



Peter J. McDonnell, MD

SAVING MEMORIES ANTI-VEGF AGENTS AND COGNITIVE LOSS PAGE 5

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SEPTEMBER 15, 2020 VOL. 45, NO. 15

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XELPROS™ (latanoprost ophthalmic emulsion) 0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

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CONTRAINDICATIONS

XELPROS is contraindicated in patients with a known hypersensitivity to latanoprost, or any other ingredients in this product.

Please see Important Safety Information on the back cover and brief summary of Full Prescribing Information inside.

Issue Highlights

work in progress

OPY

eneration of retinal
within reach

the COVID-19
ing sharp

GNOSIS

al detachment
a retinoblastoma

NOLOGY

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Brief Summary of Prescribing Information for XELPROS™ (latanoprost ophthalmic emulsion) 0.005%, for topical ophthalmic use

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See package insert for Full Prescribing Information.

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WARNINGS AND PRECAUTIONS**Pigmentation**

XELPROS may cause changes to pigmented tissues. The most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as XELPROS is administered. After discontinuation of XELPROS, iris pigmentation is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

Eyelash Changes

XELPROS may gradually change eyelashes and vellus hair in the treated eye, including increased length, thickness, pigmentation, and number of lashes. The changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation

XELPROS should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

Macular Edema

XELPROS should be used with caution in aphakic patients, in pseudophakic patients with a torn posterior lens capsule, or in patients with known risk factors for macular edema.

Herpetic Keratitis

XELPROS should be used with caution in patients with a history of herpetic keratitis. XELPROS should be avoided in cases of active herpes simplex keratitis because inflammation may be exacerbated.

Bacterial Keratitis

There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

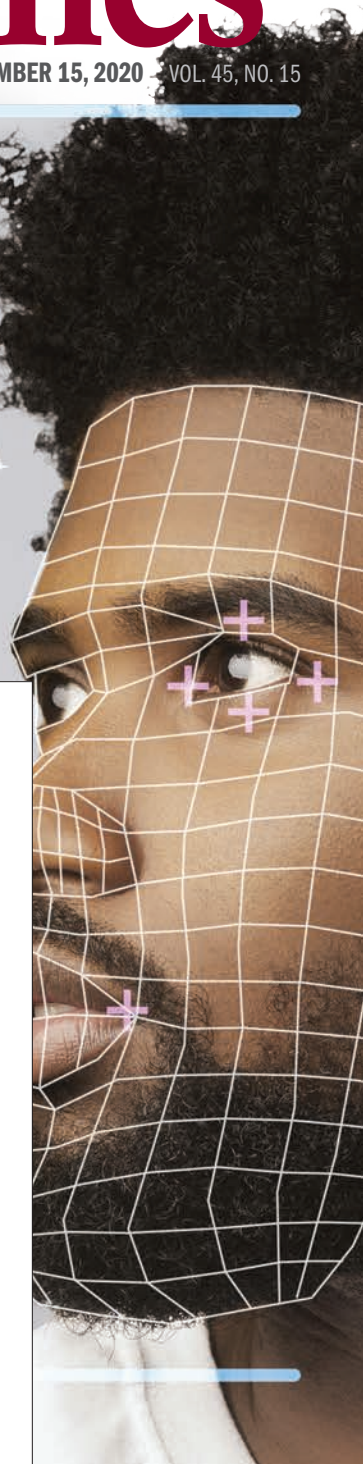
Use with Contact Lenses

Contact lenses should be removed prior to administration of XELPROS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS**Clinical Trials Experience**

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

Across multiple clinical trials conducted with XELPROS, the most frequently reported ocular adverse reactions were eye pain/stinging upon instillation and ocular hyperemia, reported in 55% and 41% of patients treated with XELPROS, respectively. Other adverse reactions reported (incidence $\geq 5\%$) were conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening. Less than 1% of patients discontinued therapy because of intolerance to the eye pain/stinging or to the ocular hyperemia.



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DRUG INTERACTIONS

Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

USE IN SPECIFIC POPULATIONS**Pregnancy**Pregnancy Category C

Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XELPROS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether latanoprost or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XELPROS is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

PATIENT COUNSELING INFORMATION**Potential for Pigmentation**

Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XELPROS.

Potential for Eyelash Changes

Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XELPROS. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated emulsions.

When to Seek Physician Advice

Advise patients that if they develop an intercurrent ocular condition (eg, trauma or infection) or have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of the multiple-dose container.

Use with Contact Lenses

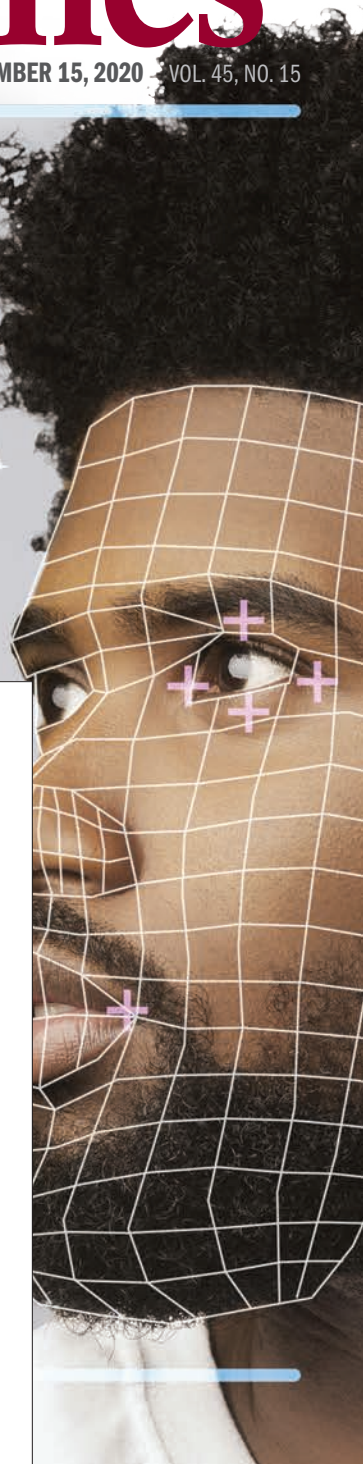
Advise patients that contact lenses should be removed prior to administration of the emulsion. Lenses may be reinserted 15 minutes following administration of XELPROS.

Use with Other Ophthalmic Drugs

Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

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ADVERSE REACTIONS

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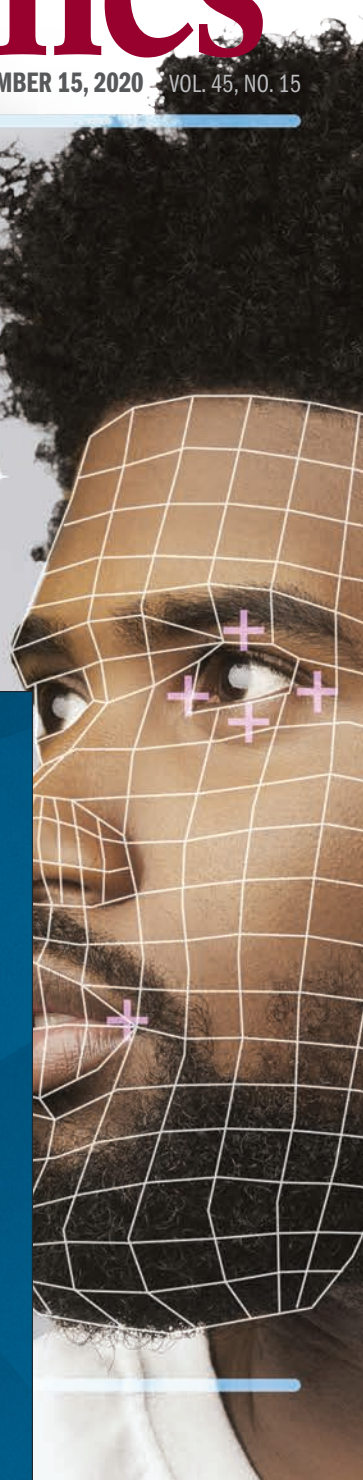
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Please see brief summary of Full Prescribing Information on the reverse side.

BAK=benzalkonium chloride.

References: 1. XELPROS [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; 2018. 2. Data on file. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.



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THERAPEUTICS

Big data drives opportunity for real-world evidence

Evidence-based medicine can lead to personalized care, better results for patients

By Matthew Roe, MD, MHS, and Theodore Leng, MD, MS;
Special to Ophthalmology Times®

THE MOST RIGOROUS data in evidence-based medicine is considered to be that generated by prospective, randomized, controlled trials (RCTs). RCTs are essential for evaluating the therapeutic impact of a drug or device while eliminating potential confounding factors. However, there are many situations in which these gold standard clinical trials are not practical or cost effective.

RCTs evaluate outcomes for very tightly defined groups of patients with highly standardized care and optimal adherence and follow-up. In the real world, however, patients present with a variety of underlying systemic conditions, prior surgery, and adherence patterns that muddy the picture. This is where retrospective, observational studies can help to fill the knowledge gap with real-world evidence (RWE).

RWE can help to answer key clinical questions, such

as how a treatment works in patients who are already on other medications, and whether switching to or adding a new pharmaceutical agent would be more beneficial. Real-world studies can demonstrate how a new glaucoma therapy compares with the prostaglandin analogues (PGAs) that most clinicians rely on for first-line therapy, rather than with timolol, the typical control used in FDA studies. In cardiology, a major ongoing RWE study, the ADAPTABLE trial (NCT02697916), is trying to settle the debate over whether patients with coronary artery disease do better on low- or high-dose aspirin.¹

Increasingly, RWE researchers are looking at big data for answers. Very large data registries permit analysis of records from representative patient populations that are

Continues on page 14 : **Data**

FOCAL POINTS

Pearls for practicing in the COVID-19 era

Ambassadors webinar provides platform for idea-sharing by ophthalmologists

By Cheryl Guttman Krader, BS Pharm

RESULTS OF AN email survey sent to the Glaucoma Research Foundation (GRF) Ambassadors when most states were poised to ease coronavirus disease 2019 (COVID-19) restrictions showed that only three-fourths of the respondents had a plan in place for reopening their offices after stay-at-home orders were lifted.

Judging from write-in responses, whether or not the glaucoma specialists had developed strategies for returning to practice, they were interested in having colleagues share ideas for establishing safety and for optimizing practice efficiency and patient care delivery. They were also keen to receive post COVID-19 patient education and support materials from GRF.

These topics and more were addressed in a vir-

tual GRF Ambassador Round Table on managing a glaucoma practice during COVID-19. Held on May 8, the discussion was moderated by Andrew Prince, MD, of Glaucoma Consultants of Greater New York & New Jersey, and Andrew Iwach, MD, of Glaucoma Center of San Francisco, and included input from several GRF Ambassadors that showed the clinicians were meeting the new challenges with different approaches; in part, these reflect variations in practice settings.

Recognizing that the pandemic situation will be evolving and that ideas about best practices are likely to change based on actual experience and changing circumstances, the group looked forward to reconvening to share their practical insights and take away new ideas.

Continues on page 8 : **Practicing**

Issue Highlights

IMAGING

AI algorithms: A work in progress

GENE THERAPY

Harnessing regeneration of retinal tissues: Almost within reach

SURGERY

Surgery during the COVID-19 pandemic: Staying sharp


CLINICAL DIAGNOSIS

Persistent retinal detachment associated with retinoblastoma

DEVICE TECHNOLOGY

Robotics allow surgeons to perform the seemingly impossible

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Fall: A season for innovation

Mike Hennessy Sr, Chairman and founder of Ophthalmology Times® parent company, MJH Life Sciences™

SEPTEMBER is a wonderful month, offering cooler weather and, hopefully, a return to the classrooms for students. For many, it often paves the way for innovation.

In the cover of this issue of *Ophthalmology Times*®, we take a look at innovation in all areas, including our lead article in therapeutics, examining how big data can drive opportunity in ophthalmology. Matthew Roe, MD, MHS, tells us how it can lead to clinical insights and pave the way for more personalized ophthalmic care.

Our cover also features an interesting look at a Glaucoma Research Foundation study examining ophthalmic practice during the coronavirus disease 2019 (COVID-19) era. An array of topics were addressed in a virtual GRF Ambassador Round Table on managing a glaucoma practice during COVID-19.

Innovation is highlighted by Roberto Gonzalez-Salinas, who details a fascinating study about a novel topical drop TP-03 found to be safe and effective for treating Demodex infestation, a frequent cause of blepharitis. The drop began working in 2 weeks and lasted through the 90-day study period.

Treating dry eye disease can be a challenge, especially for patients in need of short-term management. Marjan Farid, MD, offers some pearls that she follows when treating her DED patients,

including the use of short-term anti-inflammatory therapy for some patients at their initial diagnosis to manage the acute inflammation quickly while starting chronic therapy, which has a longer onset of action, or to bring dry eye under control before cataract or other ocular surgery.

Clinical diagnosis remains an area where innovation can have an immediate impact. We look at persistent retinal detachment associated with retinoblastoma. These can be challenging clinical cases especially when they persist. A study concluded that vitrectomy should not be performed until the patient is free of RB for 2 years to avoid spreading the tumor and metastatic disease. Investigated noted that the waiting period affects the surgical results and even questions its necessity.

In another study detailed in our clinical diagnosis section, patients noted they are not happy with the efficacy of their eye drops. Specifically, they said they believe that their eye drops are effective only some of the time or not at all. This could prove to be an important detail as ophthalmologists plan treatment plans.

In our special section, we look at pioneering research in ocular oncology. We talked to Justine S. Paradis, PhD, who detailed results of a preclinical study indicate there is hope for an effective treatment for the GNAQ-driven metastatic uveal melanoma, an aggressive form of the disease. The

importance of this potential treatment is underscored by the fact that uveal melanoma is the most frequently occurring ocular cancer in adults, and it becomes metastatic in 50% of patients in whom it develops.

Gene therapy continues to be a key area of innovation in ophthalmology. Harnessing the regeneration of retinal tissues is an innovation that is almost within reach. Investigators point out that stem cells are a key to cell replacement therapies. Russell N. Van Gelder, MD, PhD, explains that there are now methods to create equivalently totipotent stem cells from individual induced progenitor stem cells derived from an individual's blood or epithelial cells.

Device technology continues to be ripe for innovation, and robotics offer surgeons the opportunity to perform the seemingly impossible. The benefits of medical robots include high positional stability, precision, and accuracy along the x-, y-, and z-axes, removal of time constraints on subretinal and intraretinal drug delivery, and reduction of surgeon fatigue, according to Richard B. Rosen, MD, DSC(HON).

In imaging, artificial intelligence screening systems of diabetic retinopathy are not all created equal. In this issue, we will tell you why.

