EDITORIAL **KEEPING TO SCHEDULE** SOMETIMES, A DELAY IS THE RIGHT THING TO DO PAGE 7

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Ophthalmology Times®

CUTTING-EDGE ADVANCEMENTS

JANUARY 2021 VOL. 46, NO. 1

DEVICE TECHNOLOGY

Pearls for selecting a syringe for intravitreal injection

Investigators outline the pros and cons of different products

By Cheryl Guttman Krader, BS Pharm; Reviewed by Gustavo B. Melo, MD, PhD

THE IDEAL SYRINGE for administering intravitreal injections does not exist. With improved awareness of the drawbacks of existing devices and the characteristics desired for intravitreal use, however, syringe manufacturers are stepping up to design products that will help maximize the safety and efficiency of intravitreal injection, said Gustavo B. Melo, MD, PhD.

"Retina specialists are well aware that intravitreal injection can lead to the presence of silicone droplets in the vitreous. The droplets come from the syringes used for injection because most are manufactured with silicone oil to allow for better glide of the plunger. In addition, almost all needles are dipped in a silicone oil bath to coat the outer surface to enable tissue penetration," said Melo, an associate researcher at the Federal University of São Paulo and the head of the ophthalmology residency at Sergipe Eye Hospital, Brazil.

Continues on page 25 : ***Syringe***

In the 2018 American Society of Retina Specialists PAT survey, **5%** of US retina specialists said they had done vitrectomy for symptomatic droplets and **2%** have patients seeking legal action for their floaters.

Syringes from different models and brands outlined throughout the text. *(Photo courtesy of Gustavo B. Melo, MD, PhD)*

THERAPEUTICS

ZEROING IN ON DRY EYE TREATMENT FOR PATIENTS WITH CATARACTS

Study supports preoperative ocular surface optimization with artificial tears

By Cheryl Guttman Krader, BS Pharm

EVEN PATIENTS WITHOUT pre-existing dry eye disease (DED) who are scheduled for cataract surgery can benefit from perioperative use of artificial tears, particularly by starting the treatment preoperatively, according to the findings of a retrospective study conducted by Italian investigators.

The researchers analyzed data from the Standard Patient Evaluation of Eye Dryness (SPEED) questionnaire, tear breakup time (TBUT) measurements, and corneal fluorescein staining (CFS) in 3 groups of patients. The groups comprised those who did not use any artificial tears perioperatively (n = 140); patients who began to instill artificial tears 1 week preoperatively and continued for 2 months postoperatively (n = 139); and a cohort that used artificial tears postoperatively for 2 months (n = 140). The DED-related evaluations were performed preoperatively and at follow-up visits occurring at 1, 4, and 8 weeks after surgery. The artificial tear product was a commercially available lubricant formulation containing hydroxypropyl guar and hyaluronic acid, and all patients were treated with the same perioperative regimen of antibiotic and anti-inflammatory medications.

The results, published in *Clinical Ophthalmology*,[1] showed statistically significant benefits of treatment with the artificial tears for mitigating surgically induced signs and symptoms of DED. Statistically significant differences favoring the group that started using the artificial tears preoperatively compared with the group using the ocular lubricant only after surgery were seen in analyses of SPEED scores and TBUT.

Based on the findings, the investigators concluded that the artificial tears were effective in protecting the ocular surface,

Continues on page 39 : ***Cataract patients***

Issue Highlights

OphthalmologyTimes.com

FIRST AND ONLY
FDA-APPROVED TREATMENT FOR THYROID EYE DISEASE

IT'S TIME FOR A BREAKTHROUGH
IT'S TIME FOR TEPEZZA

INDICATION

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

IMPORTANT SAFETY INFORMATION

Warnings and Precautions

Infusion Reactions: TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Reported infusion reactions have usually been mild or moderate in severity. Signs and symptoms may include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache, and muscular pain. Infusion reactions may occur during an infusion or within 1.5 hours after an infusion. In patients who experience an infusion reaction, consideration should be given to premedicating with an antihistamine, antipyretic, or corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Preexisting Inflammatory Bowel Disease: TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

EXPLORE THE VIRTUAL BOOTH AT
TEPEZZAexperience.com

Visit the interactive virtual booth to test your knowledge of Thyroid Eye Disease (TED), see the breakthrough data for TEPEZZA, and experience TED through a patient's eyes.

Hyperglycemia: Increased blood glucose or hyperglycemia may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be managed with medications for glycemic control, if necessary. Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

Adverse Reactions

The most common adverse reactions (incidence ≥5% and greater than placebo) are muscle spasm, nausea, alopecia, diarrhea, fatigue, hyperglycemia, hearing impairment, dysgeusia, headache, and dry skin.

Please see Brief Summary of Prescribing Information on following page.

HORIZON

TEPEZZA®
teprotumumab-trbw

TEPEZZA™
teprotumumab-trbw

For injection, for intravenous use

Brief Summary - Please see the TEPEZZA package insert for full prescribing information.

