmet need in Cambodia. In a country that was ravaged by a tragic past during the Khmer Rogue era and only now slowly recovering, there are only 38 ophthalmologists available to serve a nation of 15 million.

Close to 28,000 Cambodians go blind every year and, sadly, 90% of blindness is avoidable. The scale of the issue is possibly underestimated due to incomplete epidemiological data but the logic is irrefutable; socioeconomic deprivation and having a disability creates a vicious cycle of poverty.

As clinicians in Europe, we often take for granted what goes on behind the running of a successful eye service. We walk into our clean workspace in the morning, prepared by the invisible cleaning fairy, and sit in our well-equipped office, where the magical equipment elf has been stocking the cupboards overnight with lenses, devices and all sorts of drugs.

In your usual theater, The Magical Force delivers what you need—biometries, IOLs, microscopes, clean instruments, and a working phacoemulsification machine. You do not challenge The Magical Force.

The truth is, a lot goes into providing a high-quality and high-volume service. To start it from almost scratch with limited resources, for a
population that may not have had eye health as their priority, is truly not a walk in the proverbial park. It is more like a marathon. Whilst wearing flip-flops.

We need to deliver good, quality care—but within practical means. Everything has a cost to it, either in terms of time, manpower, or equipment. Ophthalmology is an equipment-heavy specialty and our clinics and theaters use up a lot of consumables.

Stock is expensive and donated from various charitable sources, so the supply is limited. Working in Cambodia makes one realize how much we truly waste when we are back home!

Another challenge is that often, despite the best intentions of the treating doctor and the translator, it can still be difficult to obtain the patient’s full history. This could be due to the patient’s understanding of their condition, their knowledge, the chronicity of their untreated disease, or a combination of these factors.

General medical practice can be quite paternalistic, and patients often prefer it that way (“just make the decision for me, doctor”). I observed, however, that we Western-trained doctors naturally try to reach for patient-centered decisions (“what would you like to have done?”). This does not work all the time; in Cambodia, we became adept at making quick decisions in patients’ best interests.

Theater is another challenge, owing to sterilization techniques, the sharing of equipment (for example, one phaco cassette for four to five patients), a mixed variety of IOLs, the lack of specialist equipment (limited anterior vitrectomy kits), inexperienced staff, and most importantly, dense and difficult cataracts.

**HELPING HAPPIER PATIENTS**

Funnily enough, despite being on the other side of the world, one patient group remains consistent. The patient with chronic dry eyes. At least in Cambodia, they seem to be actually slightly pleased after you prescribe some eye drops.

Postoperative corneal edema was a real issue, but fortunately it does settle with time.

‘Everything has a cost to it, either in terms of time, manpower, or equipment. Ophthalmology is an equipment-heavy specialty and our clinics and theaters use up a lot of consumables.’
The main challenges that Cambodia face are lack of expertise (they have one of the lowest number of ophthalmologists per capita in the world) and lack of access (many destitute patients live in rural areas with poor access to healthcare).

For a Cambodian villager to go from screening to clinic to eye doctor to surgery is a real mammoth task in terms of organization and logistics. Fortunately, every villager owns a mobile phone or at least knows someone who does.

I am sure I echo the sentiments of all the volunteers who visited when I say that it was a refreshing and humbling experience—and we would like to take this opportunity to thank KSF, Sean Ngu and the people of Cambodia for welcoming us.

Cambodia is rebuilding itself. The deep scars of her past will always be palpable but the resilience of her youthful generation stands out. The new generation of Cambodians will be her greatest resource, and education, training and self-sufficiency the most worthwhile investments.

EyePoint Pharmaceuticals secures pass-through payment status

EYEPOINT PHARMACEUTICALS announced that the Centers for Medicare and Medicaid Services (CMS) has approved transitional pass-through status and reimbursement through a C-code for dexamethasone intraocular suspension 9% (DEXYCU).

The company’s FDA-approved product for the treatment of postoperative inflammation is administered as a single intraocular dose at the end of ocular surgery, noted the company in a prepared statement.

The code, C9034, will become effective on Oct. 1, 2018.

“The receipt of pass-through status and the assignment of a C-code from CMS marks another important step forward in our commercialization preparation for [dexamethasone intraocular suspension 9%],” said Nancy Lurker, president and chief executive officer, EyePoint Pharmaceuticals.

“Our team continues to make progress on our commercialization strategy, hiring and scale-up initiatives in support of our planned commercial launch expected in the first half of 2019,” Lurker said. “We believe [dexamethasone intraocular suspension 9%] has the potential to address the unmet need and limitations of steroid drops, the current standard of care available for patients to treat inflammation following eye surgery, by providing [the product] as a convenient and long-acting single injection alternative therapy.”

About 40% of patients who undergo cataract surgery are covered by Medicare Part B. Drugs that are administered as part of cataract surgery can be covered under a CMS administered transitional-pass-through payment.

The pass-through payment was established by the U.S. government to help foster innovative drug development, according to the statement. Drug applications must meet certain qualifications for inclusion. The transitional pass-through status is temporary for three years and products are reimbursed under a C-code, which are issued quarterly by CMS.
We are a Nationwide Ophthalmology Billing Service. We have been in business over twenty years. Our staff consists of billers who are certified Ophthalmic Techs, Ophthalmic assistants, and fundus photographers who are dual certified ophthalmic coders and billers. This combination of clinical backgrounds in ophthalmology with the certified coding degree is the ideal combination of expertise that you need to dramatically increase your revenue. We will get you paid on every procedure every single time. No more bundling, downcoding or denials…

Primary, Secondary, Tertiary and Patient Billing

Relentless and meticulous follow up.

- Experts in Forensic Billing. Specializing in old AR cleanup
- Credentialing and Re-Credentialing our Specialty. We have a separate Credentialing Department who has cultivated years of contacts to expedite the process as well as getting providers on plans that are technically closed.
- We can offer you our own Practice Management software at no cost to you or we can VPN into your system if that is what you prefer.
- Totally Hippy compliant. We are certified Hippy and have invested in the most secure Hippy connection that Google and Cisco use.
- Monthly custom reports provided.
- We do not outsource any of your billing. All billing done in our office in the U.S.A.

We presently work on all of the following Practice Management systems:

- NextGen, MD Office, Centricity, Medisoft, Office Mate, MD Intellus, Medware, Medcomp, Management Plus, AGS, Revolution EHR, EyeMd EMR, Next Tec, Open Practice Solutions, Cerner Works and more…

All of our clients were paid the PQRI and E-prescribe bonuses and we are ready for the ICD-10 change.