Innovation could make this a September to remember. ■

What's Trending

See what the ophthalmic community is reading on

OphthalmologyTimes.com

1 Identifying the value of physician assistants in ophthalmology

OphthalmologyTimes.com/view/value-of-physician-assistants-ophthalmology

2 Researchers identify pink eye as possible primary symptom of COVID-19

OphthalmologyTimes.com/view/coronavirus-pink-eye-symptoms

3 Experts review state of AMD in 2020

OphthalmologyTimes.com/view/experts-review-state-of-amd-2020

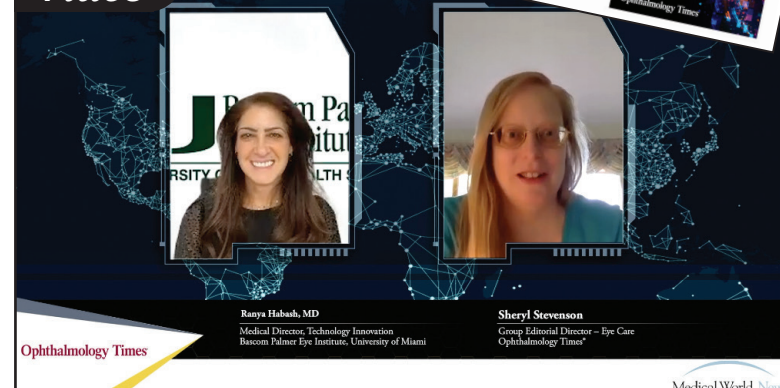
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Video



Ranya Habash, MD, medical director, Technology Innovation, Bascom Palmer Eye Institute, University of Miami, speaks on the growing capabilities of telemedicine available to ophthalmologists in the ongoing pandemic. Go to **OphthalmologyTimes.com/view/capabilities-of-telemedicine-during-pandemic-part-i**

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VP Sales
John Hydrusko
jhydrusko@mjlhifesciences.com

National Account Manager
Cherie Pearson
cpearson@mjlhifesciences.com

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EDITORIAL

Saving memories

Do anti-VEGF agents contribute to cognitive loss?



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*®.

He can be reached at 727 Maumenee Building 600 N. Wolfe St., Baltimore, MD 21287-9278
Phone: 443/287-1511 Fax: 443/287-1514
Email: pmcdonn1@jhmi.edu

HERE IS A potentially very interesting observation. According to Subhransu K. Ray, MD, PhD, and colleagues in his retina practice, patients who receive more intravitreal injections with anti-VEGF agents are more likely to experience cognitive decline.

In a cross-sectional study, they compared the results of cognitive testing in 300 patients with neovascular AMD and 100 patients with dry AMD between the ages of 65 to 85. An interim analysis of the first 116 patients studied revealed a higher prevalence of cognitive impairment in patients who received more than 20 intravitreal injections and the difference was statistically significant.

Patients who received no intravitreal injections had a 27.6% risk of cognitive impairment, those who received 1 to 20 injections had a 31.8% risk and those who received more than 20 injections had a 41.9% risk.

The authors, appropriately in my view, point out that their data do not establish a causal link and need to be confirmed by others. But they do suggest that the optic nerve plays a role.

I think it is premature, based on preliminary findings, to alert our patients to a danger of their AMD treatment contributing to their development of dementia. It is an interesting exercise to consider alternative explanations of the data, including:

- The apparent association is not real, and additional studies by other groups will not confirm the association.
- Injecting anti-VEGF agents into the vitreous cavity results in some fraction of these molecules accessing the optic nerve and/or CSF, reaching the cerebral cortex, impairing the vasculature and causing cognitive dysfunction on the basis of ischemic injury.
- Anti-VEGF agents are toxic to cortical

neurons and cause cognitive loss on the basis of neuronal loss.

■ The pathogenic mechanism(s) at work in AMD and dementia are similar. Thus, people with more advanced AMD, requiring more intravitreal injections, are also the people who are losing cortical neurons at a more rapid rate and therefore more likely to show evidence of cognitive decline during the two years of this study.

■ People who are developing cognitive decline are more likely to have family members step in to take care of them and make sure they show up to their doctors' appointments. Thus, the patients with dementia are missing fewer follow up appointments and therefore are getting more injections.

■ Patients with more severe degrees of AMD, requiring more injections of an anti-VEGF agent, are more likely to experience substantial vision loss than are patients with less severe forms of the disease. The vision loss causes these more severely affected patients to read less, become less socially interactive, and overall to become less involved with their surroundings and others. This leads to an acceleration of their cognitive decline.

■ Having a needle inserted into one's eye is stressful and anxiety-provoking. This stress and anxiety heightens cognitive decline.

■ People who are well-insured or wealthy are more able to afford to pay for their doctor visits and retina drugs than are the poor, who therefore elect to have fewer injections. Thus the two groups (few injections and many injections) may not be equivalent with regard to other variables, such as socioeconomic status and diet.

Perhaps you have some alternative hypotheses of your own. Whatever the truth is, I think it is worth examining in greater detail whether anti-VEGF agents might play a role in cognitive loss.

Ray presented "Cognitive Testing in patients receiving intravitreal anti-vascular endothelial growth factor therapy for wet age-related macular degeneration" at the American Society of Retina Specialists 2020 virtual annual meeting.

Peter J. McDonnell

Drop shows effectiveness for *Demodex* blepharitis in phase 2a study

FDA approval would allow TP-03 as treatment for blepharitis caused by mites

By Roberto Gonzalez-Salinas, MD; Special to Ophthalmology Times®

IN A PHASE 2a study, the novel topical drop TP-03 (Tarsus Pharmaceuticals) was found to be safe and effective for treating *Demodex* infestation, a frequent cause of blepharitis.¹ The drop began working in 2 weeks and lasted through the 90-day study period.



Gonzalez-Salinas

Blepharitis affects at least 20 million individuals in the United States and is frequently the reason patients visit an eye care provider.²⁻⁵ As the most common type of ectoparasite found in humans, *Demodex* mites are highly prevalent in low numbers.^{6,7} An infestation of *Demodex* folliculorum,

however, causes 45% of blepharitis cases—an estimated 9 million Americans.⁸⁻¹¹ Currently, there is no FDA-approved treatment for *Demodex* blepharitis.

The single-arm, open-label Mars study included 15 patients who received 1 drop of TP-03 in each eye twice a day for 28 days. The prespecified efficacy end points were a decrease from baseline in mean collarette score and mite density at 28 days. The decrease in both mean collarette score and mite density demonstrated statistical significance—*P* value of less than or equal to .013 and less than .001, respectively—as early as 14 days after treatment

initiation. TP-03, which targets the mites' nervous system, causing paralysis, was well tolerated, with no treatment-related adverse events (AEs) reported.

DEMODEX INFESTATION

Collarettes, sometimes called cylindrical dandruff, are a pathognomonic sign of *Demodex* infestation and are easily seen with a routine slit-lamp examination.

When mites scratch and feed on the skin, collarettes form as the partially digested epithelial cells, keratin, mite waste, and eggs combine.^{12,13} Collarettes are typically found at the base of the lash but can migrate up the shaft as hair grows.¹² Other signs of *Demodex* infestation include eyelash disorders, crusting and redness of the lid margin, blepharoconjunctivitis, and blepharokeratitis.

Patients with anterior blepharitis present with red, irritated, or itchy eyelids and eyelash debris. If not properly managed, the condition can lead to tear film instability that causes fluctuating and



Demodex mites are the most common type of ectoparasite found in humans.

blurred vision, lid and lash abnormalities, and inflammation of the conjunctiva and surrounding skin. Surgical patients with inadequately controlled *Demodex* blepharitis are at risk of sub-optimal surgical outcomes. Erythema is often noticeable. Patients may experience contact lens intolerance and reduced wear time and, overall, a reduced quality of life.^{2,3,11-13}

MARS STUDY

The Mars study included patients who had at least 10 collarettes on the upper lid, mild to severe lid margin erythema, and at least 1.5 mites per lash on the upper and lower eyelids combined. During the study period, patients were directed to discontinue use of any other treatment for blepharitis, including lid hygiene, to isolate the effect of TP-03.

Patients administered 1 drop in each eye twice a day for 28 days and were followed for 90 days. Efficacy was measured by a decrease in collarettes and in mite density. Safety was assessed via

A clinical image showing baseline and day 28.



◀ BASELINE



DAY 28 ▶

Figure 3. Collarette Score

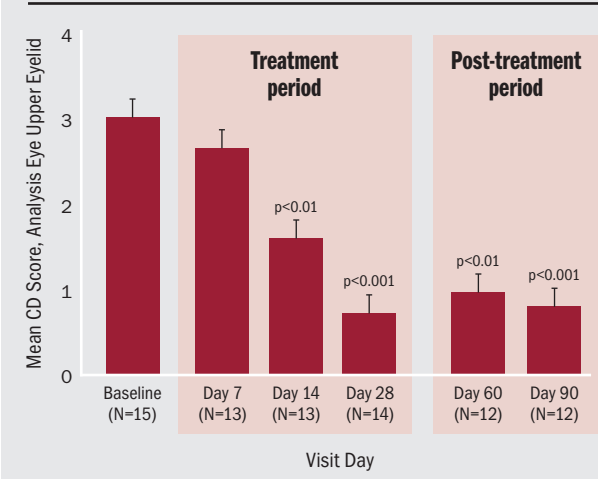
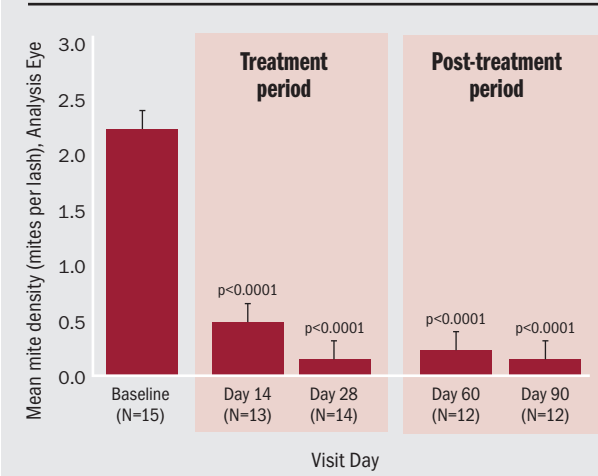


Figure 4. Density Score



All data and images courtesy of Roberto Gonzalez-Salinas, MD

treatment-related AEs and an evaluation of any changes in visual acuity, IOP, and slit-lamp biomicroscopy.

A statistically significant reduction in collarettes and mite density began at day 14 and was maintained through 90 days. No treatment-related AEs were observed, and there were no clinically significant changes in visual acuity, IOP, or slit-lamp biomicroscopy findings. At 97% of visits, patients rated the drop as “neutral” to “very comfortable.”

JUPITER

Following the Mars study, TP-03 results from the Jupiter study, a randomized controlled trial that included 60 participants, were recently presented by Milton Hom, OD.¹⁴ The findings further demonstrated that TP-03 was well tolerated and effective in reducing collarettes and *Demodex* density through 90 days in patients with *Demodex* blepharitis.

Hom reported that the change in collarette grade demonstrated statistically significant decreases for both eyes, upper and lower eyelid margins, compared with the vehicle arm as early as day 14. TP-03 showed statistically significant decreases in mite density at day 28, and its effect on both measures persisted for an additional 2 months following treatment.

There were no treatment-related AEs, and patients reported that the drop was comfortable.

CONCLUSION

An effective and comfortable treatment for *Demodex* blepharitis remains a large unmet need because there is currently no FDA-approved treatment. TP-03 has been studied in 4 phase 2 investigations that include a total of nearly 100 patients on active drug. Data show rapid, complete, and durable efficacy, with no treatment-related AEs. Notably, patients report that the drop is comfortable, and none have discontinued use due to tolerability. Tarsus is developing TP-03 in a multidose, preserved formulation and expects to begin a phase 3 trial this year. ■

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ROBERTO GONZALEZ-SALINAS, MD

E: dr.gonzalezsalinas@apec.com.mx.

Gonzalez-Salinas is an associate researcher at the Asociación para Evitar la Ceguera en México in Mexico City. He is a consultant for Allegro Ophthalmics, Kedalion Therapeutics Inc, Laboratorios Sanfer, and LayerBio Inc.

Letter to the Editor

IN THE JULY 15, 2020 edition of *Ophthalmology Times*,® Y. Alvin Liu, MD, Ferdinand K. Hui, MD, and Philip H. Phan, PhD, address some of the unique features of ophthalmology in the adoption of telehealth. However, they omit one particularly important unique feature among many of our ophthalmology patients: Their visual impairment.

Even before the coronavirus disease 2019 (COVID-19) pandemic, blind and visually impaired patients found travel to and from their doctors' offices to be difficult. Often, they require specialized transportation when public transportation is not accessible. The possibility of receiving care at home for this group of patients through telehealth is of significant value. Telehealth also makes the patients less dependent upon family members, friends, and others to help them with their transportation needs.

Blind and visually impaired patients often have depression and other mental health conditions associated with their vision loss. At Lighthouse Guild, an important part of the services we provide are in the areas of behavioral and mental health. For blind patients, the need for video communication with their doctors is certainly much less than with sighted patients. Often many of our patients do not have access to a smartphone or computer, and a land line or a traditional cell phone maybe their only access to Telehealth.

Our therapists have found that audio conferences with their patients, while not ideal, certainly provides continuity of care until the patients are able to come into the office for their usual appointments. Over these past few months, using Telehealth, our cancellation rate for appointments has dropped by more than 30% and our “no-show” rate is nearly zero.

While in-person patient examination is clearly the ideal, we have found that telehealth, particularly in patients who are visually impaired can be extremely effective and we support initiatives that will allow insurance reimbursement for telehealth to continue.

Calvin W. Roberts, MD

President and CEO
Lighthouse Guild
New York, New York

PRACTICING

(Continued from page 1)

GEARING UP FOR
IN-OFFICE VISITS

Once stay-at-home orders were issued in California, only patients needing emergency care or a postoperative follow-up visit were being seen at the Glaucoma Center of San Francisco. In planning for reopening, staff had to review charts to identify patients who should be given priority for an appointment, according to Iwach.

Patients who have an upcoming visit are being contacted by phone and are being screened for COVID-19 symptoms and informed about new processes in the office. The latter include requirements to wear a mask and enter alone unless they need to be accompanied by someone for language or other reasons.

A screening station has been set up at the entrance to the building where patients are checked for fever and COVID-19 symptoms, asked to clean their hands with a hand sanitizer, and given a mask if they did not bring one. Changes were made in the office, including removal of magazines, removal and rearrangement of furniture in the waiting area to create proper social distancing, and installation of plastic shields at the front desks.

Iwach and his associate, Terri-Diann Pickering, MD, identified restaurant supply companies and neighborhood hardware stores as good sources for acquiring protective equipment, including plastic shields, hand sanitizers, gloves, and masks.

Prince mentioned that individuals with an Amazon business account can register as a health care professional; then, they will be put on the top of a queue for getting supplies. He also noted that in his practice, a solution containing 70% ethanol

with hydrogen peroxide and glycerin that comes in large spray bottles is being used with paper towels for surface disinfection and offers a less expensive alternative to disinfectant wipes.