INDICATIONS AND USAGE

TEPEZZA is indicated for the treatment of Thyroid Eye Disease.

WARNINGS AND PRECAUTIONS

Infusion Reactions

TEPEZZA may cause infusion reactions. Infusion reactions have been reported in approximately 4% of patients treated with TEPEZZA. Signs and symptoms of infusion-related reactions include transient increases in blood pressure, feeling hot, tachycardia, dyspnea, headache and muscular pain. Infusion reactions may occur during any of the infusions or within 1.5 hours after an infusion. Reported infusion reactions are usually mild or moderate in severity and can usually be successfully managed with corticosteroids and antihistamines. In patients who experience an infusion reaction, consideration should be given to pre-medicating with an antihistamine, antipyretic, corticosteroid and/or administering all subsequent infusions at a slower infusion rate.

Exacerbation of Preexisting Inflammatory Bowel Disease

TEPEZZA may cause an exacerbation of preexisting inflammatory bowel disease (IBD). Monitor patients with IBD for flare of disease. If IBD exacerbation is suspected, consider discontinuation of TEPEZZA.

Hyperglycemia

Hyperglycemia or increased blood glucose may occur in patients treated with TEPEZZA. In clinical trials, 10% of patients (two-thirds of whom had preexisting diabetes or impaired glucose tolerance) experienced hyperglycemia. Hyperglycemic events should be controlled with medications for glycemic control, if necessary.

Monitor patients for elevated blood glucose and symptoms of hyperglycemia while on treatment with TEPEZZA. Patients with preexisting diabetes should be under appropriate glycemic control before receiving TEPEZZA.

ADVERSE REACTIONS

The following clinically significant adverse reactions are described elsewhere in the labeling:

- Infusion Reactions [see Warnings and Precautions]
- Exacerbation of Inflammatory Bowel Disease [see Warnings and Precautions]
- Hyperglycemia [see Warnings and Precautions]

Clinical Trials Experience

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

The safety of TEPEZZA was evaluated in two randomized, double-masked, placebo-controlled clinical studies (Study 1 [NCT:01868997] and Study 2 [NCT:03298867]) consisting of 170 patients with Thyroid Eye Disease (84 received TEPEZZA and 86 received placebo). Patients were treated with TEPEZZA (10 mg/kg for first infusion and 20 mg/kg for the remaining 7 infusions) or placebo given as an intravenous infusion every 3 weeks for a total of 8 infusions. The majority of patients completed 8 infusions (89% of TEPEZZA patients and 93% of placebo patients).

The most common adverse reactions (≥5%) that occurred at greater incidence in the TEPEZZA group than in the control group during the treatment period of Studies 1 and 2 are summarized in Table 1.

Table 1. Adverse Reactions Occurring in 5% or More of Patients Treated with TEPEZZA and Greater Incidence than Placebo

Adverse Reactions	TEPEZZA N=84 N (%)	Placebo N=86 N (%)
Muscle spasms	21 (25%)	6 (7%)
Nausea	14 (17%)	8 (9%)
Alopecia	11 (13%)	7 (8%)
Diarrhea	10 (12%)	7 (8%)
Fatigue[a]	10 (12%)	6 (7%)
Hyperglycemia[b]	8 (10%)	1 (1%)
Hearing impairment[c]	8 (10%)	0
Dysgeusia	7 (8%)	0
Headache	7 (8%)	6 (7%)
Dry skin	7 (8%)	0

a - Fatigue includes asthenia
b - Hyperglycemia includes blood glucose increase
c - Hearing impairment (includes deafness, eustachian tube dysfunction, hyperacusis, hypoacusis and autophony)

Immunogenicity

As with all therapeutic proteins, there is potential for immunogenicity. The detection of antibody formation is highly dependent on the sensitivity and specificity of the assay.

In a placebo-controlled study with TEPEZZA, 1 of 42 patients treated with placebo had detectable levels of antidrug antibodies in serum. In the same study, none of the 41 patients treated with TEPEZZA had detectable levels of antidrug antibodies in serum.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Based on findings in animals and its mechanism of action inhibiting insulin-like growth factor-1 receptor (IGF-1R), TEPEZZA may cause fetal harm when administered to a pregnant woman. Adequate and well-controlled studies with TEPEZZA have not been conducted in pregnant women. There is insufficient data with TEPEZZA use in pregnant women to inform any drug associated risks for adverse developmental outcomes. In utero teprotumumab exposure in cynomolgus monkeys dosed once weekly with teprotumumab throughout pregnancy resulted in external and skeletal abnormalities. Teprotumumab exposure may lead to an increase in fetal loss [see Data]. Therefore, TEPEZZA should not be used in pregnancy, and appropriate forms of contraception should be implemented prior to initiation, during treatment and for 6 months following the last dose of TEPEZZA.

If the patient becomes pregnant during treatment, TEPEZZA should be discontinued and the patient advised of the potential risk to the fetus.

The background rate of major birth defects and miscarriage is unknown for the indicated population. In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies are 2-4% and 15-20%, respectively.