Our staff has years of Attendance at AAO and ASCRS and attends all ongoing Ophthalmology billing and Practice Management continuing education classes. We are always knowledgeable and prepared for all government and commercial changes.

On staff MBA consultants

Call today to schedule a free on site consultation. We will travel to you anytime to evaluate your AR and show you how we can dramatically increase your Revenue.

Our Prestigious National Ophthalmology Clients reference list will be provided at your request.

PM (Practice Management) Billing will keep an EYE on your Billing so you can keep an EYE on your patients.
Ophthalmology Times

PRACTICE FOR SALE

Ophtalmologist to share offices with long-established ophthalmologist in Danbury, CT 06811. OCT, Zeiss Fieldmaster etc. $2,250/mo or adjoining office without equipment $1,750/m. 203 545 3539, mehrimd@aol.com

Reach your target audience. Our audience.

Ophthalmologists and allied eye care professionals. Contact me to place your ad.

Joanna Shippoli
Account Manager
440-891-2615
joanna.shippoli@ubm.com

Orlando Florida Area
Solo ophthalmology practice for sale.
Established 1980
3 equipped lanes with room for 4th
Modern optical 100% negotiable
Details call Lyle 407-927-7450 or
email: cooceoophthalmology@gmail.com

PRODUCTS & SERVICES

SPACE TO SHARE

Narrow your candidate search to the best.

Place a recruitment ad in Ophthalmology Times — in print or online.

Joanna Shippoli
Account Manager | 440-891-2615
joanna.shippoli@ubm.com

Ophthalmology Times

ADVERTISE NOW!

Combine Ophthalmology Times Marketplace print advertising with our online offerings to open up unlimited potential.
Why physicians should be on lookout for debt scams

Be wary of pre-payment penalties and advice that sounds too good to be true

By Janet Kidd Stewart

The ads from debt relief companies can be alluring, particularly for residents nearing the end of their training and doctors just starting out, when disposable time and money are short.

“Resolve debt in 24 months!” “Free consultation,” and “No hidden fees” are common refrains in pitches that end up in residents’ e-mail inboxes and text messages.

Practicing physicians with business loan debt from opening their offices often fall for these pitches as well, experts say.

Many promotions claim to be able to cut debts to a fraction of their face value, which is false, regulators warn.

Beyond outright scams, busy residents and physicians alike can fall prey to deceptive advertising. Avoiding both is a must and requires borrowers to stay alert.

As a financial aid officer for a large academic medical center, Christine McDonough, MBA, has seen more deceptive ads than outright fraud when private lenders swarm around residents and fellows who are nearing graduation, but these ads can still do serious damage in the long run to borrowers.

“The ads will list all these fabulous rates, but I’m not seeing anybody actually getting them [after going through approvals],” said McDonough, director of student financial services at The Ohio State University College of Medicine in Columbus, OH.

Often, these are simply teaser rates that lure borrowers into refinancing, but by the time a refinancing offer is made, the terms are far less favorable to the physician, she said. Often, borrowers accept the unfavorable terms simply because they have invested time into the process, an unfortunate outcome, she noted.

She tries not to scare physicians completely away from seeking to improve their debt repayment plans, particularly those who may benefit from shorter payback periods and who aren’t going to qualify for income-based repayment plans, which typically go to those working for nonprofit institutions. But she points out they may be targeted by lenders who prey on physicians’ large medical school debt and their potentially high salaries after training. Many of them are banking on physicians reaching a point where they can see higher attending-physician pay on the horizon but are so busy finishing their training that they needlessly pay for loan services they could easily have handled themselves, such as consolidating payments and making automated bank withdrawals.

McDonough and other financial experts say it’s important for debt-laden physicians to keep a few key guidelines in mind to avoid scams or debt-elimination plans that just aren’t the best fit:

1. **Call around.** Physicians should never agree to a repayment plan without seeking out other offers, said Chad Chubb, CFP, a financial adviser and founder of WealthKeel LLC in Philadelphia. He advises clients to compare rates and terms among several providers, including SoFi, Credible, Laurel Road, and CommonBond. Even local banks sometimes have more competitive rates than what physicians may be offered through text solicitations, he said.

2. **Beware pre-payment penalties.** Onerous pre-payment penalties for business loans are another red flag to heed, experts say. Never take a loan with a prepayment penalty for the life of the loan, said David Zetter, CHCC, CHBC, founder of Zetter HealthCare in Mechanicsburg, PA. He has worked with medical practice clients who receive pitches for business loans that are available regardless of the physician’s credit rating, and these are the ones that most frequently come with unfavorable terms.

   “The loans may be legitimate, but they come with huge prepayment penalties, so the lender is guaranteed the interest no matter when the borrower pays,” he said. More reputable firms, he said, allow borrowers to pay off up to 20% of the loan each year, so it could be retired completely in five years if the borrower so desires.

3. **Read the fine print.** Watch out for terms buried deep in lending agreements, said Julie Fresne, senior

TAKE-HOME

» Physicians are prime targets for scams, with large medical school debt and potential for high salaries.

» Know how to spot false claims so you can evaluate genuine offers to reduce debt.
Physician workloads dropping as mental health concerns rise

By Lisa Grabl

I SPEND a good deal of time thinking about workloads. My leadership team and I are always looking to find the right balance between improving productivity and efficiency while creating an engaging, caring culture for our people.

I also think about the workloads of the physicians we work with, many of whom turn to locum tenens when their lives feel out of balance. For the last few years, I’ve seen the weight upon physicians’ shoulders continue grow heavier and heavier.

I recently read through the 2018 physician workload survey report from locumstory.com. As with any report, there was both good news and bad. I was glad to see the demands on physicians—while still high—appear to be lessening, but I was concerned by data showing that physicians’ mental health concerns are largely ignored. Here are a few points from the survey that jumped out.

Of the physicians surveyed, 51% reported their workload affected their mental health, but only 17% sought help. An alarming statistic: two-thirds said they would not even consider meeting with a mental health professional. Even worse, more than half of survey respondents said mental health is a taboo topic among healthcare providers. Why is there such an aversion to getting help?

It is distressing that in this day and age, mental healthcare is still taboo, especially among physicians who understand the associated risks. The survey also found 6% of physicians had contemplated suicide and 11% take medication for anxiety or depression resulting from their work. Another interesting finding was that 74% of physicians reported frequently seeing burnout in their colleagues, while only 52% reported feeling burnout themselves. It’s not a stretch to surmise that many of the physicians who don’t think they are burned out likely appear that way to others.

This isn’t surprising. The vast majority of the physicians I speak with went into medicine because of a personal desire to help others. That passion for service is also what makes the profession so demanding, as there are always more people to help.