Practices differed in their use of gloves for staff versus frequent hand washing and sanitizing, but all participants agreed that it was critical for patients to witness attention being given to hygiene.

Minimizing patient time in the office was a universal goal. In general, patients are undergoing necessary testing in the office. Oluwatosin Smith, MD, of Glaucoma Associates of Texas, said her practice is looking at establishing a dedicated center for glaucoma testing that would be separate from the rest of the clinic and might be opened for extended hours to meet the pent-up demand for services.

In-office physician-patient interaction is being limited. Patients are mostly being contacted following their visit once the provider has a chance to review the results from the diagnostic evaluations. Depending on the need for follow-up, the results may be discussed over the phone or patients may be offered a telehealth or subsequent in-office visit.

IOP AND VISUAL
FIELD ASSESSMENTS

The participants agreed that home monitoring of IOP using a self-tonometer suffers from suboptimal accuracy. A few have reduced the use of Goldmann applanation tonometry except when they are not able to get an accurate or reliable measurement with other tonometers that are noncontact or involve minimal time up close with the patient.

Davinder Grover, MD, MPH, of Glaucoma Asso-

ciates of Texas, said that his group is using a non-contact device to measure corneal-compensated IOP in most patients, but a Tono-Pen is used to check IOP of postsurgical patients during the first month of follow-up.

Visual field testing presents a particular concern, given the special care that needs to be taken to avoid damaging the perimeter bowl. Participants felt that guidance on disinfection from the manufacturer lacked clarity, and many were exploring alternative methods for checking visual fields.

Both Grover and Iwach mentioned that their practices are pursuing other methods of perimetry that can be performed with a low risk to the patient, such as virtual reality goggle-type visual field testing.

Robert Feldman, MD, of the Robert Cizik Eye Clinic, Houston, Texas, said that visual field testing at his practice has been put on hold while

the potential to use an ultraviolet (UV)-C lamp for sanitization is being investigated. He noted, however, that the perimeter manufacturer cautioned that UV-C light could damage the equipment.

Prince said that an air purifier was installed in his practice's testing room.

"While there is no direct evidence yet that filtration works to reduce transmission of the novel coronavirus, it can be assumed from what we know of similar viruses that air purifiers might help in some situations," he said.

Prince added that, theoretically, if an air purifier removes or reduces the viral load from the air, the potential for exposure is lessened.

"The novel coronavirus itself is 0.125 microns, but the droplets it travels in when people cough, talk, or

Continues on page 9 : Practicing

TAKE-HOME

► A Glaucoma Research Foundation survey found that ophthalmologists are interested in hearing from their colleagues about their experiences in optimizing practice efficiency and patient care delivery.

GRF Ambassadors Survey

Glaucoma Research Foundation (GRF) Ambassadors are a national leadership group of eye doctors dedicated to improving access to educational materials for glaucoma patients.

On April 30, a short survey was sent to 70 Glaucoma Research Foundation Ambassadors to gather information in preparation for an upcoming webinar discussion on the challenge of managing a glaucoma practice during the coronavirus disease 2019

(COVID-19) pandemic.

Twenty-four surveys were returned by the time the response period closed. The responses to the first 3 questions are shown below.

A fourth open-ended question asked for input on topics that would be most helpful to address during the webinar. Responses showed interest in patient screening, in-office disinfection, testing, and telemedicine, along with dealing with the new financial strains.

The final question asked what GRF could do to help with post-COVID-19 patient education and support. According to their comments, the Ambassadors were interested in materials that could reassure patients so they would feel safe being seen in the office, educate them on general measures for reducing their risk of infection and on new in-office processes, and remind them about the importance of medication and visit adherence.

Q1: Are you still seeing patients in your office?

Answered: 24 Skipped: 0

Response	Percentage
Yes	54%
Yes, but for emergencies only	38%
No	8%
Other (please specify)	0%

Q2: Are you able to offer telemedicine options for your patients?

Answered: 23 Skipped: 1

Response	Percentage
Yes, video and phone	61%
Yes, phone only	17%
Yes, by email or smartphone	2%
Not yet, but planning on it	4%
No	17%
Other (please specify)	0%

Q3: Do you have a plan in place once shelter-in-place is lifted?

Answered: 24 Skipped: 0

Response	Percentage
Yes	75%
Not yet	25%

ACP calls for science to stop the spread of COVID-19

Group says public health authorities should base their decisions on science

By Keith A. Reynolds

THE AMERICAN COLLEGE of Physicians (ACP) is calling for public health policies aimed at ending the coronavirus disease 2019 (COVID-19) pandemic to be based on science.

In a statement from ACP Board of Regents Chairwoman Heather E. Gantzer, MD, FACP, the organization urges local public health authorities to use science, based on the best available evidence in the fight against COVID-19. She also urged them not be pressured or influenced to issue any policies that are not based on evidence or the recommendations of their own scientists.

Making decisions not based on evidence can have a detrimental effect on the public's trust and adherence to evidence-based guidelines. With the pandemic still a widespread public health emergency, guidance must be developed in a highly transparent

process without any interference, the statement says.

In the statement, the ACP said that the recent revision of the CDC's COVID-19 testing guidelines limiting the push for the testing of asymptomatic patients lacks transparency and clarity which sends a confusing message to physicians and patients on appropriate and necessary testing. Asymptomatic patients help spread COVID-19 and the ability to perform widespread tests is critical to manage the spread of the disease. The ACP recommends more testing to identify cases in the absence of a currently effective vaccine or treatment.

The ACP urges the Centers for Disease Control and Prevention, the Food and Drug Administration, and the National Institute of Health to transparently convey the scientific rationale for their guidance or any changes to their recommendations.

"While ACP is encouraged by the rapid development of the COVID-19 vaccine, the development process must be fully transparent, and not circumvent regulatory standards for safety and effectiveness," Gantzer said in the statement. "Physicians, in particular, must be informed about the safety and standards for approvals of any vaccines. Hesitance to receive the vaccine remains a concern amongst patients, and rushing vaccines to approval that have not been shown through clinical trials to be safe and effective would be dangerous to health, and potentially undermine confidence in all vaccines, not just ones for COVID-19 vaccines." ■

FROM THE PAGES OF **Medical Economics**
SMARTER BUSINESS. BETTER PATIENT CARE.

PRACTICING

(Continued from page 8)

breathe are around 1 µm," he said. "That is a size easily captured by air purifiers with HEPA filters."

TELEMEDICINE

In the GRF Ambassador survey, the majority of respondents indicated that they had been using a telemedicine approach to some extent.

Ambassadors participating in the discussion agreed that telemedicine has limitations for following patients with glaucoma.

Certain patient queries can be handled by phone, and a video visit can be helpful for reviewing medication use or for checking whether a red eye in a surgically treated patient is worrisome. Patients gain reassurance knowing that a physician has looked at their red eye, and the interaction itself can be a boost for patients who are socially isolated during the pandemic, Iwach said.

A NOVEL MODEL

Steven Vold, MD, in private practice at Vold Vision in Fayetteville, Arkansas, noted that because of the conducive physical setting of his office building, his practice created a "curbside clinic" where patients

could be quickly checked for possible progression of their glaucoma.

"We know that compliance with glaucoma medication is an issue, and the concern when patients are not being seen is that some who have moderate-to-advanced glaucoma could be having asymptomatic worsening," Vold said.

In Vold's "clinic," patients remain in their cars and go from station to station for a "visit" that is completed within 5 to 10 minutes. After gathering insurance information and then a history, vision is tested with a device like that used at state motor vehicle departments, IOP is measured with a rebound tonometer, and anterior and posterior segment photographs are taken using a retinal camera through a 3-mm pupil.

Patients are contacted by a physician later in the day.

"I am not saying that it is ideal and I am not advocating this approach as a standard of care," Vold said. "But I can say we have picked up numerous disc hemorrhages and elevated IOPs, and I think we have actually saved vision for some patients."

He added that the service has also been a practice builder. Patients who have seen its availability on the practice's website have traveled as far as 1000 miles to get access to in-person care.

The encounter is charged as a telehealth visit. Before offering the service, the plan was reviewed

with the Arkansas Department of Health and Arkansas State Medical Board.

PATIENT EDUCATION

The GRF Ambassadors' focus is on patient education, and some of the write-in responses on the GRF Ambassadors survey indicated interest in materials that would give patients confidence about the safety of in-office visits and inform them about new processes.

The physicians continue to do their part.

Vold said that his practice has created some videos with those goals in mind, and Smith noted that she is currently working with the Cure Glaucoma Foundation to develop patient information.

Thomas Brunner, president and CEO of GRF, said that GRF is also collaborating with this effort to inform and educate patients.

"Starting in early April with financial support from Industry, GRF began hosting a number of patient webinars and we recently launched a new video series that includes steps doctors are taking to ensure the safety of their patients," Brunner added. "GRF can play a unique role in supporting both doctors and patients during this extraordinary time." ■

STEVEN VOLD, MD

E: svold24@gmail.com

Vold has no financial disclosures related to this content.

TRUST THE POWER OF



EYLEA Offers Dosing Flexibility in Wet AMD¹

3 FDA-Approved Dosing Regimens in Wet AMD¹

Q4

Q8
following 3 initial
monthly doses

After one year of
effective therapy

Q12

The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).¹

AMD = Age-related Macular Degeneration; Q4 = every 4 weeks; Q8 = every 8 weeks; Q12 = every 12 weeks.

IMPORTANT SAFETY INFORMATION AND INDICATIONS

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

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

Q12 DOSING REGIMEN IN WET AMD¹⁻³

As Demonstrated in Phase 3 Clinical Trials¹⁻³

Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every-4-week (monthly) dosing after the first 12 weeks (3 months).

Although not as effective as the recommended every-8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

Visit HCP.EYLEA.US to see the data.

WARNINGS AND PRECAUTIONS (cont'd)

- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

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

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON



BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE

EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of:

Neovascular (Wet) Age-Related Macular Degeneration (AMD); Macular Edema Following Retinal Vein Occlusion (RVO); Diabetic Macular Edema (DME); Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

EYLEA is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

EYLEA is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

EYLEA is contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments.

Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [see Adverse Reactions (6.1)]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [see Patient Counseling Information (17)].

5.2 Increase in Intraocular Pressure.

Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA [see Adverse Reactions (6.1)]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.

5.3 Thromboembolic Events.

There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS

The following potentially serious adverse reactions are described elsewhere in the labeling:

- Hypersensitivity [see Contraindications (4.3)]
- Endophthalmitis and retinal detachments [see Warnings and Precautions (5.1)]
- Increase in intraocular pressure [see Warnings and Precautions (5.2)]
- Thromboembolic events [see Warnings and Precautions (5.3)]

6.1 Clinical Trials Experience.

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

A total of 2980 patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).

Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

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

Adverse Reactions	Baseline to Week 52		Baseline to Week 96	
	EYLEA (N=1824)	Active Control (ranibizumab) (N=595)	EYLEA (N=1824)	Control (ranibizumab) (N=595)
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

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

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

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

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

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

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

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

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

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

Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

6.2 Immunogenicity.

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

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

8 USE IN SPECIFIC POPULATIONS.

8.1 Pregnancy

Risk Summary

Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [see Animal Data].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

Data

Animal Data

In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg.

Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 6 times higher than systemic exposure (AUC) observed in humans after a single intravitreal dose of 2 mg.

8.2 Lactation

Risk Summary

There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA is not recommended during breastfeeding.

The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA and any potential adverse effects on the breastfed child from EYLEA.

8.3 Females and Males of Reproductive Potential

Contraception

Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 3 months after the last intravitreal injection of EYLEA.

Infertility

There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed humans with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

8.4 Pediatric Use.

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

8.5 Geriatric Use.

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

17 PATIENT COUNSELING INFORMATION

In the days following EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients to seek immediate care from an ophthalmologist [see Warnings and Precautions (5.1)]. Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations [see Adverse Reactions (6)]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON

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

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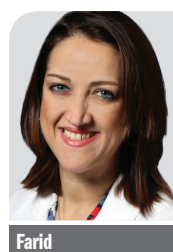
Boosting short-term dry eye management in patients

Fast-acting efficacious options are key to treating acute inflammation

By Marjan Farid, MD; Special to Ophthalmology Times®

Given the 17.2 million diagnosed cases of dry eye disease in the United States,¹ ophthalmologists know the condition is a frequent cause of vision fluctuation, discomfort, and eye fatigue. The inflammatory-driven disorder requires a comprehensive treatment plan, including both short- and long-term therapies.

Patients whose symptoms are episodic rather than continuous may need short-term treatment, whereas those who experience chronic discomfort may benefit from long-term therapy or a combination of both. We see this commonly in patients with other inflammatory conditions such as atopic dermatitis, asthma, and Sjögren syndrome.



Farid

More often, patients need short-term therapy for periodic inflammatory flares, a normal part of the disease that affects a large majority of patients with dry eye, even when using chronic therapy. We also use short-term anti-inflammatory therapy for some patients at their initial diagnosis to manage the acute inflammation quickly while starting chronic therapy, which has a longer onset of action, or to bring dry eye under control in a relatively short period before cataract or other ocular surgery.

TREATING PERIODIC FLARES

A dry eye flare is an acute inflammatory response, usually brought on by triggers such as excessive screen time, allergies, dry indoor heating or cooling, smoke, contact lenses, or medications.² According to surveys, about 80% of people who have received a diagnosis of dry eye experienced flares,³⁻⁵ which lasted from a few days to a few weeks.⁶ Close to half of patients had no chronic symptoms and experienced only periodic flares that require short-term treatment.^{4,5}

I always tell patients that dry eye disease has its ups and downs, like a roller coaster. Chronic therapy makes the ups and downs less severe but will not prevent flares, so patients sometimes need short-term treatment.

For example, a patient who is satisfied with chronic therapy might have a tough work deadline and spend long hours working on a computer, day after day. At some point, their eyes become painful, burning, gritty, and red, and visual tasks can no longer be performed

clearly and comfortably. In the exam, we see worsening of corneal and/or conjunctival lissamine green staining, revealing degenerated epithelium across the entire ocular surface. MMP-9 testing is positive for the inflammatory marker in the tear film.

To treat dry eye flares, I prescribe steroids such as loteprednol etabonate or fluorometholone alcohol for 1 or 2 weeks. This is an off-label use, because there is currently no steroid approved for treating dry eye disease. Short-term steroid therapy knocks down the acute inflammatory response quickly and cools the eye.

Medications such as cyclosporine and lifitegrast, which take several weeks to reach full efficacy, are not as immediate acting for short-term therapy. After initial use, I instruct patients to use their steroid drops for 1 to 2 weeks as needed for any future episodic flares.

In addition to seeing flares in existing patients with dry eye, it is common for patients to present with the acute symptoms of a flare and receive the diagnosis for the first time. Some have had mild or moderate symptoms for some time, and the acute flare finally drives them to see a doctor. These patients need to cool down the acute inflammation with immediate short-term steroid therapy. They can then be started on a chronic therapy such as cyclosporine or lifitegrast.