Data

Animal Data

In an abridged pilot embryofetal development study, seven pregnant cynomolgus monkeys were dosed intravenously at one dose level of teprotumumab, 75 mg/kg (2.8-fold the maximum recommended human dose [MRHD] based on AUC) once weekly from gestation day 20 through the end of gestation. The incidence of abortion was higher for the teprotumumab treated group compared to the control group. Teprotumumab caused decreased fetal growth during pregnancy, decreased fetal size and weight at caesarean section, decreased placental weight and size, and decreased amniotic fluid volume. Multiple external and skeletal abnormalities were observed in each exposed fetus, including: misshapen cranium, closely set eyes, micrognathia, pointing and narrowing of the nose, and ossification abnormalities of skull bones, sternebrae, carpals, tarsals and teeth. The test dose, 75 mg/kg of teprotumumab, was the maternal no observed adverse effect level (NOAEL).

Based on mechanism of action inhibiting IGF-1R, postnatal exposure to teprotumumab may cause harm.

Lactation

Risk Summary

There is no information regarding the presence of TEPEZZA in human milk, the effects on the breastfed infant or the effects on milk production.

Females and Males of Reproductive Potential

Contraception

Females

Based on its mechanism of action inhibiting IGF-1R, TEPEZZA may cause fetal harm when administered to a pregnant woman (see Use in Specific Populations). Advise females of reproductive potential to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Pediatric Use

Safety and effectiveness have not been established in pediatric patients.

Geriatric Use

Of the 171 patients in the two randomized trials, 15% were 65 years of age or older; the number of patients 65 years or older was similar between treatment groups. No overall differences in efficacy or safety were observed between patients 65 years or older and younger patients (less than 65 years of age).

OVERDOSAGE

No information is available for patients who have received an overdosage.

PATIENT COUNSELING INFORMATION

Embryo-Fetal Toxicity

Advise females of reproductive potential that TEPEZZA can cause harm to a fetus and to inform their healthcare provider of a known or suspected pregnancy.

Educate and counsel females of reproductive potential about the need to use effective contraception prior to initiation, during treatment with TEPEZZA and for 6 months after the last dose of TEPEZZA.

Infusion-Related Reactions

Advise patients that TEPEZZA may cause infusion reactions that can occur at any time. Instruct patients to recognize the signs and symptoms of infusion reaction and to contact their healthcare provider immediately for signs or symptoms of potential infusion-related reactions.

Exacerbation of Inflammatory Bowel Disease

Advise patients on the risk of inflammatory bowel disease (IBD) and to seek medical advice immediately if they experience diarrhea, with or without blood or rectal bleeding, associated with abdominal pain or cramping/colic, urgency, tenesmus or incontinence.

Hyperglycemia

Advise patients on the risk of hyperglycemia and, if diabetic, discuss with healthcare provider to adjust glycemic control medications as appropriate. Encourage compliance with glycemic control.

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HORIZON

A new year offers new hope

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

THE BALL HAS dropped on 2021, bringing with it all of the hopes of a brand new year. Just a year ago, we brimmed with hope, viewing 2020 as "the year of the eye." But the coronavirus found its way to our shores, and life was dramatically changed, possibly forever.

While pharmaceutical companies are developing vaccines for the virus at a record pace, the coronavirus disease 2019 (COVID-19) pandemic continues to impact in-person meetings. We learned recently that the Association for Research in Vision and Ophthalmology (ARVO) announced it will move its ARVO 2021 Annual Meeting to a fully virtual event. The event was originally scheduled for May 2 to 6, 2021, in San Francisco. In this virtual environment, the *Ophthalmology Times*® team will continue to provide the event coverage you have come to expect, including video interviews.

Device technology kicks off the cover of this issue. We talk with Gustavo B. Melo, MD, PhD, who discusses pearls for selecting a syringe for intravitreal injections. While all syringes used for intravitreal injections have pros and cons, some recently marketed and forthcoming products are coming closer to meeting "ideal" criteria.

Therapeutics is seeing myriad innovations, and a study zeroing in on dry eye treatment of cataract patients is in the spotlight on the cover of this issue. In a retrospective study, perioperative use of artificial tears was found to reduce ocular discomfort, tear instability, and ocular surface damage after cataract surgery. Investigators found that initiating the treatment preoperatively was associated with better outcomes than if the artificial tears were used only after the procedure.

In our surgery section, we look at straightforward procedures for leaking blebs … with no incision required. Neeru Gupta, MD, PhD, MBA, considers an option, which preserves the bleb. The procedure is relatively simple, inexpensive, efficient, and accessible. Patients are comfortable postoperatively and can return to normal activities. The section also includes an article from Arun C. Gulani, who focuses on raising the bar for premium peterygium surgery. He explains that "premium" is more than an IOL: It is the complete experience starting with reception to customer care to artistic surgery to elegant ambience and most importantly, consistent, successful outcomes.