Often, the last person cared for is the caregiver. It’s easy to see how burnout, and even mental health issues, could be seen as “just part of the job.”

On a brighter note, it appears that the working lives of physicians are improving. Locumstory.com issued a similar survey in 2016 that found 64% of physicians had less free time outside of work than when they first started their careers. In this year’s survey, the number dropped to 55%. The same goes for feeling overworked compared to when they started their careers. In 2016, 65% felt overworked compared to 56% today.

For many, many years, there has been an expectation that physicians work a lot of hours. From 80-plus hour weeks in residency to 60-80 or more hours in practice.

Then add in EHRs, increased government regulations, and dropping Medicaid reimbursements. It’s no wonder that physicians are overworked.

The survey also found 6% of physicians had contemplated suicide and 11% take medication for anxiety or depression resulting from their work. Another interesting finding was that 74% of physicians reported frequently seeing burnout in their colleagues, while only 52% reported feeling burnout themselves. It’s not a stretch to surmise that many of the physicians who don’t think they are burned out likely appear that way to others.

This isn’t surprising. The vast majority of the physicians I speak with went into medicine because of a personal desire to help others. That passion for service is also what makes the profession so demanding, as there are always more people to help.

Often, the last person cared for is the caregiver. It’s easy to see how burnout, and even mental health issues, could be seen as “just part of the job.”

On a brighter note, it appears that the working lives of physicians are improving. Locumstory.com issued a similar survey in 2016 that found 64% of physicians had less free time outside of work than when they first started their careers. In this year’s survey, the number dropped to 55%. The same goes for feeling overworked compared to when they started their careers. In 2016, 65% felt overworked compared to 56% today.

For many, many years, there has been an expectation that physicians work a lot of hours. From 80-plus hour weeks in residency to 60-80 or more hours in practice.

Then add in EHRs, increased government regulations, and dropping Medicaid reimbursements. It’s no wonder that physicians are overworked.

From 80-plus hour weeks in residency to 60-80 or more hours in practice.

Then add in EHRs, increased government regulations, and dropping Medicaid reimbursements. It’s no wonder that physicians are overworked.

From 80-plus hour weeks in residency to 60-80 or more hours in practice.

Then add in EHRs, increased government regulations, and dropping Medicaid reimbursements. It’s no wonder that physicians are overworked.

From 80-plus hour weeks in residency to 60-80 or more hours in practice.

Then add in EHRs, increased government regulations, and dropping Medicaid reimbursements. It’s no wonder that physicians are overworked.
Sometimes, your practice just needs a social media boost

“That’s not part of the test, but just so you remember to like our clinic on Facebook.”

Artwork by Jon Carter

in case you missed it

Corneal inlay offers improvement

OPHTHALMOLOGYTIMES.COM/INLAY

Eye drop provides balance between cost, compliance

OPHTHALMOLOGYTIMES.COM/COMPLIANCEDROP

Consider pneumatic vitreolysis for VMT PAGE 12

Telehealth service cuts unneeded referrals PAGE 18

Molecular signature could indicate CXL outcomes PAGE 36

Khmer Sight Foundation goes to Cambodia PAGE 39

Advertiser Index

<table>
<thead>
<tr>
<th>Advertiser</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>DIOPSYS</td>
<td>17</td>
</tr>
<tr>
<td><a href="http://www.diopsys.com">www.diopsys.com</a></td>
<td></td>
</tr>
<tr>
<td>973/244-0622</td>
<td></td>
</tr>
<tr>
<td>GLAUKOS</td>
<td>CV2</td>
</tr>
<tr>
<td><a href="http://www.glaukos.com">www.glaukos.com</a></td>
<td></td>
</tr>
<tr>
<td>800/452-8567</td>
<td></td>
</tr>
<tr>
<td>MODERNIZING MEDICINE INC.</td>
<td>CVTP</td>
</tr>
<tr>
<td><a href="http://www.modmed.com">www.modmed.com</a></td>
<td></td>
</tr>
<tr>
<td>561/235-7502</td>
<td></td>
</tr>
<tr>
<td>NIDEK INC.</td>
<td>13</td>
</tr>
<tr>
<td>usa.nidek.com</td>
<td></td>
</tr>
<tr>
<td>510/226-5700</td>
<td></td>
</tr>
<tr>
<td>NOVARTIS OPHTHALMICS</td>
<td>CV3</td>
</tr>
<tr>
<td><a href="http://www.pharma.us.novartis.com">www.pharma.us.novartis.com</a></td>
<td>CV4</td>
</tr>
<tr>
<td>888/669-6682</td>
<td></td>
</tr>
<tr>
<td>OCULUS INC.</td>
<td>11</td>
</tr>
<tr>
<td><a href="http://www.oculususa.com">www.oculususa.com</a></td>
<td></td>
</tr>
<tr>
<td>888/519-5375</td>
<td></td>
</tr>
<tr>
<td>SHIRE OPHTHALMIC</td>
<td>4-6</td>
</tr>
<tr>
<td><a href="http://www.shire-eyes.com">www.shire-eyes.com</a></td>
<td></td>
</tr>
<tr>
<td>800/828-2088</td>
<td></td>
</tr>
<tr>
<td>TTI MEDICAL</td>
<td>15</td>
</tr>
<tr>
<td><a href="http://www.ttimedical.com">www.ttimedical.com</a></td>
<td></td>
</tr>
<tr>
<td>800/322-7737</td>
<td></td>
</tr>
</tbody>
</table>

This index is provided as an additional service. The publisher does not assume any liability for errors or omissions.
DUREZOL® (difluprednate ophthalmic emulsion) 0.05%

Initial U.S. Approval: 2008

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.

4 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.

5 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 oculocutaneous steroids may prolong the course and may exacerbate the severity of many viral infections of the eye (including herpes simplex). If treatment of herpes simplex keratitis or stromal keratitis is required, the use of a powerful antiviral agent that is active against herpes simplex virus should be considered.

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 include cataract formation, 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 include decreased visual acuity, punctate keratitis, eye inflammation, and iritis. Ocular adverse reactions occurring in less than 1% of subjects include application site discomfort or irritation, corneal pigmentation and striae, episcleritis, eye pruritis, eyelid irritation and crusting, foreign body sensation, increased lacrimation, macular edema, sclera hyperemia, and uveitis. Most of these reactions may have been the consequence of the surgical procedure.

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, limbal and 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 teratogenic. 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%. No overall differences in safety or effectiveness have been observed between elderly and younger patients.

U.S. Pat.: www.alconpatents.com
©2013, 2016 Novartis
Distributed by:
Alcon Laboratories
Fort Worth, Texas 76134 USA
T2017-52
April 2017
In clinical studies of ocular surgery patients, DUREZOL® Emulsion demonstrated significant efficacy and safety.