IMPROVING SURGICAL OUTCOMES

Some 80% of patients have at least 1 positive test for dry eye when they present for cataract surgery.⁷ We know that dry eye can affect the accuracy of preoperative measurements and become exacerbated by surgery itself, so we put surgery off a bit and try to bring the dry eye under control. Certainly, where premium IOLs are concerned, there is no room for error, so we need to nail the refraction with a pristine ocular surface.

As a member of the American Society of Cataract and Refractive Surgery Cornea Clinical Committee, I helped develop the algorithm for treatment of the ocular surface prior to cataract surgery. One of the goals was to take a multifaceted approach to treatment. We also wanted to achieve results in the ocular surface quickly so physicians can proceed with measurements and surgery.

Again, for surgical patients with significant ocular surface inflammation, I use topical steroids off-label for short-term therapy. I also have patients follow a regimen of lid management treatment and artificial

tears, as well as a course of oral doxycycline if indicated in concomitant lid margin inflammation from rosacea. Patients are happy to wait 1 or 2 months for surgery once they understand that improving the ocular surface is key to achieving good surgical outcomes.

LOOKING TOWARD THE FUTURE

Currently, there is no FDA-approved, fast-acting medication that can improve signs and symptoms of dry eye. Although I prescribe steroids for that purpose, there is some concern among my colleagues who also treat dry eye disease about the potential adverse effects. I look forward to having an FDA-approved product in this space for the treatment of episodic disease. Short-term therapy is a crucial component of dry eye management, whether it is used before cataract surgery or to treat flares in patients who are otherwise well controlled. ■

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MARJAN FARID, MD

P: 949/824-2020

Farid is a professor of ophthalmology and director of Cornea, Cataract, and Refractive Surgery at Gavin Herbert Eye Institute at University of California, Irvine.

DATA

(Continued from page 1)

orders of magnitude larger than the number of subjects typically found in a phase 3 clinical trial.

Verana Health, through our partnership with the American Academy of Ophthalmology, is actively engaged in curating and analyzing data from the IRIS Registry (Intelligent Research in Sight) to better inform clinical practice in ophthalmology. The IRIS Registry is the largest specialty clinical database in medicine, with 343 million patient visits and billions of data points reported by more than 15,000 ophthalmologists through their electronic health records (EHR) systems. Large registries like this offer the opportunity to gather RWE about clinical outcomes. They facilitate research on questions that are critical to patient care but may be less likely to garner industry support such as head-to-head comparisons of new and long-established treatments.

REAL-WORLD OPHTHALMIC INSIGHTS

Large registry studies are relatively new but have already led to changes in ophthalmic practice. For example, a retrospective analysis of all procedures in the Swedish national cataract registry over a multi-year period revealed that intracameral antibiotics were an important factor in reducing the rate of endophthalmitis.² This led to a prospective European study of intracameral antibiotics³ and widespread adoption of this method of infection prophylaxis in Europe. A large health maintenance organization (HMO) in the United States also reached similar conclusion about the value of injected antibiotics in cataract surgery after reviewing a large data set from its own EHR system.⁴

Another national registry helped to establish corneal collagen cross-linking as the standard of care for keratoconus. In this case, analysis of healthcare resource utilization in the Netherlands before and after the introduction of crosslinking showed that the procedure was associated with a 25% reduction in corneal transplantation over three years.⁵

We have been able to use the IRIS Registry data to evaluate real-world anti-VEGF injection intervals in 56,672 treatment-naïve patients with wet age-related macular degeneration.⁶ In this study, the authors found that the mean number of injections per eye was approximately five per year.

By the end of year 1, approximately 40% of eyes continually treated with anti-VEGF medications needed injections more frequently than every 8 weeks, including 17%-18% who still needed monthly injections.

In another retrospective review of IRIS Registry data for 12.5 million patients seen by an eye care provider in 2017, researchers evaluated the relationship between smoking and IOP.⁷ After adjusting for many factors, including age and glaucoma diagnosis, smokers (both current and those with a history of smoking) had higher mean IOP than those who

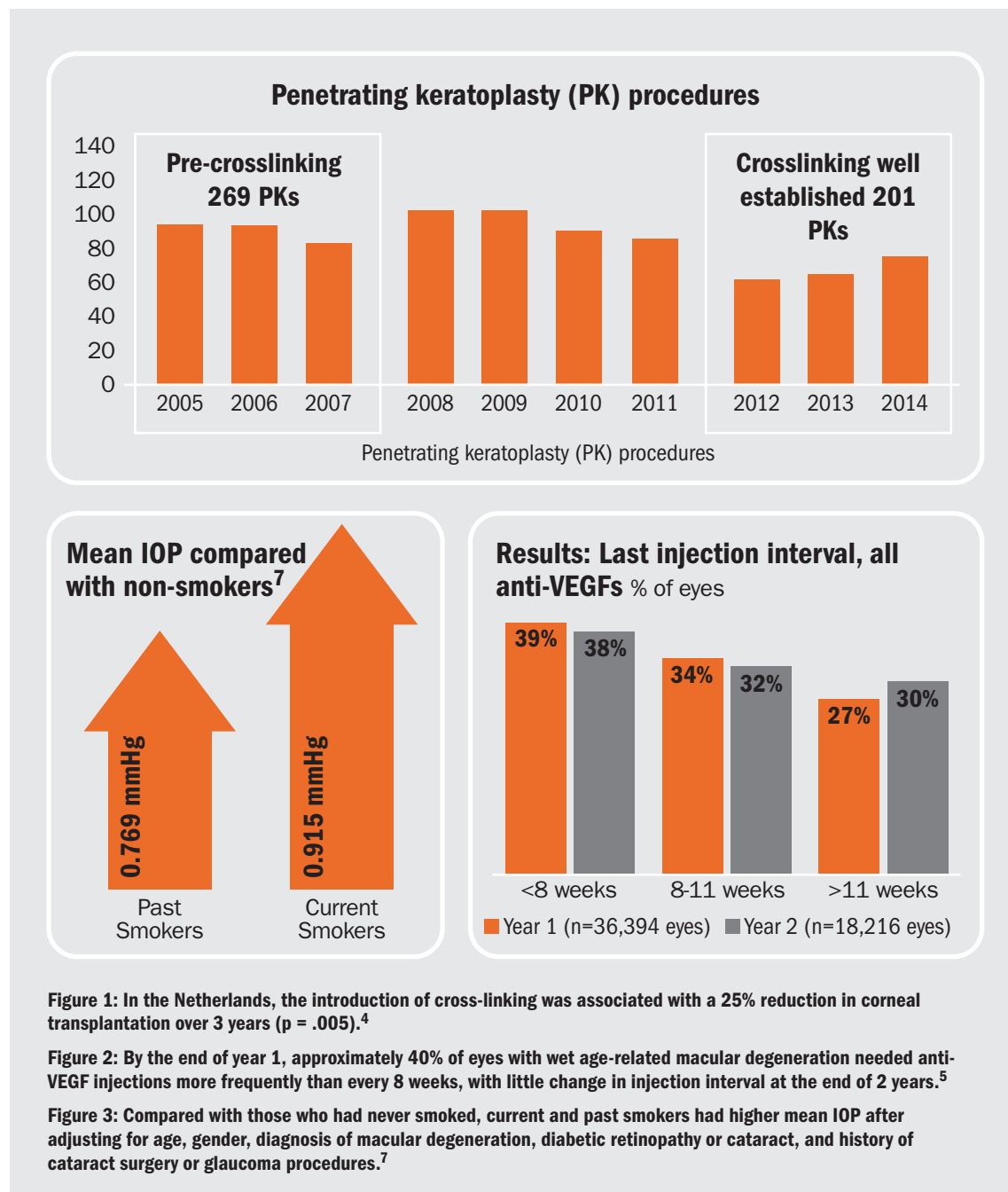


Figure 1: In the Netherlands, the introduction of cross-linking was associated with a 25% reduction in corneal transplantation over 3 years ($p = .005$).⁴

Figure 2: By the end of year 1, approximately 40% of eyes with wet age-related macular degeneration needed anti-VEGF injections more frequently than every 8 weeks, with little change in injection interval at the end of 2 years.⁵

Figure 3: Compared with those who had never smoked, current and past smokers had higher mean IOP after adjusting for age, gender, diagnosis of macular degeneration, diabetic retinopathy or cataract, and history of cataract surgery or glaucoma procedures.⁷

had never smoked. In fact, smoking was the most important predictor of IOP after the glaucoma diagnosis (Figure 3).

CHALLENGES OF BIG DATA

The ability to access large amounts of information to improve medicine is very exciting. But large data sets can be quite challenging to interpret. Imagine a spreadsheet with billions of rows and columns. No human can realistically check it over for errors; sophisticated algorithms are needed to catch and remove errors in a systematic way. The raw data must be cleaned, harmonized, and structured in such a way that it can be used for clinical research.

To better understand this, consider something as simple as visual acuity (VA)—an important outcome measure in ophthalmic studies. Data comes into the IRIS Registry every day from thousands of doctors using more than 50 different EHR platforms, each of which collects VA in slightly different fields or formats.

VA may have been measured using a Snellen or ETDRS (Early Treatment Diabetic Retinopathy Study) chart, autorefraction, or a pinhole test. The patient may have been tested with or without correction, monocularly or binocularly. All of that VA data needs to be harmonized so that “20/20” has the same meaning across millions of records.

At Verana, we are using machine-learning techniques to refine algorithms that characterize important information from “unstructured” data, such as free text and images. Imaging is very important in ophthalmology, so the ability to develop algorithms that can mine images for precalculated measurements such as retinal nerve fiber layer thickness, as well as pathological features (eg, drusen) is highly relevant for future research.

FUTURE DIRECTIONS

In fact, real-world data from large registries opens up many new avenues for clinical research and the advancement of medicine. The sheer volume of pa-

tients offers a chance to drill down into specific subgroups that are underrepresented in clinical trials and to better understand how a disease process or treatment response might vary by gender, race or ethnicity. We are also passionate about the opportunity to use RWE from the IRIS Registry and other large registries to develop more personalized patient care. Currently, a new glaucoma patient is typically treated first with a prostaglandin analog—the best available treatment, based on the literature. But what if we had a robust algorithm that could take into account not just the basic diagnosis, but age, ethnicity, gender, and comorbidities, to identify the best treatment paradigm for that individual patient? Ironically, big data has the power to change how we approach small, daily decisions.

And as large as these registries are, there are opportunities to deepen them further through data linking. If we link records from pharmacy prescription databases or serum testing laboratories to the IRIS Registry data, we could get a much clearer picture of diabetic patients' glycemic control, and potentially be able to evaluate how glycosylated hemoglobin levels or metformin usage correlate with diabetic retinopathy changes.

We now have the ability to access large volumes of real-world data from very broad patient populations. The possibilities for using that data to improve patient care and drive scientific insights are limitless. ■

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MATTHEW ROE, MD, MHS

E: matthew.roe@veranahealth.com

Roe is chief medical officer of Verana Health. A cardiologist by training, he spent 20 years at Duke University and as an investigator at the Duke Clinical Research Institute in Durham, North Carolina, where he focused on research initiatives leveraging real-world data. He was a principal investigator in the ADAPTABLE trial.

THEODORE LENG, MD, MS

E: tedleng@stanford.edu

Leng is a practicing retinal specialist, assistant professor of ophthalmology and director of Clinical and Translational Research at Stanford University Medical School in Stanford, California. He has a research background in image analysis, machine learning algorithms, and clinical trial design and execution. He serves as a medical adviser to Verana Health.

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surgery

Surgery during the COVID-19 pandemic: Staying sharp

Ophthalmologists remain in touch with colleagues while maintaining social distancing

By Lynda Charters; Reviewed by Manjool Shah, MD

In uncertain times, it is important to remain in contact with fellow surgeons in order to continue learning, growing, and developing.

“As I train my residents [and] fellows and work with my colleagues, we all recognize both the importance of maintaining surgical skills and how difficult this may be when the surgical volume dries up,” Manjool Shah, MD, emphasized, and provided some pearls that can help alleviate this situation.

Shah, a clinical assistant professor at the University of Michigan Kellogg Eye Center in Ann Arbor, equated being a surgeon and maintaining skills to being a member of a football team. The majority of players are off the field most of the time. He pointed out that coaches use certain strategies for those players not on the field to keep them prepared and ready to perform when called upon.

Surgeons can prepare themselves for action by creating mental representations of themselves “in the game” through mindful and direct observation. They also can play the “anticipation game” by imagining what they would do next when faced with the current situation, he explained.

Additionally, Shah advised that surgeons have hands-on tasks that they can work on while side-

lined; these tasks are directly related to the anticipated surgeries.

“These steps enable players to maintain a direct connection with what is happening in the operating room,” he said.

PHILOSOPHIES TO LIVE BY

“Surgical skills start in your head and not in your hands,” Shah said. He pointed out that one way for surgeons to refine their skills is by watching videos of routine cases, such as a cataract procedure.

Shah suggested starting from the beginning without fast-forwarding the recording, even when nothing remarkable is happening.

“Feel that agony of stasis,” he said.

“Watch actively, take notes, draw diagrams, imagine hand placement during the procedure and place incisions; pause, rewatch, rewind. Focus on fundamentals such as hand and phaco positions and second instrument position. Be critical of yourself and seek the ‘why’ behind every action or inaction that may occur and try to understand every nuance of the procedure.”

Importantly, Shah also suggested trying to devise at least 1 actionable change that can be implemented during the next surgery in the operating room.

After mastering a simple case, surgeons can advance to a more complicated surgery, such as a case of a dropped nucleus, in which things do not necessarily proceed as expected. The same steps outlined previously can be applied to these cases, too.

“Focus on the complications but instead [move] forward and backward in time in the video to determine how it happened, starting from the beginning, and how it was managed,” Shah said. “Find the cause before the root cause and imagine all the steps from the initial event to the complication and then beyond.” Most importantly, the surgeon can deter-

mine productive tasks to work on to avoid this in the future in the operating room.

“Learn from others by standing on the shoulders of giants,” Shah said.

This can be tackled by reading the steady stream of surgical techniques that have been described in the literature.

“The act of reading a description before watching an accompanying video is useful. *The Journal of Cataract & Refractive Surgery* may be a good place to begin,” Shah noted.

Following reading, now is the time to watch the videos. This can facilitate the learning of new techniques and how to manage challenging cases. The American Society of Cataract and Refractive Surgery clinical education site and YouTube are all good sources.

“Be critical and [apply] those same watching skills. Pause the video at key intervals and ask ‘What would I do next?’” he suggested.

Shah also pointed out that surgeons can share the information they gained with colleagues and the community and discuss best practices, challenges, complications, and resources.

“We have opportunities to leverage teleconferencing options to build bonds and practice [distance] socializing,” he said.

Finally, Shah advised working on technical skills using a microscope or surgical supplies.

“Devices and implants are often available from reps, and model eyes can be made specifically for many surgical techniques and can be reused,” he said.

The current environment will change, and ophthalmologists must be prepared for it.