Imaging continues to set the pace for innovation. Justis P. Ehlers, MD, discusses the value of new diagnostics and personalized medicine in retinal treatment. He explains that precision medicine and image-guided metrics will help optimize diagnostic efficiency, risk stratify patients more quickly and accurately, and determine treatment risk and benefit.

In clinical diagnosis, Richard W. Hertle, MD, explains that it takes a village to beat visual system diseases in children. He explains that new standards have emerged for treating visual diseases in pediatric populations during the previous 2 decades, thanks to community involvement and external funding of research. He also describes the progress achieved in various diseases as a result of those factors.

Always an area ripe with new developments, gene therapy continues to offer cutting-edge advancements you need to know about. In this issue, Paul Park, PhD, details research that is unfolding the proteins in retinitis pigmentosa. Investigators are focusing on the biophysical method to study protein-protein interactions. Investigators have learned that there is variability in the severity of misfolding and aggregation depending on specific mutations.

Our gene therapy content also includes research identifying a link vetween inflammation and diabetic retinopathy. Patricia R. Taylor, MD, explains that investigators have found that interleukin 17A is a key player in diabetic retinopathy.

Our special section in this issue focuses on innovations in glaucoma.

As we start a new year, we would like to wish each of you a safe, healthy, and prosperous 2021. Thank you for joining the *Ophthalmology Times*® team on this journey. ■

What's Trending

See what the ophthalmic community is reading on **OphthalmologyTimes.com**

1 Researchers identify pink eye as possible primary symptom of COVID-19
OphthalmologyTimes.com/view/coronavirus-pink-eye-symptoms

2 Robert Jampel, MD, PhD, ex-director of Kresge Eye Institute, dies at 94
OphthalmologyTimes.com/view/robert-jampel-md-phd-former-director-of-kresge-eye-institute-dies-at-94

3 CMS approves physician fee schedule, including Medicare cuts to ophthalmology
OphthalmologyTimes.com/view/cms-approves-physician-fee-schedule-including-medicare-cuts-to-ophthalmology

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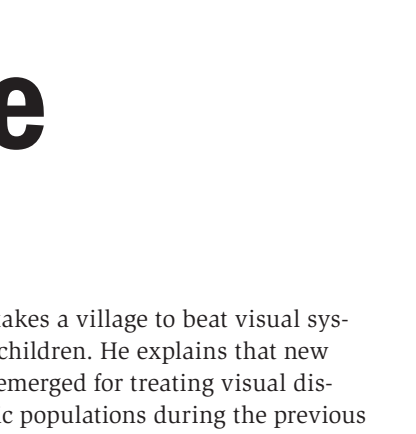
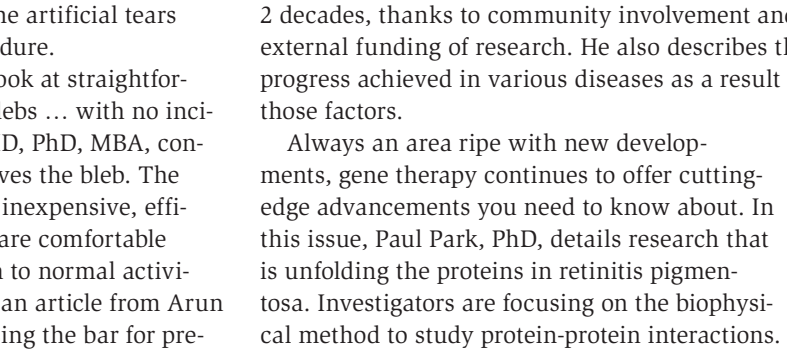


Video



John A. Hovanesian, MD, discusses the highlights of a clinical study evaluating dexamethasone vs prednisolone acetate 1% in controlling postop pain and inflammation in sequential cataract surgery patients.
Go to **OphthalmologyTimes.com/view/drug-delivery-vs-drops-controlling-postop-pain-inflammation-in-cataract-surgery-patients**

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EDITORIAL

Keeping to the schedule

Sometimes, physicians may find that falling behind is the right thing to do

By Peter J. McDonnell, MD

director of the Wilmer Eye Institute, Johns Hopkins University School of Medicine, Baltimore, and chief medical editor of *Ophthalmology Times*®.

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LIKE MANY physicians, I am not the most patient person in the world. I do not like waiting for responses to my emails, so when people email me I try to respond quickly (assuming it is a straightforward question to which I know the answer). I do not like wasting time when meetings start late, so when it is my meeting I always try to start on time. And I definitely do not like sitting in doctors' waiting rooms, so I have always tried to run my clinics like a well-oiled machine.

Some physicians I know show up in clinic an hour or two after it "starts." They figure it will take their staff some time to check people in, for the technicians to bring them back to the exam room, for the technicians to do their thing (checking vision, pupils, IOP, etc.) and maybe put in dilating drops. These physicians arrive at 9 or 10 am to see patients scheduled at 7:45 am.

My practice has been to arrive at the clinic when my first patient is due to arrive so that I know that everything gets off to a quick start. Some patients do not need a lot of testing, so I can see them right away. Other patients might need testing and dilation, and I will pop in to see them as soon as they are ready, while clearing out every patient as soon as I can with the goal of never getting behind.