**INDICATIONS AND USAGE**

DUREZOL® (difluprednate ophthalmic emulsion) 0.05% is a potent and effective ocular steroid that has been prescribed for millions of patients.1,2

**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 beginning 24 hours after surgery and continuing throughout the first 2 weeks of the postoperative period, followed by 2 times daily for a week and then a taper based on the response.

**Contraindications**

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

**Warnings and Precautions**

- 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. If this product is used for 10 days or longer, IOP should be monitored.

**Efficacy**

- **Zero Inflammation** in nearly 3x more patients at days 8 and 15
  - 22% versus 8% on day 8
  - 41% versus 12% on day 15

- **Zero Pain** in nearly 2x more patients at days 3, 8, and 15
  - 45% versus 25% on day 3
  - 58% versus 27% on day 8
  - 63% versus 35% on day 15

**How could DUREZOL® Emulsion help more of your patients?**

**Average Co-Pay**

- Eligible Commercial patients may pay as little as $30* with Commercial and Medicare Part D plans3

*Eligibility terms and conditions apply. Please see co-pay savings materials for details.

**References:**


**Alcon Pharmaceuticals**
Targeting Anterior Uveitis: A Focus on Iontophoresis and Other Advanced Technologies

Visit https://tinyurl.com/iontophoresisCME for online testing and instant CME certificate.

CME Monograph

ORIGINAL RELEASE: SEPTEMBER 1, 2018

EXPIRATION: SEPTEMBER 30, 2019

PROGRAM CHAIR

JOHN SHEPPARD, MD, MMSc, FACS
Professor of Ophthalmology
Eastern Virginia Medical School
President
Virginia Eye Consultants
Medical Director
Lions Eye Bank of Eastern Virginia
Norfolk, Virginia

FACULTY

JORDANA G. FEIN, MD, MS
Retina Specialist
Retina Group of Washington
Fairfax, Virginia

MICHAEL S. KORENFELD, MD, ACOS
President
Comprehensive Eye Care, Ltd
Washington, Missouri

STEVEN M. SILVERSTEIN, MD, FACS
Clinical Professor of Ophthalmology
Kansas City University of Medicine and Biosciences
Cataract and Refractive Surgeon
Silverstein Eye Centers
Kansas City, Missouri

CME REVIEWER FOR NEW YORK EYE AND EAR INFIRMARY OF MOUNT SINAI

RONALD C. GENTILE, MD, FACS, FASRS
Professor of Ophthalmology
Icahn School of Medicine at Mount Sinai
Chief, Ocular Trauma Service (Posterior Segment)
New York Eye and Ear Infirmary of Mount Sinai
New York, New York

MedEdicus

This continuing medical education activity is supported through an unrestricted educational grant from Bausch & Lomb Incorporated.

Distributed with Ophthalmology Times
LEARNING METHOD AND MEDIUM
This educational activity consists of a supplement and ten (10) study questions. The participant should, in order, read the learning objectives contained at the beginning of this supplement, read the supplement, answer all questions in the post test, and complete the Activity Evaluation/Credit Request form. To receive credit for this activity, please follow the instructions provided on the post test and Activity Evaluation/Credit Request form. This educational activity should take a maximum of 1.0 hour to complete.

ACTIVITY DESCRIPTION
Anterior uveitis is the most common form of uveitis. It can be associated with significant morbidity, including permanent loss of vision, as a result of complications that can develop without appropriate treatment. Topical corticosteroid treatment to control inflammation is the mainstay for management of anterior uveitis, but there are limitations associated with its use. This educational activity reviews the challenges accompanying topical corticosteroid therapy and presents information on emerging therapeutics, with a focus on corticosteroid delivery by iontophoresis as a novel approach.

TARGET AUDIENCE
This educational activity is intended for ophthalmologists, including ophthalmology fellows.

LEARNING OBJECTIVES
Upon completion of this activity, participants will be better able to:
• Describe the mechanism of action of iontophoresis and other advanced drug-delivery technologies
• Review the safety and efficacy data on dexamethasone treatment via iontophoresis for the treatment of anterior uveitis
• Use dexamethasone treatment via iontophoresis in appropriate patient scenarios

ACCREDITATION STATEMENT
This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of New York Eye and Ear Infirmary of Mount Sinai and MedEdicus LLC. The New York Eye and Ear Infirmary of Mount Sinai is accredited by the ACCME to provide continuing medical education for physicians.

In July 2013, the Accreditation Council for Continuing Medical Education (ACCME) awarded New York Eye and Ear Infirmary of Mount Sinai “Accreditation with Commendation,” for six years as a provider of continuing medical education for physicians, the highest accreditation status awarded by the ACCME.

AMA CREDIT DESIGNATION STATEMENT
The New York Eye and Ear Infirmary of Mount Sinai designates this enduring material for a maximum of 1.0 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

GRANTOR STATEMENT
This continuing medical education activity is supported through an unrestricted educational grant from Bausch & Lomb Incorporated.

DISCLOSURE POLICY STATEMENT
It is the policy of New York Eye and Ear Infirmary of Mount Sinai that the faculty and anyone in a position to control activity content disclose any real or apparent conflicts of interest relating to the topics of this educational activity, and also disclose discussions of unlabeled/unapproved uses of drugs or devices during their presentation(s). New York Eye and Ear Infirmary of Mount Sinai has established policies in place that will identify and resolve all conflicts of interest prior to this educational activity. Full disclosure of faculty/planners and their commercial relationships, if any, follows.

DISCLOSURES
Jordana G. Fein, MD, MS, has no relevant commercial relationships to disclose.

Michael S. Korenfeld, MD, had a financial agreement or affiliation during the past year with the following commercial interests in the form of Consultant/Advisory Board: EyeGate; Novartis AG; and Orasis Pharmaceuticals; Ownership Interest (Stock options, or other holdings, excluding diversified mutual funds): EyeGate; and Orasis Pharmaceuticals.

John Sheppard, MD, MMSc, FACS, had a financial agreement or affiliation during the past year with the following commercial interests in the form of Consultant/Advisory Board: Alcon; and Bausch & Lomb Incorporated; Contracted Research: Alcon; and Bausch & Lomb Incorporated; Honoraria from promotional, advertising or non-CME services received directly from commercial interests or their Agents (eg, Speakers Bureaus): Alcon; and Bausch & Lomb Incorporated.