“The crisis will end and we will be called off the bench,” Shah said, pointing out that the reduced surgical volume and delayed care can translate into some cases that may present increased complexity.

“Stay safe, stay sane, stay healthy, and stay sharp,” he concluded. “These directives apply with and without a pandemic.” ■

TAKE-HOME

► During the pandemic, surgeons can develop contacts with their peers to continue to grow professionally.

MANJOO SHAH, MD

E: manjool@med.umich.edu

Shah has no financial interest in this subject matter.



Reducing burden on veterans undergoing cataract surgery

Streamlining preoperative process can offer some relief during stressful time

By Lynda Charters; Reviewed by Ariana Levin, MD



THE CURRENT PREOPERATIVE requirement for a short evaluation regarding patient histories and physicals may offer an opportunity to streamline the preoperative process for patients scheduled to undergo a cataract surgery. In many cases, excess travel time and associated costs of lost work, food, and lodging place an unnecessary burden on patients who are not at high-risk of a complication associated with the surgery.

“One of our goals is to maximize accessible, affordable, and efficient care, and to do so we should reevaluate the requirement for preoperative histories and physicals for patients undergoing cataract surgery,” according to Ariana Levin, MD, a resident at the Moran Eye Institute at the University of Utah in Salt Lake City.

The preoperative requirements for this patient group have decreased over time in order to decrease unnecessary costs and waste. The savings positively impact the patients, physicians, surgery system, and the health care system.

The American Academy of Ophthalmology (AAO) stated “routine medical tests performed on patients before cataract surgery are unnecessary, because they do not increase the safety of the procedure.”

What remains now is the mandate for histories and physicals to be performed within 30 days of the scheduled cataract surgery. Levin pointed out that this is generally a 15-minute appointment that does not include an ocular examination, receipt of eye drops, or discussion of cessation of medications.

Considering the limits of this 15-minute appointment, Levin emphasized, some patients who attend the Veterans’ Administration facility in Salt Lake City can travel up to 5.5 hours for what is likely an unnecessary visit and suggested that telemedicine could play a future role in such an evaluation.

This 15-evaluation is not required in all VA facilities and some schedule it for the day of the cataract evaluation with an update on the surgical day. However, despite this, Dr. Levin emphasized that the preoperative requirement must be streamlined even further. A recent publication reported what should seem obvious, i.e., that cataract surgery is very safe for most patients, the few patients who do need further screening can be screened before the surgery, and the interventions that take place on the day of the surgery are generally for hypertension or bradycardia.¹

Another study that compared the before-and-after effects of the preoperative history and physicals requirement based on a risk stratification questionnaire; in this study low-risk patients did not undergo the history/physical evaluation.² The investigators reported that there was no difference found in the major medical events, and no events were associated with elimination of the history/physical visit.

“These observations show that the value of the history/physical evaluation is questionable, and our patients can travel a long distance,” she said and noted that the important consideration is not so much the burden on the health care system, although that is a concern, but the burden on the patients.

Surveys of patients treated at the Salt Lake City VA indicate that patients have a mean 1-way travel time of 96 minutes over 72 miles and a median 1-way travel time 60 minutes over 33 miles. The other data are equally impressive in that 6.2% missed work, 23% had a family member who missed work, 8.6% had associated child and pet care costs, and 32% expressed concern about the cost of medical care. Patients tallied the costs of food, time, and time off work equaling about \$300, Levin said.

“This is an opportunity to restructure preoperative requirements to decrease the burden on patients while maintaining superb patient care,” the investigators concluded. “While our institution is inside the VA system in Salt Lake City, these points likely apply to patients outside the VA system, especially in rural areas.” ■

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ARIANA LEVIN, MD

E: Ariana.levin@hsc.utah.edu

Levin has no financial interest in this subject matter.



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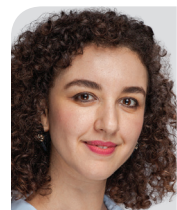
clinical diagnosis

Persistent retinal detachment associated with retinoblastoma

Watchful waiting may prove to be beneficial in complicated cases

By Lynda Charters; Reviewed by Sophia El Hamichi, MD

Retinoblastoma (RB) is the most frequently seen intraocular cancer in children, a complication of which is retinal detachment (RD). While the main focus of treatment is curing the cancer and preserving the eye, the visual function is important to the patient's quality of life.



El Hamichi

These cases are not without potential hurdles. The RDs can prove to be complex problems that are persistent, and therein lies the challenge to ophthalmologists, according to Sophia El Hamichi, MD, from Murray Ocular Oncology and Retina in Miami, Florida.

STUDY

El Hamichi and her colleagues conducted a retrospective study in which they reviewed and described persistent RDs in eyes with RBs, the etiologies, treatment attempts, and outcomes in this patient population between June 2012 and December 2019.

A review of the medical records identified 62 patients with RB during the study period. Persistence of RDs was defined as the presence of subretinal fluid after the patients had been treated for RB and achieved complete tumor regression. Of these patients, a RD developed in 42 (67%), of which 35 resolved successfully. The other 7 patients (5 boys, 2 girls) had a persistent RD; in these patients, the RB was bilat-

eral in 3 patients and unilateral in 4. In all patients, the RB and RD presented simultaneously during the first ophthalmologic assessment. The mean age at diagnosis of RB was 11 months (range, 2 days-24 months). The ages at diagnosis of RD ranged from 2 days to 24 months. All eyes had an advanced stage of RB, ie, state 5B in 8 eyes and stage 4 in 2 eyes.

Intraarterial chemotherapy was applied in 6 eyes of 5 patients and systemic chemotherapy in 3 patients; 1 patient was treated with intraarterial chemotherapy bilaterally and systemic chemotherapy. One patient underwent external beam radiation therapy and a periorbital injection of carboplatin. Cryotherapy and intravitreal chemotherapy were not used on any patients.

The RDs were complex in all eyes. In 9 eyes, the detachment had exudative and tractional components. One eye had a pure tractional RD as the result of persistent fetal vasculature. The RDs were not repaired surgically in any eyes, El Hamichi said.

Following treatment, the tumors did not recur in any eyes. The eyes were anatomically stable. One patient had a globe phthisis in 1 eye, and another patient had a globe pre-phthisis; both patients had bilateral RBs and bilateral retinal detachments with poor visual outcomes.

RD TYPES IN RB

In RB, exudative, rhegmatogenous, and tractional RDs can develop. The exudative type tends to occur when an exophytic RB is present subretinally and generally is associated with subretinal tumor seeding.

In these cases, when the tumor responds to chemotherapy, the RD was reported to resolve spontaneously.¹ Another study found that the first round of chemotherapy caused exudative RDs when eyes did not receive focal consolidation treatment, possibly because of excessive inflammation from chemoreduction or rapid tumor reduction.²

Intra-arterial chemotherapy resolves 43% of total RDs and all partial RDs associated with RB.³ Exudative RDs have developed after intra-arterial chemotherapy that never resolved despite tumor regression.

Rhegmatogenous RDs probably develop as the result of focal retinal necrosis and retinal breaks that resulted from cryotherapy applied to the tumor area. The area around the tumor usually has an exudative RD present. Another theory about rhegmatogenous RDs is that focal inflammation increases in

response to cryotherapy in eyes with inflammation because of the tumor. Traction and breaks in weakened retinal zones result. These patients, most of whom undergo chemoreduction, are more susceptible to complications.

Some rhegmatogenous RDs have developed after intraarterial chemotherapy as a result of rapid tumor regression that leaves an atrophic retinal hole. Rhegmatogenous RDs seem to occur mostly in eyes with advanced disease with extensive endophytic tumors.

RD CORRECTION

The caveat in these eyes is that surgery in the presence of active RB carries a high risk of tumor metastasis.

Pars plana vitrectomy can be an option in cases of RD of more than 1 mechanism in an attempt to restore the retinal anatomy and possibly vision. However, the investigators pointed out that the risk of tumor dissemination outweighs the benefit of repairing the RD. The investigators recommended that surgery not be performed until 2 years after the patient underwent their last treatment for RB. If the RB is not controlled, enucleation is mandatory.

Based on the study findings, the investigators concluded, "the development of RD can be challenging in cases of RB, especially when it has a complex configuration leading to persistence of the RD. These RDs are difficult to treat, and the visual outcomes can be compromised. Vitrectomy should not be performed until the patient is free of RB for 2 years to avoid spreading the tumor and metastatic disease. This waiting period affects the surgical results and even calls into question its necessity." ■

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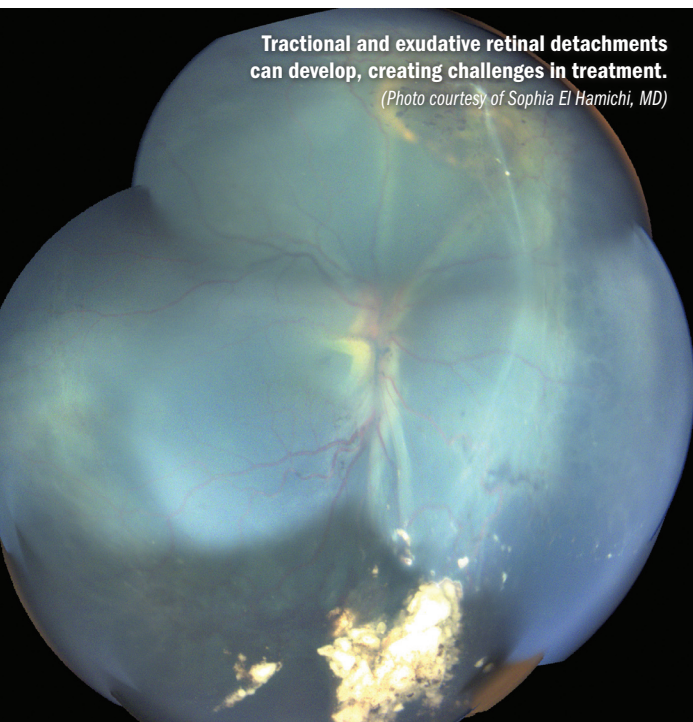
SOPHIA EL HAMICHI, MD

E: sophiaelhamichi@gmail.com

El Hamichi has no financial interest in this subject matter.

Tractional and exudative retinal detachments can develop, creating challenges in treatment.

(Photo courtesy of Sophia El Hamichi, MD)



Study: Patients at moderate risk of ectasia are stable 2 years after treatment

Researchers evaluate effects of procedure on patients with abnormal topography

By Lynda Charters

THE VISUAL OUTCOMES of the SMILE Xtra (Carl Zeiss Meditec) study of small-incision lenticule extraction with accelerated corneal cross-linking were comparable from 1 week to 2 years postoperatively, as were the safety, stability, and predictability—important findings for patients at moderate risk of ectasia.

The study was undertaken to evaluate the long-term effects of the procedure in patients who had abnormal topography, low residual stromal bed thickness, higher refractive errors, and thin preoperative corneal thickness, according to Sung Min Kim, MD, from the NUNEMISO Eye Center in Seoul, South Korea. In addition, investigators wanted to determine the

safety and clinical effect of the Xtra energy protocol in various patient subgroups.

The study included patients who underwent the SMILE Xtra treatment from March 2016 to February 2017 and had been followed for 2 years postoperatively.

The Xtra protocol included soaking with a 0.25% riboflavin solution for 90 seconds, followed by ultraviolet A light exposure at 30 mW/cm² for 60 seconds. This approach provided 1.8 J/cm² of total energy, Kim said.

The inclusion criterion for the SMILE Xtra candidates was moderate-risk patients determined based on the Randleman Ectasia Score System. The patients

were divided into 4 subgroups based on their characteristics: abnormal topography, low residual stromal bed thickness under 300 µm, high refractive errors exceeding -9.5 D or lenticule thickness exceeding 130 µm, or a thin preoperative central corneal thickness under 510 µm.

Patients were excluded if they were under 18 years old, had keratoconus or suspected they had keratoconus, had a central corneal thickness under 480 µm, had a residual stromal bed under 290 µm, had been lost to follow-up, or had undergone a reoperation.

Included were 130 eyes of 65 patients (mean age, 26.4

Continues on page 22 : Ectasia

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Platform for measuring contrast sensitivity shows potential for AMD

Using active learning approach can help gauge visual function loss in patients

By Cheryl Guttman Krader, PSP Pharm; Reviewed by Kark Csaky, MD, PhD

CONTRAST SENSITIVITY measured with an active learning approach (Manifold Contrast Vision Meter, Adaptive Sensory Technology) may be a sensitive correlate of visual function in patients with dry age-related macular degeneration (AMD), according to William C. Ou, BS.

A study using this method found that contrast sensitivity function measured in both standard and low luminance conditions decreased with increasing severity of dry AMD and was better in normal controls compared with the dry AMD subgroup representing the earliest stage of disease.

“AMD is a leading cause of vision loss in the elderly, although visual acuity tends to be spared until late in the disease course,” said Ou, a researcher at the Retina Foundation of the Southwest in Dallas, Texas. “However, patients with earlier stage AMD often have visual complaints, especially under low luminance conditions. Thus, there is a need to identify alternative measures of visual dysfunction that may better reflect the true degree of visual impairment.”

According to Ou, the study suggests that the tool investigators evaluated may be useful as a supplemental visual function measure in patients with AMD.

Although contrast sensitivity has been considered a more sensitive indicator of visual dysfunction in early AMD compared with visual acuity, measuring contrast sensitivity with traditional methods is difficult outside research settings.

The method investigated in the present study uses an active learning approach to estimate a model of the contrast sensitivity function’s global shape. The algorithm, known as the quick contrast sensitivity function (qCSF), measures the full spatial contrast sensitivity function in just 5 to 10 minutes, which makes it practical for use in clinical settings.

For the testing, patients are asked to identify 25 consecutive optotype triplets varying in size and contrast. The software generates contrast sensitivities at individual spatial frequencies. Testing for the study was done under standard photopic conditions and then repeated at low luminance created using a 2.0 log neutral density filter.

A total of 65 patients with dry AMD and 23 age-matched controls participated in the study. Those with AMD had disease in at least 1 eye and a visual acuity of 20/80 or better. To investigate correlations between AMD severity and contrast sensitivity, the patients with dry AMD were divided into 3 subgroups defined based on the presence of soft drusen only (ie, intermediate AMD, n = 26), subretinal drusenoid deposits (n = 19), and geographic atrophy (n = 20).

A plot of the qCSF data from testing at standard photopic luminance showed decreasing function with increasing AMD severity across all spatial frequencies. Losses in contrast sensitivity were greatest

at low to intermediate spatial frequencies (3 and 6 cycles per degree, equivalent to Snellen sizes of 20/200 and 20/100).

“Our finding that the group with subretinal drusenoid deposits fell in between the intermediate AMD and geographic atrophy groups is consistent with previous studies that indicated patients with subretinal drusenoid deposits appear to be phenotypically distinct from patients with soft drusen alone,” Ou said.

The results from testing under low luminance conditions were similar, although some significant floor effects were seen at the highest spatial frequencies.