One day, I was cruising along in clinic and everything was going perfectly. As soon as a patient was ready, I popped in and did my thing. All the postops were doing great, all the corneal ulcers were responding to antibiotics as they should, and any needed suture removals or little procedures took only seconds to perform.

Then I grabbed the chart in the door (yes, this happened before we went electronic) of my next patient. This nice lady was about 20 years older than me and I had performed phacoemulsification/IOL surgery on her second eye after the first eye went perfectly. The technician had recorded 20/15 uncorrected vision and normal IOP. Everything looked perfect. "This will go fast," I thought to myself. "I will tell her everything is perfect. She will thank me and tell me I am a wonderful doctor. I will feign humility, accept her praise and send her on her way. I will be in and out in a minute and everything will stay right on schedule."

I walked in the room and stood next to where she sat in the exam chair. "How are you?" I asked, and waited for her to thank me. She looked at me and burst into tears.

The sobbing continued for what seemed like a long time but was probably only a few minutes. I gave her a tissue, sat down next to her and held her hand. After a while the tears abated and she could talk. "I am sorry," she said. "My husband died this week."

I told her I was sorry. He had never accompanied her on her visits so I had not known him. "Would you tell me about him?" I asked.

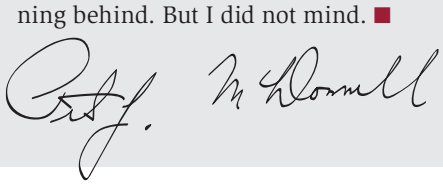
The words came pouring out. He was a very successful businessman but always came home at 5 pm to be with her. Every day, he would open a bottle of wine, pour 2 glasses and sit in the backyard with his wife and tell her about the challenges he had faced that day, ask her about what she had done that day, and ask her advice about things. He made her feel that she was the most important person in the world to him.

"Boy, he sounds like a great husband," I said. "Oh, he was," she responded, "and I will miss him so."

"I hope that when I die, someone will remember me the way you remember him," I said. She squeezed my hand and said she hoped so, too.

After a while, she thanked me for listening to her, told me she felt much better and was ready to go. She apologized for taking up so much of my time. I wished her well and we walked together out to the waiting room.

My technicians clearly wondered why I had been in the examination room so long. And we were now running behind. But I did not mind. ■



Not an actual patient.

*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).[3]

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. Pivotal trial data: The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. Use of artificial tears was not allowed during the studies. The study end points included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).[3]

A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.[3]

Indication

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

Important Safety Information

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

NOVARTIS

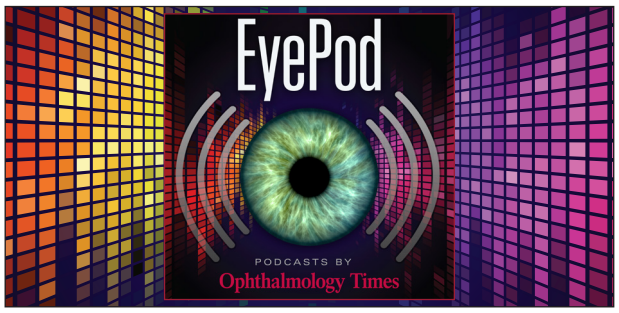
Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

Important Safety Information (cont)

- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information about XIIDRA®, please refer to the brief summary of Full Prescribing Information on adjacent page.

References: 1. US Food and Drug Administration. Code of Federal Regulations, Title 21, Volume 5 (21CFR349). Accessed April 17, 2020. https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=349&showFR=1 **2.** Jones L, Downie LE, Korb D, et al. TFOS DEWS II Management and Therapy Report. *Ocul Surf.* 2017;15(3):575-628. **3.** Xiidra [package insert]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020.



Integrating AI to manage DR in a primary care setting

Ehsan Rahimy, MD, a surgical and medical vitreoretinal specialist at the Palo Alto Medical Foundation, discusses results from a study aiming to integrate an artificial intelligence screening system for managing diabetic retinopathy referrals in a primary care setting —with limited specialty support.

OphthalmologyTimes.com/view/eyepod-integrating-ai-manage-dr-primary-care-setting

Visual and nonvisual benefits of violet light-filtering IOLs

Daniel H. Chang, MD, medical director, Empire Eye and Laser Center in Bakersfield, California, speaks on the highlights of his presentation on "Violet Light-Filtering IOLs: Visual and Nonvisual Benefits," during the virtual AAO 2020 meeting.

OphthalmologyTimes.com/view/visual-and-non-visual-benefits-of-violet-light-filtering-iols

Medication could reduce burden of steroid drops for patients

Cynthia Matossian, MD, FACS, ABES, medical director, Matossian Eye Associates, presents the highlights of a poster on outcomes with dexamethasone intraocular suspension 9% and concomitant postoperative anti-inflammatory medications.