Steven M. Silverstein, MD, had a financial agreement or affiliation during the past year with the following commercial interests in the form of Consultant/Advisory Board: Alcon; Allergan; Astellas Pharma Europe Ltd; Bausch & Lomb Incorporated; Diopsys, Inc; Glaukos Corporation; Omeros Corporation; Shire; and Sun Pharmaceutical Industries Ltd; Honoraria from promotional, advertising or non-CME services received directly from commercial interests or their Agents (eg, Speakers Bureaus): Alcon; Allergan; Astellas Pharma Europe Ltd; Bausch & Lomb Incorporated; Diopsys, Inc; Glaukos Corporation; Omeros Corporation; Shire; and Sun Pharmaceutical Industries Ltd.

NEW YORK EYE AND EAR INFIRMIARY OF MOUNT SINAI PEER REVIEW DISCLOSURE
Ronald C. Gentile, MD, FACS, FASRS, has no relevant commercial relationships to disclose.

EDITORIAL SUPPORT DISCLOSURES
Cheryl Gurtman Krader; Diane Mc Ardle, PhD; Cynthia Tornaylay, RD, MBA, CHCP; Kimberly Corbin, CHCP; Barbara Aubel; and Michelle Ong have no relevant commercial relationships to disclose.

DISCLOSURE ATTESTATION
The contributing physicians listed above have attested to the following:
1) that the relationships/affiliations noted will not bias or otherwise influence their involvement in this activity;
2) that practice recommendations given relevant to the companies with whom they have relationships/affiliations will be supported by the best available evidence or, absent evidence, will be consistent with generally accepted medical practice; and
3) that all reasonable clinical alternatives will be discussed when making practice recommendations.

OFF-LABEL DISCUSSION
This CME activity includes discussion of unlabeled and/or investigative uses of drugs. Please refer to the official prescribing information for each drug discussed in this activity for FDA-approved dosing, indications, and warnings.

New York Eye and Ear Infirmary of Mount Sinai Privacy & Confidentiality Policies
http://www.nyee.edu/health-professionals/cme/enduring-activities

CME Provider Contact Information
For questions about this activity, call 212-870-8127.

TO OBTAIN AMA PRA CATEGORY 1 CREDIT™
To obtain AMA PRA Category 1 Credit™ for this activity, read the material in its entirety and consult referenced sources as necessary. Please take this post test and evaluation online by going to https://tinyurl.com/iontophoresisCME. Upon passing, you will receive your certificate immediately. You must score 70% or higher to receive credit for this activity, and may take the test up to 2 times. Upon registering and successfully completing the post test, your certificate will be made available online and you can print it or file it.

DISCLAIMER
The views and opinions expressed in this educational activity are those of the faculty and do not necessarily represent the views of New York Eye and Ear Infirmary of Mount Sinai, MedEdicus LLC, Bausch & Lomb Incorporated, or Ophthalmology Times.

Cover image reprinted from Journal of Controlled Release, 110, Eljarrat-Binstock E, Domb AJ. Iontophoresis: a non-invasive ocular drug delivery, 479-489, Copyright 2006, with permission from Elsevier.

This CME activity is copyrighted to MedEdicus LLC ©2018. All rights reserved. 158
Targeting Anterior Uveitis:
A Focus on Iontophoresis and Other Advanced Technologies

Anterior uveitis has an estimated annual incidence of 26.6 to 102.7 of every 100,000 adults in the United States and accounts for up to 90% of uveitis cases seen in community practices in Western countries. AFFECTED patients can experience pain, photophobia, and decreased vision. Furthermore, they are at risk for permanent loss of vision from complications that can develop without appropriate treatment.

Topical corticosteroid treatment to control inflammation is the mainstay for management of anterior uveitis, but there are limitations associated with its use. This activity reviews the challenges accompanying topical corticosteroid therapy and presents information on emerging therapeutic approaches, with a focus on corticosteroid delivery by iontophoresis as a novel approach.

ANTERIOR UVEITIS: CURRENT MANAGEMENT

Dr Sheppard: Anterior uveitis, which involves inflammation of the iris and is often accompanied by ciliary body inflammation (iridocyclitis), accounts for up to 90% of uveitis cases in Western countries and has an estimated prevalence of 1 in 4500 people. There are numerous identifiable etiologies for anterior uveitis, but they can be broadly divided into infectious and noninfectious causes. A detailed history, physical examination, review of systems, and careful ocular examination are essential for identifying underlying causes, which will direct a targeted treatment plan.

Elimination of all inflammation is the treatment goal for every case. Treatment for infectious uveitis requires pathogen-directed antimicrobial agents, with or without corticosteroids. Topical corticosteroid treatment is the standard for anti-inflammatory treatment of noninfectious anterior uveitis as well.

There are a number of topical corticosteroid products from which to choose. Difluprednate emulsion, 0.05%, is my preferred agent. In 2 phase 3 studies, difluprednate administered 4 times daily was found to be noninferior to prednisolone acetate suspension, 1%, used 8 times daily for clearing anterior chamber cells (ACCs). The rate of study discontinuation due to lack of efficacy was also lower in the difluprednate group.

What is your current approach for treating anterior uveitis?

Dr Silverstein: I also use difluprednate, along with a cycloplegic agent, and both oral and topical treatment with a nonsteroidal anti-inflammatory drug. I typically use 1% atropine as the cycloplegic agent for all uveitis cases. Depending on the uveitis etiology and severity of the inflammation, I might also prescribe high-dose oral prednisone and start systemic immunomodulatory treatment.

Dr Fein: Although difluprednate is also my corticosteroid of choice, I sometimes start with topical prednisolone because of cost and insurance issues, and I use a cyclopentolate in patients who have significant pain and/or photophobia. After ruling out infectious etiologies, I would also add high-dose oral prednisone if there is posterior segment inflammation.

Dr Korenfeld: I believe nonsteroidal anti-inflammatory drug treatment is helpful if cystoid macular edema is present. I also like to give a sub-Tenon corticosteroid injection to provide a depot effect, especially if I think systemic corticosteroid therapy might be needed, but the patient has medical comorbidities that might be affected by the side effects of systemic corticosteroids.

Dr Sheppard: Because bioavailability is limited with topical administration, corticosteroid treatment for anterior uveitis can require frequent dosing, and a prolonged course of treatment can also be necessary. Patient nonadherence, difficulties with drop administration, tearing, blepharospasm, and irritation can reduce medication absorption, thereby compromising treatment efficacy. In addition, intensive and ongoing therapy puts patients at risk for corticosteroid-related side effects, including intraocular pressure (IOP) elevation and cataract development, along with preservative-related corneal toxicity.