To allow for a statistical analysis of the results, the investigators calculated the area under the log CSF (AULCSF). The AULCSF gives a single value for each contrast sensitivity function.

Qualitatively, the data showed that the AULCSF decreased with increasing AMD severity under both standard photopic and low luminance conditions. Pairwise comparisons between the AMD severity groups showed statistically significant differences for most but not all comparisons. ■

KARL CSAKY, MD, PHD

E: kcsaky@retinafoundation.org

William C. Ou presented this research at the 2020 Association for Research in Vision and Ophthalmology virtual annual meeting. He has no financial interests to disclose.

ECTASIA

(Continued from page 21)

years). The mean preoperative sphere was -6.22 D, and the mean cylinder was -1.59 D.

“The efficacy index for the SMILE Xtra treatment was 1.13, which was comparable to that of the patients who underwent the SMILE procedure in the same clinic. Only 61% of patients achieved a visual acuity of 1.08 1 day after the procedure, but at 2 years that increased to 1.08 or better in 95% of patients,” Kim explained.

Kim noted that when the SMILE Xtra procedure was compared with the SMILE procedure, the vision on the first day postoperatively was significantly lower in the Xtra group; however, from the 1-week time point out to 2 years, the results of the 2 procedures

were comparable.

The safety, stability, and predictability of the Xtra procedure were all good. The safety index was 1.16. Only 1 line of vision was lost at 2 years among all the study patients. Two eyes were enhanced with PRK at 1 year; these eyes were excluded from the study. Finally, at the final visit at 2 years, 97.7% were within ± 0.05 D of the targeted refraction.

The analysis of the 4 subgroups did not find any significant differences in the visual recovery and refractive change over the 2 year course of study. The patients in the group characterized by a high refractive error tended toward slight regression and lower vision at the final evaluation compared with the other 3 groups. However, the differences were not significant.

The differences in the endothelial cell counts from preoperatively to postoperatively were not significant in the entire study cohort or among the subgroups.

“The Xtra corneal crosslinking did not result in significant endothelial cell loss over the long term,” Kim said.

The investigators concluded that with the exception of the early postoperative period, the SMILE Xtra treatment demonstrated comparable visual outcomes from 1 week to 2 years. The safety, stability, and predictability also were stable. Finally, the characteristics of the subgroups did not affect the clinical outcomes after SMILE Xtra.

“SMILE, in combination with the 1.8 J/cm² Xtra protocol, seems to be an effective, safe, and predictable treatment strategy in patients who are at moderate risk,” Kim concluded. ■

SUNG MIN KIM, MD

E: sung.m.kim@vumc.org

Kim has no financial interest in this subject matter.

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IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

XELPROS is contraindicated in patients with a known hypersensitivity to latanoprost, or any other ingredients in this product.

WARNINGS AND PRECAUTIONS

Pigmentation: XELPROS may cause changes to pigmented tissues. The most frequently reported changes are increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as XELPROS is administered. After discontinuation of XELPROS, iris pigmentation is likely to be permanent. Patients who receive treatment should be informed of the possibility of increased pigmentation. The long-term effects of increased pigmentation are not known.

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Intraocular Inflammation: XELPROS should be used with caution in patients with a history of intraocular inflammation (iritis/uveitis) and should generally not be used in patients with active intraocular inflammation.

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Bacterial Keratitis: There have been reports of bacterial keratitis associated with the use of multiple-dose containers of topical ophthalmic products.

Use with Contact Lenses: Contact lenses should be removed prior to administration of XELPROS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS

The most common ocular adverse reactions in clinical trials (incidence ≥5%) for XELPROS were eye pain/stinging, ocular hyperemia, conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening.

DRUG INTERACTIONS

Precipitation may occur if drugs containing thimerosal are used concomitantly with XELPROS. If such drugs are used, they should be administered at least 5 minutes apart.

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

BAK=benzalkonium chloride.

References: 1. XELPROS [package insert]. Cranbury, NJ: Sun Pharmaceutical Industries, Inc; 2018. 2. Data on file. Cranbury, NJ: Sun Pharmaceutical Industries, Inc.



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ADVERSE REACTIONS

Clinical Trials Experience

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

Across multiple clinical trials conducted with XELPROS, the most frequently reported ocular adverse reactions were eye pain/stinging upon instillation and ocular hyperemia, reported in 55% and 41% of patients treated with XELPROS, respectively. Other adverse reactions reported (incidence $\geq 5\%$) were conjunctival hyperemia, eye discharge, growth of eyelashes, and eyelash thickening. Less than 1% of patients discontinued therapy because of intolerance to the eye pain/stinging or to the ocular hyperemia.

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USE IN SPECIFIC POPULATIONS

Pregnancy

Pregnancy Category C

Reproduction studies have been performed in rats and rabbits. In rabbits, an incidence of 4 of 16 dams had no viable fetuses at a dose that was approximately 80 times the maximum human dose, and the highest nonembryocidal dose in rabbits was approximately 15 times the maximum human dose. There are no adequate and well-controlled studies in pregnant women. XELPROS should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Nursing Mothers

It is not known whether latanoprost or its metabolites are excreted in human milk. Because many drugs are excreted in human milk, caution should be exercised when XELPROS is administered to a nursing woman.

Pediatric Use

Safety and effectiveness in pediatric patients have not been established.

Geriatric Use

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

PATIENT COUNSELING INFORMATION

Potential for Pigmentation

Advise patients about the potential for increased brown pigmentation of the iris, which may be permanent. Patients should also be informed about the possibility of eyelid skin darkening, which may be reversible after discontinuation of XELPROS.

Potential for Eyelash Changes

Inform patients of the possibility of eyelash and vellus hair changes in the treated eye during treatment with XELPROS. These changes may result in a disparity between eyes in length, thickness, pigmentation, number of eyelashes or vellus hairs, and/or direction of eyelash growth. Eyelash changes are usually reversible upon discontinuation of treatment.

Handling the Container

Instruct patients to avoid allowing the tip of the dispensing container to contact the eye or surrounding structures because this could cause the tip to become contaminated by common bacteria known to cause ocular infections. Serious damage to the eye and subsequent loss of vision may result from using contaminated emulsions.

When to Seek Physician Advice

Advise patients that if they develop an intercurrent ocular condition (eg, trauma or infection) or have ocular surgery, or develop any ocular reactions, particularly conjunctivitis and eyelid reactions, they should immediately seek their physician's advice concerning the continued use of the multiple-dose container.

Use with Contact Lenses

Advise patients that contact lenses should be removed prior to administration of the emulsion. Lenses may be reinserted 15 minutes following administration of XELPROS.

Use with Other Ophthalmic Drugs

Advise patients that if more than one topical ophthalmic drug is being used, the drugs should be administered at least 5 minutes apart.

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Special Report)

PIONEERING RESEARCH IN

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ADVANCES CONTINUE TO PROGRESS FOR THE DIAGNOSIS AND TREATMENT OF METASTATIC UVEAL MELANOMA

OPTIONS GIVE 1-2 PUNCH TO METASTATIC UVEAL MELANOMA

Combining RAF/MEK signaling pathway inhibitor with FAK inhibitor raises bar

By Lynda Charters; Reviewed by Justine S. Paradis, PhD

The results of a preclinical study indicate there is hope for an effective treatment for the GNAQ-driven metastatic uveal melanoma, an aggressive form of the disease.

The treatment relies on 2 components, the MEK inhibitor trametinib or the second generation RAF/MEK inhibitor VS-6766 (Verastem Oncology) combined with defactinib, a focal adhesion kinase (FAK) inhibitor (Verastem Oncology), that work better together than apart for controlling uveal melanoma.



Paradis

The importance of this potential treatment is underscored by the fact that uveal melanoma is the most frequently occurring ocular cancer in adults, and it becomes metastatic in 50% of patients in whom it develops. The survival rate currently is 2 years, with only 8% surviving following metastasis to the liver.

“To date there is no effective treatment for metastatic uveal melanoma, and there is an urgent need to identify novel precision therapies for advanced and metastatic uveal melanoma patients,” according to Justine S. Paradis, PhD, a postdoctoral fellow at the Moores Cancer Center at the University of California San Diego.

HOW THE TREATMENT WORKS

Trametinib is an inhibitor of MEK kinase activity, and VS-6766 is a second-generation RAF/MEK inhibitor blocking both the MEK kinase activity and the ability of RAF to phosphorylate MEK. The investigators explained that VS-6766 blocks MEK signaling without the compensatory activation of MEK, which differs from how other inhibitors work.

Defactinib (VS-6063) is an oral small-molecule inhibitor of FAK and PYK2 that is being evaluated as a

potential combination therapy for various solid tumors.

The combination of the 2 inhibitors induces apoptosis of the uveal melanoma cells, which in turn leads to rapid tumor regression in the uveal melanoma xenografts. When the 2 agents were used alone, the tumor growth was inhibited, but the size of the tumors did not shrink. In addition, this combination approach also decreased the tumor burden in models of uveal melanoma liver metastasis.

The investigators described that FAK and MEK inhibition combined showed “synergistic cytotoxic effects” in metastatic uveal melanoma cells.

WHAT THEY DID

The investigators used the combination of the MEK and FAK inhibitors in a xenograft mouse model in which the animals were treated for 20 days and found that the tumor volume decreased when the 2 were used together. In contrast, when used alone, the inhibitors only stabilized the tumor size, with

a limited apoptotic response.

In a mouse model of liver metastasis, in which the animals were treated for 21 days, the investigators reported that the metastatic burden in the animals was reduced. The combination of the 2, they reported, very importantly “nearly eliminated all metastatic lesions.”

The team is evaluating residual disease and tumor burden progression after the treatments were stopped.

J. Silvio Gutkind, PhD, distinguished professor of pharmacology and associate director for Basic Science at Moores Cancer Center at the University of California San Diego, and senior investigator of the study, said results should lead to human trials.

“The study identified and reinforced FAK as a viable pathway to inhibit downstream from the GNAQ pathway, which is constitutively active in uveal melanoma,” he said. “We observed that cotargeting of FAK and RAF/MEK signaling led to tumor collapse in uveal melanoma xenograft and liver metastasis models in vivo.”

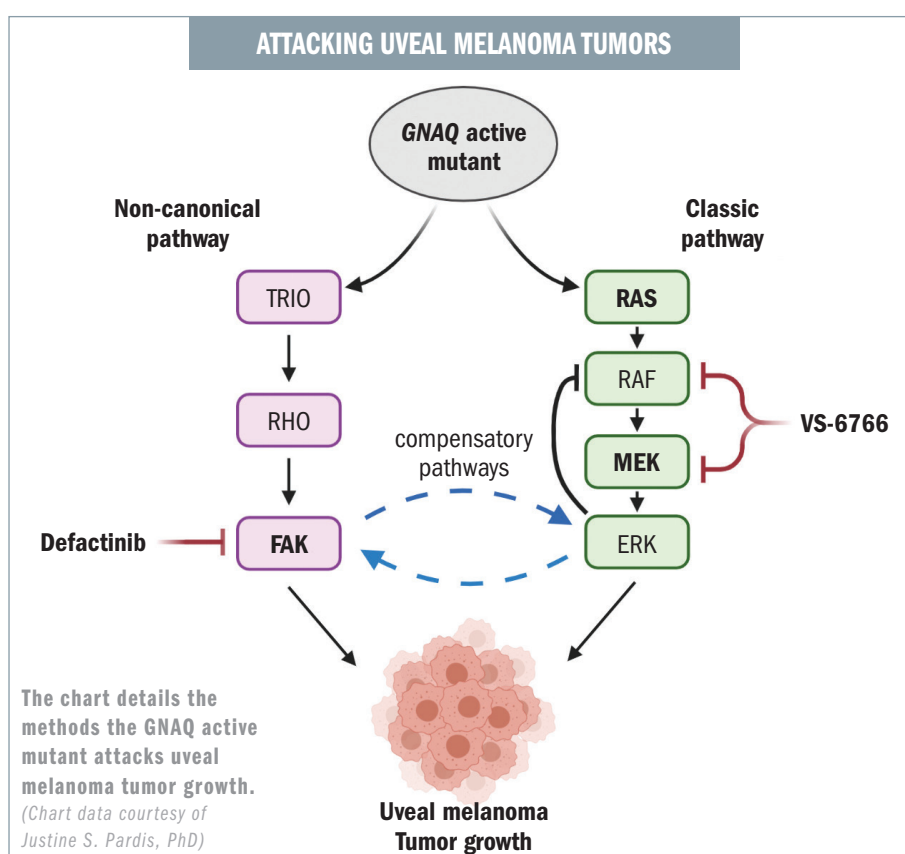
Pharmacological inhibition of FAK and MEK inhibited the growth of uveal melanoma cells and had cytotoxic effects leading to tumor collapse in uveal melanoma xenograft and liver metastasis models in vivo.

The results emphasized the importance of cotargeting with FAK and RAF/MEK to provide a new network-based precision therapeutic strategy.

The signal-transduction-based precision therapy data support clinical testing of the combination inhibition in metastatic uveal melanoma.

VS-6766 and defactinib are also being studied clinically to treat low-grade serous ovarian and KRAS mutant non-small cell lung cancers and colorectal cancer.

A phase 2 study of VS-6766 and defactinib in uveal melanoma is expected to commence in late 2020. ■



JUSTINE S. PARADIS, PHD

E: jparadis@ucsd.edu

Paradis has no financial interest in this subject matter.

gene therapy

Targeting AMD patient treatment burden

Intravitreal gene therapy continues to be well tolerated and shows robust efficacy

By **Lynda Charters**; Reviewed by **Charles Wykoff, MD, PhD**

The results achieved with intravitreally injected gene therapy for neovascular age-related macular degeneration (AMD) with ADVM-022 (Adverum Biotechnologies) indicate that the treatment is well tolerated and exhibited robust efficacy and durability in the patient population.

ADVM-022 may help solve the significant treatment burden associated with treatment of neovascular AMD that includes frequent trips by patients to undergo intravitreal injections of various anti-vascular endothelial growth factor (VEGF) agents.

“Perhaps most important is the finding that the frequency needed to achieve optimal outcomes is often not realized in the real world,” noted Charles Wykoff, MD, PhD, who is in private practice in Houston, Texas.

This adeno-associated virus (AAV) gene therapy vector comprises an AAV7m8 capsid, a promoter to achieve protein expression, and a codon-optimized cDNA to drive aflibercept (Eylea, Regeneron Pharmaceuticals) that is delivered to the intravitreal space. Two preclinical studies have demonstrated the long-term protein expression in nonhuman primates that extended up to 21 and 30 months after 1 intravitreal injection.

Wykoff suggested that 1 solution to this under-treatment is establishment of an intraocular biofactory that produces an anti-VEGF agent using gene therapy to deliver long-term efficacy, which is what ADVM-022 was designed to do.