OphthalmologyTimes.com/view/aao-2020-medication-could-reduce-burden-of-steroid-drops-for-patients

Applying real-world data on day-to-day practice

Ted Leng, MD, MS, Byers Eye Institute at Stanford, and medical adviser for Verana Health, shares data insights for retinal surgeons. Steven D. Schwartz, MD, Stein Eye Institute, UCLA, explains the highlights of his AAO presentation, "New Insight into Real-World U.S. Injection Data."

OphthalmologyTimes.com/view/aao-2020-applying-impact-of-real-world-data-on-day-to-day-practice

Straightforward procedures for leaking blebs: No incision required

Minimally invasive conjunctival surgery option is an efficient procedure

By Lynda Charters; *Reviewed by Neeru Gupta, MD, PhD, MBA*

The first attempts at bleb repair after trabeculectomy and introduction of the use of mitomycin C (MMC) to improve surgical success rates resulted in blebs that were avascular and prone to leaks.

"This scenario is a time bomb because, left unchecked, it can lead to blebitis and possibly endophthalmitis, and myriad other problems, such as hypotony with associated anatomic disruptions such as vision-blurring corneal striae, shallow anterior chambers, buildup of excess fluid leading to dome-shaped choroidals, and hypotony maculopathy," said Neeru Gupta, MD, PhD, MBA.

Gupta

Gupta is a professor of ophthalmology and chief of glaucoma at the University of Toronto, and president-elect of the World Glaucoma Association.

Techniques that have attempted to address the problem of leaky blebs include conservative treatment with antibiotics, aqueous suppressants, steroids, collagen shield, bandage contact lens, pressure patch, cyanoacrylate tissue glue, autologous blood, and argon laser or Nd:YAG laser. The microsurgical approaches include bleb resuturing, and bleb excision and conjunctival advancement with or without various grafting techniques.

Despite all this, no procedure stands out as effective.

"Despite the number of attempted procedures, we continue to struggle with managing bleb leaks," Gupta said.

TAKE-HOME

- ***Surgeons can consider this option, which preserves the bleb. The procedure is relatively simple, inexpensive, efficient, and accessible. Patients are comfortable postoperatively and can return to normal activities.***

NOVEL BLEB LEAK MANAGEMENT

Gupta developed the minimally invasive conjunctival surgery incision-free procedure to address late-onset bleb leaks close to the limbus.

For a patient with a history of high myopia, advanced pigmentary glaucoma, retinal detachment treated with pars plana vitrectomy and later with pneumatic retinopexy and cryotherapy, use of multiple glaucoma medications for advanced glaucoma, thin corneas, bilateral cataracts, and remaining central islands of vision of 20/60 to 20/70, Gupta performed bilateral trabeculectomies with MMC. Vision was stable with intraocular pressures (IOPs) of 8 to 10 mm Hg bilaterally. In 2012, however, the vision in the left eye decreased to 20/100 with an IOP of 2 mm Hg and an avascular leaking bleb. Three days later, the vision was 20/200 with an IOP of 0 mm Hg.

In surgery, Gupta acted to address this situation without undoing the previous treatments. Instead of excising the bleb and covering the area with conjunctiva, she injected subconjunctival lidocaine above the bleb. She described the conjunctival epithelium as highly voluminous and able to move freely. With gentle tugging, and without disturbing Tenon capsule, she pulled a sizable area of the conjunctival tissue to the limbus over the leaking area and put in a series of stitches (typically 3 to 4) without using a great deal of pressure that resulted in a sealed wound.

"This was a short, incision-free procedure," she said of this first such case.

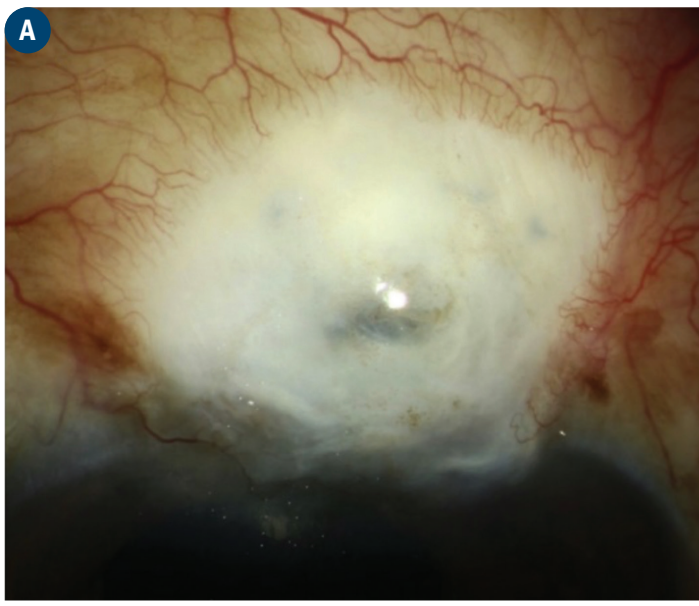
The patient has done well during the ensuing 8 years. Gupta reported that she has performed this procedure in 14 cases and reported the results in the *American Journal of Ophthalmology*.[1]

In all cases, the patients have remained stable and medication free from 2 weeks to 5 years later. She said that with time the transposed conjunctival tissue becomes translucent and seems to take on the characteristics of the early bleb that was leaking.