Several treatments are being developed for anterior uveitis, with the aim of minimizing side effects or improving drug delivery compared with those of conventional corticosteroid therapy (see Sidebar: Innovative Treatments for Anterior Uveitis). In this discussion, we are focusing on transcleral iontophoresis. This approach to ocular corticosteroid delivery is provided as an in-office procedure and is less invasive than an injection. It might overcome the toxicity, compliance, and administration issues associated with topical administration. Compared with topical administration, iontophoretic corticosteroid treatment improves intraocular drug delivery and appears to have a low risk of causing IOP elevation.

OCULAR IONTOPHORESIS

Intraocular penetration of a topically administered medication through the intact barriers of the cornea and sclera depends on passive diffusion, which is a slow process driven by a concentration gradient (Figure 1). Intraocular accumulation of most systemically administered medications also relies on passive diffusion of the compound through blood vessel walls, although some substances, such as ascorbic acid, enter the eye from the systemic circulation through an active transport mechanism in the ciliary processes.

Figure 1. Routes of absorption and elimination of topically administered agents

Reprinted from Advanced Drug Delivery Reviews, 122, Janagam DR, Wu L, Lowe TL, Nanoparticles for drug delivery to the anterior segment of the eye, 31-64, Copyright 2017, with permission from Elsevier.
Innovative Treatments for Anterior Uveitis

Reproxalap (formerly ADX-102 and NS2) is being developed as a topical treatment for uveitis, allergic conjunctivitis, and dry eye disease. It is an aldehyde “trap” that rapidly binds free aldehydes, which are potent intracellular proinflammatory compounds.1,2 The drug-aldehyde dimer is transported intracellularly, where it is quickly metabolized. In a phase 2 clinical trial, reproxalap showed promising activity as a treatment for noninfectious anterior uveitis, and it was not associated with intraocular pressure (IOP) elevation.1,3 Phase 3 studies investigating reproxalap for the treatment of uveitis and allergic conjunctivitis are ongoing,1,3 and a phase 2 study is investigating reproxalap in patients with dry eye disease.1

CLS-TA is a triamcinolone acetonide formulation delivered into the suprachoroidal space using a proprietary microinjector system. It is being developed as a treatment for macular edema associated with noninfectious uveitis, including anterior uveitis, as well as for retinal vein occlusion and diabetic macular edema. Topline results from a phase 3 study of CLS-TA for noninfectious uveitis showed the percentage of patients with a ≥15 ETDRS (Early Treatment Diabetic Retinopathy Study) letter gain from baseline to week 24 was significantly higher in the CLS-TA arm than in the control arm receiving a sham injection (46.9% vs 15.6%; P < .001).3 Elevated IOP occurred in 11.5% of patients receiving CLS-TA. There were no serious treatment-related adverse events.

In addition to transscleral iontophoresis, noninvasive transscleral delivery of dexamethasone is being developed as a treatment for anterior uveitis, using a system for diffusion-based passive delivery of the active compound. The technology involves a scleral lens-type applicator (Visulex-P) to deliver dexamethasone sodium phosphate (DSP). This system was evaluated in a phase 1/2 study that randomized 44 patients with noninfectious anterior uveitis to receive (1) prednisolone acetate, 1%, up to 6 drops daily; (2) DSP, 8%, weekly; or (3) DSP, 15%, weekly.1 Rates of resolution of anterior chamber cells were similar in the 3 treatment arms at follow-up visits on study days 8, 15, and 29. The investigational treatments were well tolerated and associated with slight IOP elevation only at the first follow-up visit on day 8.

REFERENCES


Iontophoresis, which means “ions that are being carried,” uses an electric current to promote drug penetration to its target. It is based on the electrical principle that ions with like charges repel each other. Iontophoresis has a long history of use in dentistry, dermatology, and rheumatology for improving drug delivery.4 It was not developed commercially until the 1980s, when it was introduced to treat hyperhidrosis.5 At approximately the same time, iontophoresis began to be used for the delivery of anti-inflammatory drugs into joint spaces to avoid trauma caused by intra-articular injections.6 Iontophoresis was first evaluated for ocular drug delivery more than a century ago7 and has been or is currently being studied for delivery of a variety of medications to treat several ocular diseases, including dry eye disease,8 keratoconus,8 anterior uveitis,9 and age-related macular degeneration.9

With iontophoretic delivery, application of an electric current to an aqueous drug solution using a cathodic or anodic electrode hydrolyzes the water molecules into hydroxide or hydronium ions, respectively. An opposite-charged electrode is placed at a distal site to complete the electrical circuit, and the ions generated by hydrolysis drive the like-charged drug molecule into tissues (Figure 2).9

![Figure 2. Ocular iontophoresis of a positively charged drug uses an anodic electrode to generate positively charged hydronium ions.](image)

Iontophoretic drug delivery is affected by properties of the barrier tissue (ie, mucous membrane or not, lipophilicity/hydrophilicity, charges, and thickness); the ion being delivered (ie, charge density in the pH of the delivery setting, concentration, molecular size, and molar potency); and the applied electric current (level and duration).10-12 Proof-of-concept studies show that with modulation of these parameters, a wide array of therapeutics, including small molecules, biologics, and nanoparticles, can be preferentially delivered into the anterior or posterior tissues of the eye to reach therapeutically meaningful concentrations.10,10 Preclinical studies conducted in rabbits showed that with iontophoresis, concentrations of corticosteroids (methylprednisolone and dexamethasone) in anterior and posterior segment tissues and fluids exceeded those achieved after intravenous or topical administration.10-11 The results of these studies also showed a dose-response relationship between the intraocular levels of the corticosteroids and the applied current, duration of iontophoresis, and drug concentration. Ocular iontophoresis resulted in


negligible systemic corticosteroid levels and was not associated with any clinical or histological evidence of toxicity.

A variety of active pharmaceutical ingredients are being developed for ocular iontophoresis, but only a 40-mg/mL dexamethasone phosphate solution formulated for iontophoresis (EGP-437) has advanced to a confirmatory phase 3 clinical trial.19

Iontophoretic delivery of EGP-437 is performed with a proprietary system that comprises an annular ocular applicator, an external battery, and an anodic electrode that is placed on the forehead (Figure 3).19 The ocular applicator features a foam annulus that serves as a reservoir for the dexamethasone phosphate solution. This annulus makes contact with the perilimbal conjunctiva. The applicator houses the cathodic electrode that transfers current from the battery to the drug reservoir, resulting in the creation of hydroxyl ions.

A phase 1/2 study of EGP-437 treatment for noninfectious anterior uveitis evaluated 4 electric current dose levels: 1.6, 4.8, 10.0, and 14.0 mA-min.20 It enrolled 40 patients with an ACC score ≥ 1.5 who received a single iontophoretic treatment (4-minute application) and were followed to day 28.