RESULTS

Wykoff reported the updated 24-week results on behalf of the OPTIC investigators. OPTIC (NCT03748784) is a phase 1, 2-year multicenter dose-ranging study of ADVM-022 in neovascular AMD with the primary assessment of safety and tolerability of 1 intravitreal injection. Patients in cohorts 1 and 2 received oral steroid prophylaxis to prevent ocular inflammation and respective doses of ADVM-022 of 6×10^{11} vg/eye and 2×10^{11} vg/eye. Patients in cohorts 3 and 4 received a topical steroid for prophylaxis; cohorts 3 and 4 were treated with doses of ADVM-022 of 2×10^{11} vg/eye and 6×10^{11} vg/eye. Patients could receive rescue therapy, if needed.

The durations of the follow-up periods differed among cohorts: 6 patients in cohort 1 were followed for a median of 60 weeks, 6 patients in cohort 2 a median of 36 weeks, and cohort 3 a median of 20 weeks.

The current evaluation, which extended to April 1, 2020, showed no serious safety issues at 24 weeks. Low-grade inflammation associated with treatment was seen often and responded to topical steroids. The patients in cohort 3 had fewer adverse events compared with the others, he reported.

The inflammatory events in the 6 patients in cohorts 1 and 2 were low grade and responsive to oral steroids; 2 patients in both cohorts remained on topical steroids for extended periods. In cohort 3, treated with topical prophylaxis, 1 of the 6 patients continues steroid treatment at week 20; 3 patients were still taking the initial prophylactic steroid.

Regarding the best-corrected visual acuity (BCVA), the mean change in cohort 1 was -2.7 letters over a median of 60 weeks and the central subfield thickness (CST) decreased by 26.2 microns; no patients needed rescue therapy. In cohort 2, the mean BCVA change was -2.8 letters over 36 weeks and the CST improved by 40.8 μ ; 2 of the 6 patients received rescue therapy. In cohort 3, the mean change in the BCVA was an increase of 6.8 letters over 20 weeks and the CST improved by 137.8 microns; 1 of the 5 patients who completed 20 weeks received rescue therapy.

Subjects in cohorts 1, 2, and 3 had been treated with frequent anti-VEGF injections before treatment with ADVM-022. Only 3 patients received rescue injections.

The study demonstrates that ADVM-022 is well tolerated and shows robust efficacy; the low-grade inflammation that develops frequently is responsive to steroid eye drops, and there is no need for oral baseline prophylaxis. It further shows that 1 office-based dose of ADVM-022 could reduce the anti-VEGF patient burden in neovascular AMD.

The ADVM-002 Infinity double-masked phase 2 study of recent-onset diabetic macular edema is underway with patients randomly assigned to 1 intravitreal injection of the treatment compared with 1 aflibercept injection. Patients' conditions will be followed. ■

CHARLES WYKOFF, MD, PHD

E: ccwmd@houstonretina.com

Wykoff reported performing research for and serving as a consultant to Adverum Biotechnologies.

FDA grants fourth ODD for treatment of gene mutation-associated retinal diseases

The designation targets retinitis pigmentosa caused by *PDE6B* mutations

By **David Hutton**

The FDA has granted the fourth Orphan Drug Designation (ODD) for a novel gene therapy product candidate (OCU400, Ocugen Inc.) in the treatment of *PDE6B* gene mutation-associated retinal diseases.

This designation targets retinitis pigmentosa (RP) caused by *PDE6B* mutations. RP that is a result of this mutation leads to blindness by midlife, and is characterized by the progressive loss of photoreceptors—with or without the loss of retinal pigment epithelium cells.

At least one mutation in the *PDE6B* gene has been found to cause autosomal dominant congenital stationary night blindness, which is characterized by the inability to see in low light.

According to a press release, Ocugen's modifier gene therapy platform allows ophthalmologists to address multiple diseases with a single product.

The novel gene therapy product candidate has the potential to be broadly effective in restoring retinal integrity and function across a range of genetically diverse inherited retinal diseases.

It consists of a functional copy of a nuclear hormone

receptor (NHR) gene, *NR2E3*, delivered to target cells in the retina using an adeno-associated viral vector.

As a potent modifier gene, expression of *NR2E3* within the retina may help reset retinal homeostasis and potentially offer longer benefit, stabilizing cells and rescuing photoreceptor degeneration and vision loss.

In pre-clinical studies, OCU400 has demonstrated improved vision signals in the retina where electroretinogram response reveals rescue under both scotopic (dim-lit) as well as photopic (well-lit) conditions.

According to the release, Ocugen maintains that

Harnessing regeneration of retinal tissues: An option almost within reach

This ability would unlock possibilities for repairing tissue damaged by disease

By Lynda Charters; Reviewed by Russell N. Van Gelder, MD, PhD

NEURONAL CELL REPLACEMENT therapies remain a challenge in retinal diseases. Some fish and salamanders have the innate ability to regenerate retinal tissue after injuries and, as Russell N. Van Gelder, MD, PhD, pointed out, if researchers could harness this ability in humans, the possibilities would be great for repairing or replacing damaged tissue in a wide variety of retinal diseases. Stem cells are the key to cell replacement therapies.



Van Gelder

“Stem cells are cells that have not terminally differentiated and still have the potential to become many types of terminal cells,” said Van Gelder, from the Department of Ophthalmology at the University of

Washington in Seattle. “We all started as embryonic stem cells in the earliest phases of development.”

Van Gelder went on to explain that there are now methods to create equivalently totipotent stem cells from individual induced progenitor stem cells derived from an individual’s blood or epithelial cells.

“The overarching goal is to create a cell type that needs replacement from a stem cell precursor,” he said.

A major achievement in this quest for regenerative ability occurred in 2014 when an entire eye cup was grown from progenitor stem cells.

Van Gelder also described a study¹ in which green fluorescent protein-labeled retinal precursors derived

from embryonic stem cells were transplanted into the subretinal space of macaques. Three months after the procedure, the researchers demonstrated that the bolus of cells persisted and had outgrowth of axons that were seen going to the optic nerve and on to the brain.

“This result establishes the validity of a stem cell-based approach for doing regenerative medicine in primates,” he said.

REPLACEMENT THERAPY HURDLES

As of now, however, no stem cell-based replacement treatment has received FDA approval. The problems preventing establishment of a treatment have been technical in nature and include correct cellular differentiation as well as generating adequate numbers of cells for large transplantation experiments, establishing correct cell polarity and connectivity, and ensuring the safety of these approaches regarding tumor or hamartoma formation, Van Gelder explained.

Managing inflammatory responses is a problem after cell transplantation. He cited a Japanese study² of individual progenitor cell-derived retinal progenitor cells transplanted subretinally in monkey models.

“Even with an immune HLA-matched donor, there was still a marked inflammatory response at the site of the transplantation,” Van Gelder said. “This and other inflammatory responses will have to be managed for cell transplantation to be successful.”

There are regulatory hurdles to clear. The FDA Center for Biologics Evaluation and Research regulates cellular therapy products, human gene therapy products, and certain devices related to cell and gene therapy.

Van Gelder recalled the well-publicized case of transplantation of fat-derived mesenchymal cells into patients’ eyes, resulting in loss of vision bilaterally. He pointed out that it is important to temper patient expectations regarding these therapies and to ensure that the work is being done with the highest degree of ethical integrity.

“While great progress has been made in this field, significant barriers remain to the successful adoption in the clinical setting in the coming years,” Van Gelder concluded. “The barriers to cell replacement should be overcome.” ■

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RUSSELL VAN GELDER, MD, PHD

E: russvg@uw.edu

Van Gelder has no financial interests in this subject matter. He serves on the advisory committee for the National Eye Institute Audacious Goals Initiative.

targeting multiple diseases with one product could also offer a smoother regulatory pathway and the ability to recover development costs over multiple therapeutic indications.

Following up on a recent announcement of an ODD for RHO mutation-associated retinal degeneration and previous ODDs for both *NR2E3* and *CEP290* mutation-associated retinal degeneration, the ODD for *PDE6B* gene mutation-associated retinal degeneration continues to support Ocugen’s modifier gene therapy platform’s potential to treat multiple blindness diseases with a single product.

RP is a group of heterogenic inherited retinal diseases associated with over 150 gene mutations, affecting over 1.5 million individuals worldwide.

In addition, ~40% of RP patients cannot be genetically diagnosed, confounding the ability to develop

personalized RP therapies.

OCU400 is a novel gene therapy product candidate with the potential to be broadly effective in restoring retinal integrity and function across a range of genetically diverse inherited retinal diseases.

Traditional gene therapy or gene editing approaches may require more than 150 products to rescue these patients from vision loss.

As a single product candidate, OCU400 has the potential to address broad-spectrum RP.

Carl D. Regillo, MD, FACS, has served as a principal investigator of numerous major clinical trials developing new medical and surgical treatments for retinal disorders.

He is a member of Ocugen’s Retina Scientific Advisory Board and is a professor of ophthalmology at the Sidney Kimmel Medical College at Thomas

Jefferson University, chief of the Retina Service at Wills Eye Hospital and founder and former director of the Wills Eye Clinical Retina Research Unit in Philadelphia.

“I am very encouraged by the potential for OCU400 given the uniqueness of Ocugen’s Modifier Gene Therapy Platform and the fact that FDA has issued four ODDs for this product,” Regillo said in a statement. “I look forward to Ocugen commencing clinical trials for OCU400 next year and the potential of helping patients by restoring retinal integrity and function across a range of genetically diverse inherited retinal diseases including broad-spectrum RP.”

Ocugen is planning to initiate two parallel phase I/II clinical trials next year targeting two unique IRDs. ■

device technology

Robotics allow surgeons to perform the seemingly impossible

Automated assistance controls tremor, reduces fatigue, and helps avoid inadvertent injury

By Lynda Charters; Reviewed by Richard B. Rosen, MD, DSC (HON)

Medical robots are revolutionizing medicine. Their applications can facilitate superhuman dexterity, enabling the performance of surgical steps otherwise considered impossible and automating repetitive tasks.

The benefits include high positional stability, precision, and accuracy along the x-, y-, and z-axes, removal of time constraints on subretinal and intraretinal drug delivery, and reduction of surgeon fatigue, according to Richard B. Rosen, MD, DSC(HON), of the New York Eye and Ear Infirmary of Mount Sinai in New York, New York.



Rosen

The robotic approaches being developed in ophthalmology include assistive handheld devices, such as the steady-hand stabilizer (Johns Hopkins Group); a comanipulation strategy to stabilize the surgeon's movement (University of California, Los Angeles); and telemanipulation, which uses a separate robotic manipulator operated by the surgeon (Eindhoven Group).

Rosen presented study findings that showed the advantages of robotics over manual procedures during retinal surgery. The study was conducted by his associates, Reza Ladha, MD, of the Department of Ophthalmology at the Centre Hospitalier Universitaire (CHU) Saint-Pierre and CHU Brugmann in Brussels, Belgium, and Marc D. de Smet, MD, of Microinvasive Ocular Surgery Center in Lausanne, Switzerland, and an employee of Preceyes in Eindhoven, the Netherlands. The investigators used the Preceyes surgical robot with Zeiss Microscopy with integrated optical coherence tomography.

The robot filters tremors to under 10 μm , which is 10 times better than the human performance. The arm of the robot permits intuitive motion with positional stability and memory and allows exchange of instruments, Rosen said.

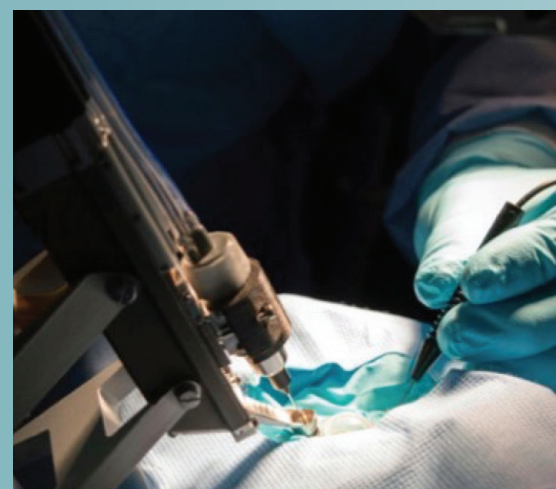
When the investigators compared the accuracy and precision of the robotic and manual performances, improvement with the robot was markedly greater. Rosen showed that the robot improves precision and accuracy by at least an order of magnitude. The manual static task performed by an experienced surgeon with minimal tremors of about 100 μm , with additional microjerks reaching 200 μm , became more intense the longer the surgeon remained static.

Other research also supports the use of robotics in ophthalmology. In an Eyesi simulator experiment, retinal injuries were decreased substantially using the robot compared with manual peeling.

PRECEYES Surgical Robot



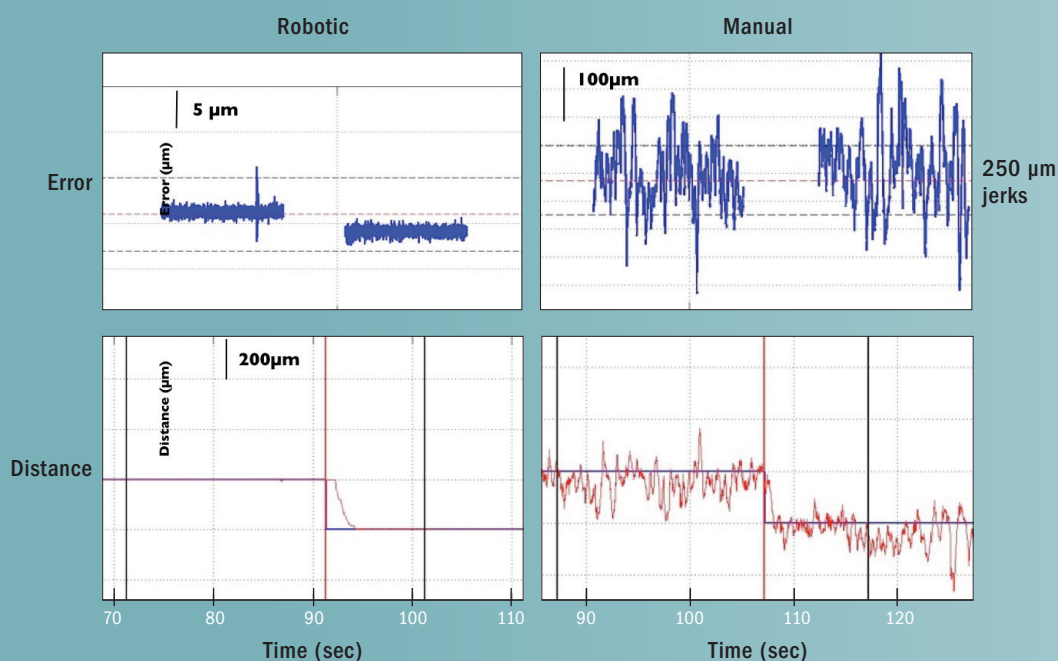
Manipulator External to Surgical Field



Surgeon Using Robotic Arm along with Manual Light probe

Robotic devices can help surgeons perform surgical steps considered impossible.

Robotic Tremor Reduction in Stationary Tasks



Charts detail tremors with human performance and with robots.