Gupta enumerated the surgical benefits of this procedure.

"It is short and incision free with good success; the bleb is preserved; the procedure is relatively simple, inexpensive, efficient, and accessible; and the patients are comfortable postoperatively and can return to normal activities," she said. "They leave after the surgery with an antibiotic and a steroid.

She advised that studies are needed to determine the long-term outcomes. ■



(A) An avascular bleb and conjunctival defect with (B) evidence of bleb leak by Seidel test showing fluorescein stream over the cornea under cobalt blue light. *(Photo courtesy of Neeru Gupta, MD, PhD, MBA)*

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Gupta has no financial interest in this subject matter.

Raising the bar for premium pterygium procedure

Physician pioneers technique offering higher perspective in surgery, outcomes

By Arun C. Gulani, MD; *Special to* Ophthalmology Times®

IN OPHTHALMOLOGY, THE meaning of the word premium has come to be associated closely with cataract surgery and in particular the premium intraocular lenses. This misdirected allocation has led to continued confusion among enlightened patients and providing surgeons.

I I teach surgeons that premium is more than simply a lens technology. It is the complete experience, starting with reception and continuing to customer care to artistic surgery and, most importantly, to consistent, successful outcomes.

We are privileged to be in a profession for which industry strives to provide us with exotic innovations and technologies, and we should shoulder the responsibility to use these correctly and to their best potential. If surgeons consider a premium lens as an ingredient, certainly a very important one but merely a portion of the entire "vision recipe," they will finally lose their anxiety and patients will lose their distrust and enjoy the fruits of these innovations.

Add to this my experience with LASIK since the early 1990s, long before its FDA approval in the United States, when I would encourage colleagues and industry to measure vison beyond 20/40, and that on day 1 post-LASIK, and you have both of my principles regarding premium.

Apply these 2 concepts to pterygium surgery1, which has most often been handed to a low-level resident in training or at least kept in the unimportant category with less-than-cosmetic expectations or accountability.

What if we could perform pterygium surgery like an artist and deliver postoperative cosmetic outcomes on day 1 in a sutureless, comfortable, and visually responsible approach––one that could also make patients candidates for premium cataract and laser vision surgery? That indeed would be raising the bar to premium.[2]

APPLYING PREMIUM APPROACH TO PTERYGIUM CORRECTION

Pterygia are not new pathologies and have been recognized from antiquity. Being such, their correction is relegated to surgeries that aim for a very low bar, i.e., one with a lowest recurrence rate with moderate pain and not-so-amazing cosmetic outcomes.[3]

Over 3 decades, however, I have raised this corrective procedure to an art and turned it into a premium cosmetic procedure SPARKLE (**S**utureless **P**terygium **A**mniotic **R**econstruction with **L**amellar peel **K**eratectomy).[3-5]

This premium approach includes the following: receiving patients with pterygium from all over the world; creating a personalized, caring, and empathic ambience; planning for cosmetic outcomes with enhanced vision impact along with the use of tissue glue, mitomycin C, and human placenta technology; and employing techniques (ie, Gulani No-Stitch Iceberg technique)6,7 with a painless and smooth recovery, along with day 1 cosmetic end points focused on a long-term zero recurrence rate.

This concept and approach further includes turning patients who previously were not candidates for premium cataract and laser vision surgery into candidates, thus facilitating freedom from glasses and contact lens dependence and upholding my motto: see good and look good.

Such an approach does, of course, come at a price similar to premium cataract and laser vision surgery, the price surgeons pay for living up to goals and expectations (without guarantees to patients). It comes not only from your patients taking to social media immediately after surgery, sharing pictures of their eyes and holding you accountable to a worldwide audience 24/7/365, but also from their daily interactions with their "new" eyes on display, a testimony to the surgeon's skill.

During my 30 years of performing this technique, I have included the human placenta (amniotic membrane) as a primary ingredient in the approach. Its transparent and elegant appearance, along with its supportive and ocular surface–rejuvenation properties, compliment the surgical artistry.

Further, the ambience in our institute-based surgery suite, along with elegantly designed instrumentation (Gulani Premium Pterygium Surgery Instruments, Bausch + Lomb) and options for premium vision corrective surgery, elevate the continuum of care from appearance to vision.

PINGUECULA

The consistent success of the SPARKLE procedure over decades has resulted in patients with pinguecula, who are often concerned with their cosmetic appearance, being able to have surgery. Many of them either have already had vision corrective surgery or anticipate having it in the near future.

The premium approach is underscored in this patient population, in which a simple mistake can be considered a complication of what was an elective and cosmetic situation to begin with.

When teaching LASIK and laser vision surgeries, I remind surgeons that they need to be consistently confident in their outcomes and that patients with small refractive errors also can be offered a chance to improve their vision beyond 20/20. Any mistakes at this level would be catastrophic, because the patient had near normal sight to begin with.