An ACC score of 0, analyzed as the primary efficacy end point, was achieved by 47.5% and 60.0% of patients on days 14 and 28, respectively.20 At both visits, the highest response rates were achieved in the 2 lower-dose groups (Table 1), presumably because the higher current levels drove the dexamethasone deeper into the eye, rendering it less effective for treating inflammation in the anterior segment.

<table>
<thead>
<tr>
<th>Dose Group*, mA-min</th>
<th>Percentage of Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 14</td>
</tr>
<tr>
<td>1.6</td>
<td>80</td>
</tr>
<tr>
<td>4.8</td>
<td>60</td>
</tr>
<tr>
<td>10.0</td>
<td>20</td>
</tr>
<tr>
<td>14.0</td>
<td>30</td>
</tr>
<tr>
<td>Total</td>
<td>47.5</td>
</tr>
</tbody>
</table>

* n = 10 in each dose group

pressure remained relatively stable and in the normal range in most patients. The most commonly reported adverse events were conjunctival hyperemia (16%), punctate keratitis (11%), conjunctival edema (10%), eyelid edema (6%), and eye pain (6%). There were no serious adverse events or nonocular systemic corticosteroid-mediated effects.

Two phase 3 studies investigating EGP-437 for the treatment of noninfectious anterior uveitis have been recently completed, and results have yet to be published. The initial phase 3 study included 193 patients with an ACC score ≥ 1 who were randomized to receive EGP-437 delivered for 3 minutes on days 0 and 7 or a 14-day tapering regimen of prednisolone acetate, 1% (8 times daily for 1 week, then 6 times daily for 1 week).24 The primary efficacy end point was the percentage of patients with an ACC count of 0 at day 14.

Enrollment in a confirmatory phase 3 study was completed in April 2018.24 In this study, patients were randomized to receive EGP-437 or a tapering regimen of topical prednisolone acetate, 1%. The primary outcome measure was the proportion of patients with an ACC count of 0 at day 14.

**IONTOPHORESIS IN THE CLINICAL SETTING: PRACTICAL AND SAFETY CONSIDERATIONS**

**Dr Sheppard:** EGP-437 iontophoresis is a procedure that is very easy to learn and perform. It can be done by a technician, an optometrist, or a physician assistant instead of by an ophthalmologist. The setup is simple and straightforward. There is no need for a speculum. The applicator is placed by the doctor or technician after anesthetizing the eye with topical anesthetic. I find it is helpful to have the patient look at me directly when I am placing the applicator. Because it can be difficult for patients to keep both eyes open, I put a drop of anesthetic in the fellow eye as well. The applicator is held in place throughout the procedure while another assistant manages the control unit. The treatment takes just 3 minutes, and it is very well tolerated. Removing the sticky electrode from the forehead might be the worst part of the procedure for patients.

What is known about the half-life of dexamethasone phosphate in the eye after iontophoretic delivery?

**Dr Korenfeld:** With iontophoresis, the drug is delivered not only into the relatively dynamic aqueous humor, but also into tissues, where it reaches higher levels than those after topical administration and is eliminated more slowly than from the aqueous humor.19

**Dr Sheppard:** Does the application of electric current with iontophoresis create any particular safety concerns?

**Dr Korenfeld:** Ocular iontophoresis is performed using a weak current that is applied for a short time at just a few sessions. It does not seem to pose any safety issues. Some patients report a mild tingling sensation that is localized around the forehead electrode, but it is not a feeling of discomfort. Patients with implanted electronics, such as pacemakers or defibrillators, were excluded from participating in the clinical trials, which seems prudent, because the electrical discharge from the iontophoresis device could potentially interfere with the proper functioning of these types of devices.

**Dr Sheppard:** Some patients treated with EGP-437 developed punctate keratopathy. This event was mild and resolved by the first posttreatment day. Was the event associated with exposure to the electric current?
Dr Korenfeld: I think that the punctate keratopathy developed as a result of the ocular surface being exposed while the eye is kept open for 3 minutes during the treatment. Instilling a drop of an artificial tear to keep the cornea hydrated during the treatment might prevent punctate keratopathy.

Dr Sheppard: Topical dexamethasone and prednisolone are known to cause clinically significant IOP elevation. Intraocular pressure has been minimally affected in patients treated with EGP-437 delivered via iontophoresis. The reason for the relative safety of iontophoretic dexamethasone administration is not fully understood, but considering the available data, would you use this delivery system in a patient who is a known steroid responder?

Dr Fein: I think the experience is very encouraging. I would consider using iontophoresis to deliver dexamethasone in a patient who is a known steroid responder or even in a patient with mild glaucoma, assuming I can rely on the person to return for IOP monitoring.

Dr Korenfeld: Because I think that iontophoresis delivers a more potent treatment than anything else we have available to target inflammation in anterior uveitis, I would prefer to use it on any patient, even if it meant prescribing another medication for the short term to control steroid-induced IOP elevation.

CASE 1: ACUTE ENDOGENOUS NONINFECTIOUS ANTERIOR UVEITIS
From the Files of John Sheppard, MD, MMSc, FACS

Case History
A 25-year-old white man presents with a 2- to 3-week history of cloudy vision in his left eye. He reports seeing “black hairs floating by” and occasional erythema. He denies any pain or tearing. He has borderline hypertension. Topical medication includes an over-the-counter vasoconstrictor, as needed. He has no allergies, history of surgery or trauma, or remarkable social history. Findings on examination are as follows:

- Visual acuity: 20/80 (pinhole: 20/25) OD; count fingers at 2 feet (pinhole: no improvement) OS
- Pupils 5 x 3 reactive and no afferent pupillary defect OD; 5 x 4.5, minimal reaction, and presence of relative afferent pupillary defect OS
- Extraocular movement: Full, with no pain
- Visual field: Full OD; peripherally constricted OS
- Intraocular pressure: 16 mm Hg OD; 14 mm Hg OS
- Anterior segment: Normal OD; trace conjunctival injection, inferior keratic precipitates, and 2 to 3+ cells without hypopyon OS
- Posterior segment: Clear media, normal fundus examination results, and optic nerve margins and vessels OD; retinal whitening in the periphery but hazy media is obscuring visualization OS

The acute onset and unilateral presentation of the uveitis in this patient suggested an infectious process. The differential diagnosis would include toxoplasmosis, syphilis, tuberculosis, Lyme disease, viral infections, and sarcoid. Laboratory testing confirmed a syphilitic etiology.

The patient was admitted to the hospital to begin intravenous treatment with aqueous crystalline penicillin G and discharged with a peripherally inserted central catheter to complete the intravenous treatment. Concurrently, he was diagnosed as being positive for human immunodeficiency virus. At 1 week after starting penicillin, the vitreitis in his left eye was improved, the retinitis had resolved, and visual acuity had improved to 20/250 (pinhole: 20/80 +1). The patient was then started on oral prednisone and continued on intravenous antibiotics.