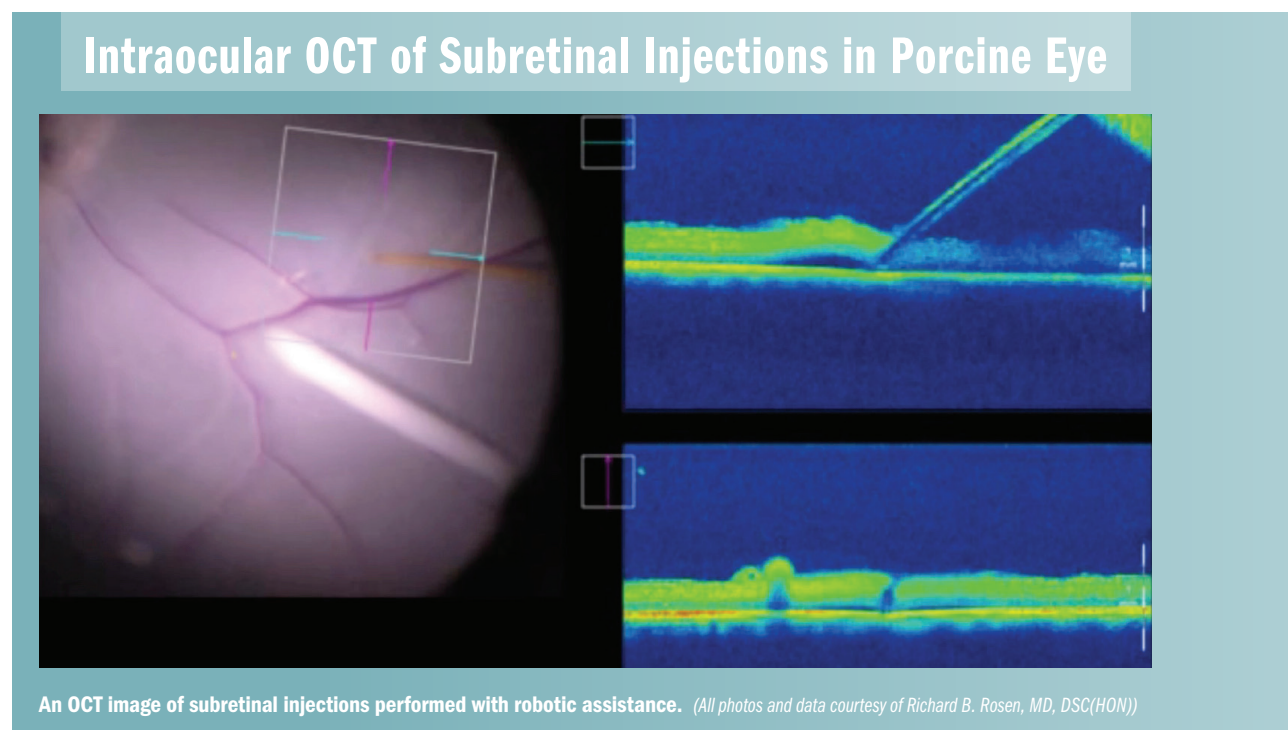
In addition, a simulation study looked at manual and robot bleb creation, with the goal of elevating a retinal membrane and avoiding reflux. The manual injection created a great deal of reflux and an enlarging bubble of fluid on the membrane's surface compared with the robotic injection, which formed no bubble.

The investigators also performed subretinal injections in a porcine eye manually and with robotic assistance. Rosen reported a 40% success rate of bleb creation with the manual procedure, with leakage in all cases during injection and when the needle was withdrawn; all cases were considered failures. In contrast, the robotic-assisted technique had a 100% success rate in bleb creation; there was leakage in 20% of cases when the needle was withdrawn, considered an 80% success rate.

"Bleb generation with robotic assistance was more precise and more consistent. Robotic assistance prevented motion and leakage during injection," Rosen said. "Static manual subretinal positioning showed repeated contact with the underlying retinal pigment epithelium."

Based on the above results, the investigators noted that robotic assistance removes the time constraints of delivery and allows high-precision positioning for controlled subretinal drug delivery.

"Robotic assistance controls tremor, reduces fatigue, and helps avoid inadvertent injury in tight spaces,"



An OCT image of subretinal injections performed with robotic assistance. (All photos and data courtesy of Richard B. Rosen, MD, DSC(HON))

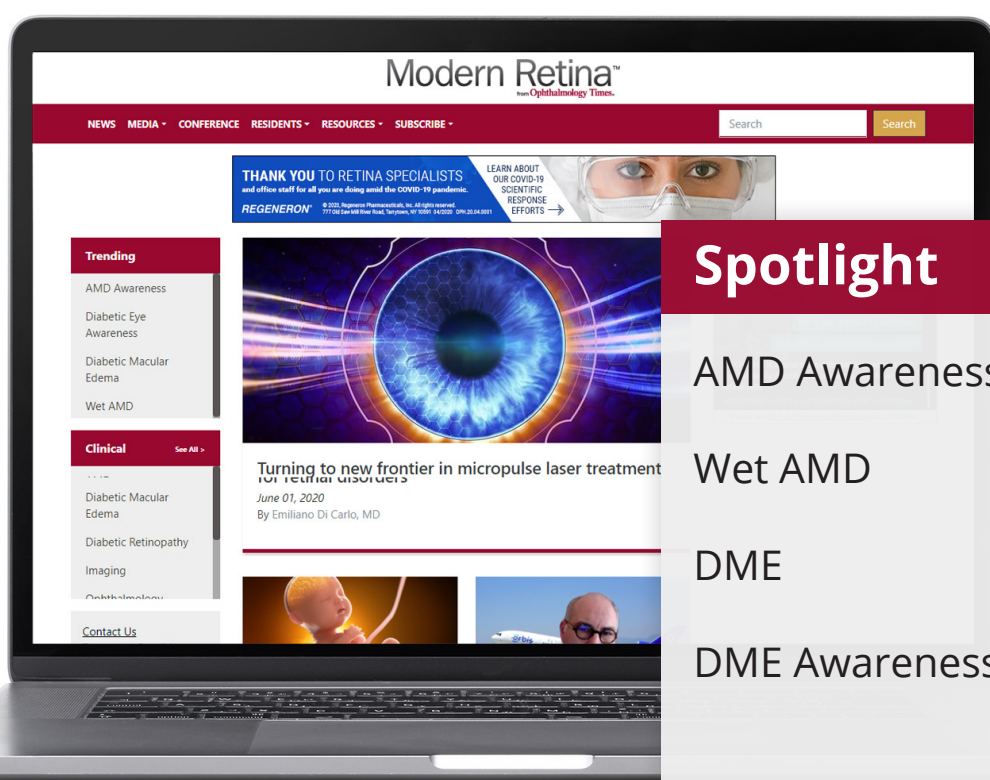
they concluded. "Robotic-assisted ocular surgery shows promise for advancing the surgeon's ability to perform more complex maneuvers necessary for the next generation of retinal interventions." ■

RICHARD B. ROSEN, MD, DSC(HON)

E: RRosen@nyee.edu

Rosen has no financial interest in this subject matter.

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AI algorithms: a work in progress

Dilation may be an important step to reduce the rate of ungradable images

By Lynda Charters; Reviewed by Aaron Y. Lee, MD, MSCI

Artificial intelligence (AI) screening systems of diabetic retinopathy (DR) are not all created equal, and as a result, their performances differ.

Researchers compared several AI screening systems using the US Department of Veterans Affairs (VA) screening program. The results highlight the need for independent validation studies before clinical use, according to Aaron Y. Lee, MD, MSCI, from the University of Washington in Seattle.

THE STUDY

Initially, 23 companies were invited to participate in the masked study. Several agreed to participate and contributed AI models: ADCIS (Advanced Concepts in Imaging Software), Airdoc, Eyenuk, Ret-

ina-AI Health, and Retmarker.

The investigators extracted data from the VA teleretinal screening program for VA Puget Sound in Seattle and the Atlanta VA Health Care System



“The most important finding: the performance of the sensitivity of the various algorithms with different severities of retinopathy.”

—Aaron Y. Lee, MD, MSCI

in Georgia, including the images and the original VA teleretinal grades. This created a data set of 311,604 images from 23,724 patients with diabetes for the full data set and a subset of about 7000 images that was set aside for arbitration. All the patients had type 2 diabetes and no previous diagnoses of the disease. The 7 algorithms were run, and the output indicated whether the patients should be referred. The performances were then compared with the VA teleretinal grades. In the subset used for arbitration, 2 ophthalmologists graded the images independently and a retinal specialist performed masked arbitration, according to Lee.

A few baseline differences were seen between the Atlanta and Seattle groups. Investigators found a 10-fold difference in the proliferative DR (PDR) rate between the 2 locations. In Atlanta, dilatation is a routine practice, but, Lee noted, that is not the case in Seattle. This resulted in a large discrepancy in the rate of ungradable images between the 2 sites.

The algorithm output, he explained, was set for no DR versus the presence of any degree of DR because of the VA's practice pattern.

RESULTS

Analysis of the full data sets from both sites showed an overall high negative predictive value and a low positive predictive value. In the arbitrated data set, the VA teleretinal grader was compared directly with the AI models: Algorithm A had

a significantly lower sensitivity but higher specificity, B had lower sensitivity and specificity, C and D had the same sensitivity but lower specificity, E and F had significantly higher sensitivity and

lower specificity, and G could not be differentiated from the VA grader.

Lee explained what he considers to be the most important finding: the performance of the sensitivity of the various algorithms with different severities of retinopathy.

“The VA grader demonstrated 100% sensitivity for moderate and severe non-PDR [NPDR] and PDR. Algorithms E, F, and G were statistically similar to the VA grader for moderate NPDR or higher, and these algorithms were carried forward for future analysis,” he said.

The investigators simulated a 2-stage screening system to measure the amount of labor savings in a cost analysis if the 3 algorithms were implemented within the VA. The cost of an ophthalmologist reading the images would be about \$15 per encounter.

A limitation of this study is that some analyses, including cost, are applicable to the VA setting.

According to Lee, the investigators found that dilation may be important to reduce the rate of ungradable images.

“The algorithms varied tremendously in performance despite having regulatory approval and/or having been clinically deployed somewhere,” he concluded. “It is important to understand that the AI models in the context of the underlying disease prevalence in order to understand the negative and positive predictive values. We believe that external, independent validation with real-world imaging is crucial before deployment, even after algorithms receive regulatory approval.” ■

AARON Y. LEE, MD, MSCI

E: leeay@uw.edu

Lee is a consultant to Genentech, Verana Health, and Topcon.

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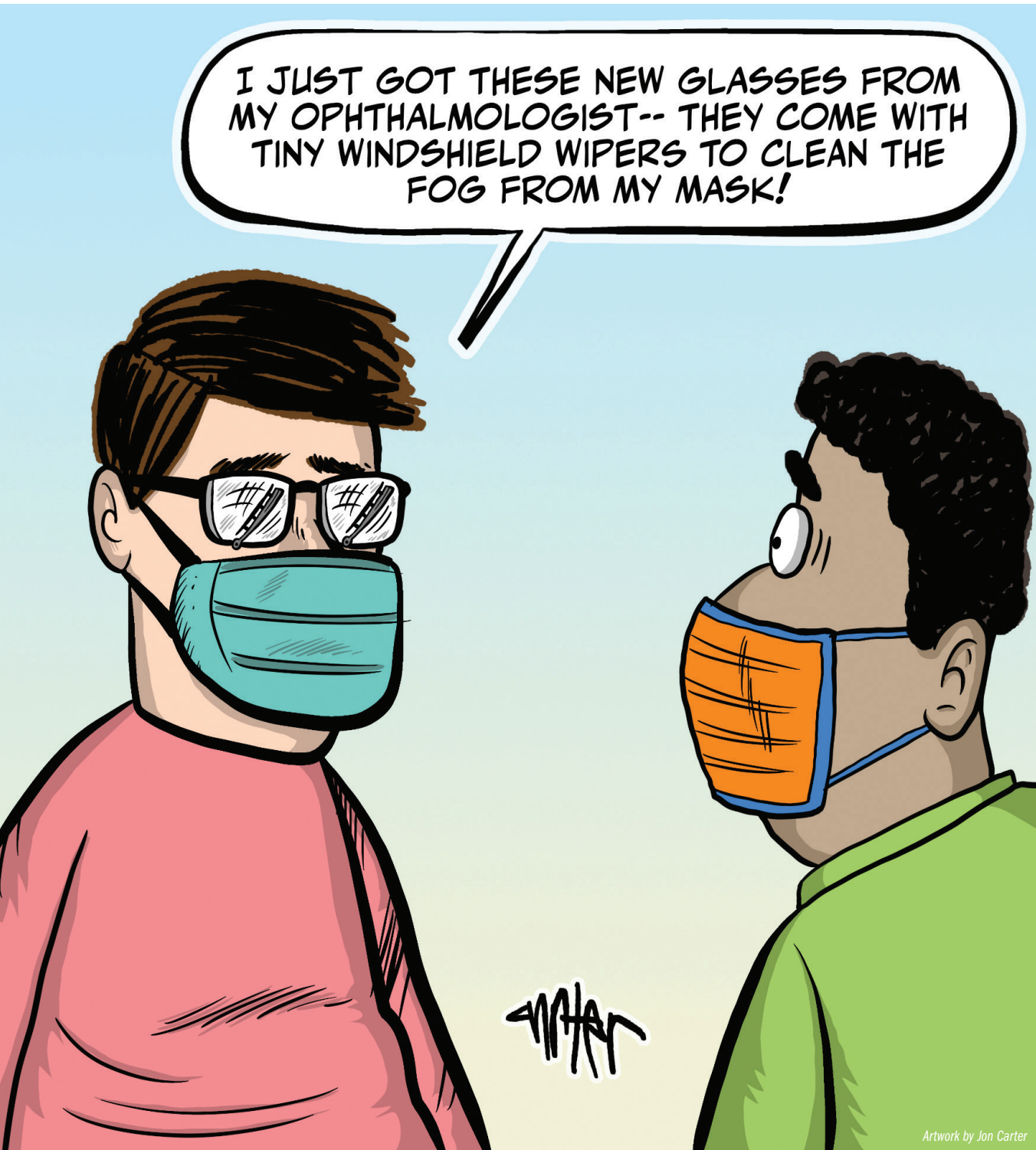
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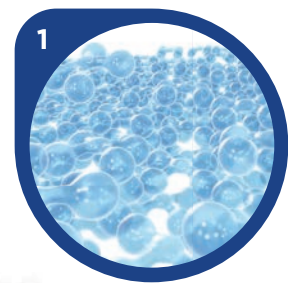
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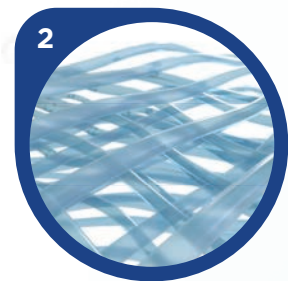
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