Discussion

Dr Sheppard: Syphilitic uveitis is treated with penicillin, according to guidelines for the treatment of neurosyphilis. Once the antibiotic is started, corticosteroid therapy is an important adjunct to control the inflammation and prevent damage to anterior and posterior segment tissues.

What are your thoughts about using iontophoresis to deliver the corticosteroid in this setting?

Dr Korenfeld: I think it would be a good option. With proper selection of the treatment parameters, iontophoresis can deliver high effectiveness...
levels of dexamethasone into posterior segment tissues and fluids. For a patient such as this who is immunocompromised, I would much rather use iontophoresis to administer a corticosteroid than violate the globe by giving an intraocular injection.

Dr Fein: I also feel that the iontophoresic treatment has a safety advantage for this patient, and might have been an adjuvant therapy were it available at the time. Data from a pilot phase 1b/2a study investigating EGP-437 for the treatment of macular edema provide clinical evidence supporting its efficacy for controlling inflammation in the posterior segment. The study enrolled 25 patients with macular edema associated with retinal vein occlusion, diabetic retinopathy, or post-surgical cystoid macular edema. Iontophoresis with EGP-437 was performed on days 0, 4, and 9 at 14.0 mA-min (3.5 mA). The primary outcome was reduction in mean central subfield thickness on days 4, 9, 14, and 21. As a control, patients with no improvement at day 14 were given the dexamethasone intravitreal implant and reevaluated at day 21 or 28.

Data were reported from 19 patients, and the interim results indicate that noninvasive treatment with iontophoresis can deliver dexamethasone to the posterior segment. Responses were better in pseudophakic eyes than in phakic eyes. There were no serious treatment-related adverse events. There were also no IOP elevations, perhaps because the higher electric current level delivers the dexamethasone into the posterior segment and avoids the anterior segment.

Dr Korenfeld: One possible explanation for the better response rate in the pseudophakic eyes might be the intraocular lens acted as a platform for prolonged release of the corticosteroid.

Dr Silverstein: The current used in the macular edema study was higher than that used in the anterior uveitis studies. Did the higher current seem to cause problems with comfort?

Dr Sheppard: I have not gotten any feedback on that issue. According to my observations during the dose-ranging phase 2 anterior uveitis study, some patients experienced greater discomfort, and I suspect they were in the higher current group. Nevertheless, the patients found the treatment tolerable.

TAKE-HOME POINTS

Topical corticosteroid treatment is the cornerstone of therapy for anterior uveitis, but it has limitations relating to intraocular penetration, patient compliance, and side effects.

Iontophoretic corticosteroid delivery shows promise as an alternative method for addressing some of the challenges of topical treatment:

- Preclinical studies show that high corticosteroid concentrations are attained in anterior and posterior segment tissues and fluids
- Clinical trials show that EGP-437, a dexamethasone phosphate formulation for ocular iontophoresis, cleared ACCs after just 1 or 2 treatments, was noninferior to intensive treatment with topical prednisolone acetate, and had minimal to no adverse effect on IOP

Other modalities under investigation for the treatment of anterior uveitis include a novel aldehyde trap compound, surprachoroidal trimacinolone acetonide, and a diffusion-based dexamethasone delivery system.

REFERENCES

CME POST TEST QUESTIONS

To obtain AMA PRA Category 1 Credit™ for this activity, complete the CME Post Test and course evaluation online at https://tinyurl.com/iontophoresisCME. Upon successful completion of the post test and evaluation, you will be able to generate an instant certificate of credit.

See detailed instructions under To Obtain AMA PRA Category 1 Credit™ on page 2.

1. Transscleral iontophoresis increases intraocular delivery of a compound by:
   A. Altering epithelial tight junctions
   B. Changing the compound’s charge
   C. Electrorepulsion
   D. Increasing active transport

2. Which of the following is NOT a reason for interest in ocular iontophoresis as an alternative to topical administration for corticosteroid treatment?
   A. Avoids preservative-related ocular surface toxicity
   B. Improves bioavailability
   C. Has a lower cost
   D. Overcomes compliance issues

3. What is the anti-inflammatory mechanism of action of reproxalap?
   A. Binds free aldehydes
   B. Binds to intercellular adhesion molecule-1
   C. Prevents release of proinflammatory cytokines by immune cells
   D. It has the same mechanism of action as corticosteroids but has a unique route of delivery

4. Top-line results from a phase 3 study evaluating CLS-TA (triamcinolone acetonide delivered into the suprachoroidal space) for the treatment of noninfectious uveitis showed the investigational agent:
   A. Caused no IOP elevations
   B. Failed to meet its primary end point
   C. Was associated with a significantly higher percentage of patients gaining ≥ 15 ETDRS letters at week 24 compared with the control group
   D. Was associated with a significantly higher percentage of patients achieving an ACC score of 0 by day 7 compared with the control group

5. The efficacy of iontophoretic drug delivery is affected by properties of the:
   A. Electrical current density
   B. Barrier tissue
   C. Ion being delivered
   D. All the above

6. In a phase 1/2 study evaluating EGP-437 for the treatment of noninfectious anterior uveitis, the treatment response rate was higher in groups treated with:
   A. Higher electric current dose levels
   B. Higher concentration of dexamethasone phosphate
   C. Lower electric current dose levels
   D. Topical difluprednate

7. In a phase 1/2 study of noninfectious uveitis, 47.5% and 60.0% of patients receiving EGP-437 at days 14 and 28, respectively, had which of the following responses?
   A. Increased IOP
   B. Decreased IOP
   C. ACC score of 0
   D. No change in ACC score

8. Which was the most commonly reported adverse event in the phase 1/2 study evaluating EGP-437 for the treatment of noninfectious anterior uveitis?
   A. Conjunctival hyperemia
   B. Eye pain
   C. Eye burning
   D. Eyelid bruising

9. Which uveitic anatomic location might be appropriately treated with iontophoretic delivery of EGP-437?
   A. Choroid
   B. Iris
   C. Optic nerve
   D. Pars plana

10. In a phase 1/2 study, the rate of resolution of ACCs at serial follow-up visits in eyes treated with a system for passive delivery of dexamethasone using a topical scleral lens-type applicator (Visulex-P) was:
    A. Dose related, depending on the concentration of dexamethasone used
    B. Dose related, depending on the electric current used
    C. Higher than that of the control group treated with topical prednisolone acetate
    D. Similar to that of the control group treated with topical prednisolone acetate