The premium approach holds our feet to the fire, as we invite each patient on day 1 after surgery to look at their eye in a mirror and comment on its condition.

The ability to produce great outcomes should attract affected patients worldwide who have been told that the surgery is worse than the lesion regarding discomfort, recurrence rate, and the outcome, which may not be an improvement over their preoperative status.

The time has come to raise ocular surface surgery to an art, and the experience and outcomes to a premium level. ■

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Gulani, an anterior segment specialist and creator of the Corneoplastique concept of vison correction, is the founder of Gulani Vision Institute in Jacksonville, Florida.

Pearls to help surgeons improve when using nondominant hand

For ophthalmologists, practice makes perfect in becoming ambidextrous

By Lynda Charters; *Reviewed by Valentina Lozano, MD; Ticiana de Francesco, MD*

EYE SURGEONS SHOULD be comfortable performing procedures with either hand, and complex cases—especially glaucoma procedures—require a good level of dexterity with both hands, according to Valentina Lozano, MD, and Ticiana de Francesco, MD.

Lozano and de Francesco were glaucoma fellows at the University of Toronto in Canada. Lozano is in practice in Gainesville, Florida, and de Francesco has returned to practice in her native Brazil.

> "Using the nondominant hand can be frustrating. It is slow. Practice once a week." – *Valentina Lozano, MD*

When performing pupillary cerclage, surgeons place guides for the iris sutures around the pupil. In this case, the surgeon holds the needle driver with the nondominant hand, which requires good control of the needle to prevent any iatrogenic iris defect.

If the dominant hand is used to hold the needle driver, the nose will be in the way and it will be difficult to make the incision. When using the nondominant hand, there is better surgical access and the procedure will be much easier.

THREE STEPS TO PROFICIENCY

When practicing using the nondominant hand, Lozano and de Francesco advise performing 3 steps of increasing difficulty to train the nondominant hand.

Step 1 requires using the nondominant hand to perform normal daily routines at home and during personal hygiene practices. Examples might include brushing teeth or applying makeup, such as eyeliner, or nail polish.

Step 2 requires the physician using the nondominant hand to do a fun activity such as a hobby, with the intention of training that hand. Some suggestions might include doing a diamond painting by applying the diamonds to the picture with the nondominant hand, or coloring on an iPad using an Apple pencil.

Step 3, the most difficult, requires using the nondominant hand to practice at work without slowing down. Examples of activities that can be pursued include switching hands while using a computer mouse, practicing instilling drops during clinic, or carrying out a full slit lamp examination.

TAKE-HOME

- ***Ophthalmologists can gain a level of comfort when using their nondominant hand through practice and consistency.***

REMAIN CALM

According to Lozano and de Francesco, it is important not to become overwhelmed. And like anything, practice certainly can make perfect.

"Using the nondominant hand can be very frustrating," Lozano said. "It is slow. Practice once a week. Take breaks and remember that no one is rushing you."

According to de Francesco, practice makes perfect, and this is true for becoming ambidextrous.

"With consistency, surgeons can become comfortable using the nondominant hand," she said. "Finally, have fun and more will be accomplished with a positive attitude." ■

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Lozano and de Francesco have no financial interest in this subject matter.

ARVO 2021 going fully virtual

The Association for Research in Vision and Ophthalmology (ARVO) announced a switch to a virtual format for its annual meeting, originally scheduled for May 2-6 in San Francisco, California.

While vaccinations have started in the United States, the coronavirus disease 2019 (COVID-19) pandemic continues to impact in-person meetings.

ARVO announced the decision in December to hold the meeting in a virtual setting.

"Due to the pervasive spread of the virus, in addition to limitations on the venue capacity and strict travel restrictions in place by worldwide governments and our members' universities and institutions, the Board of Trustees has decided to move the ARVO 2021 Annual Meeting to a fully virtual event," ARVO President Stephen Pflugfelder, MD, FARVO, said in a statement.

According to Pflugfelder, the health, safety and well-being of the ARVO global community continues to be the orgnaizations highest priority, and prmpted the decision to move to a virtual format.

Pflugfelder also pointed out that amid the pandemic, ARVO officials believe it is important to continue to provide a forum in which scientific research can proceed and be shared globally.

"ARVO is focused on providing a robust and meaningful scientific exchange in a virtual format to help ensure the health and safety of all," he said in the statement. "A virtual event allows for an expanded reach of the Annual Meeting to more people than ever, in real-time and asynchronously, with live chats that encourage meaningful dialogue."

The ARVO 2021 Annual Meeting Registration was scheduled to open on December 14, 2020.

According to the statement, additional details regarding the virtual event will be provided soon.

"I look forward to active participation in the ARVO 2021 Annual Meeting by eye and vision researchers across the globe," Pflugfelder concluded. ■

Image courtesy of nimon_t @Adobe Stock

Cleaning, disinfection guidelines designed to promote safety

Organization shines spotlight on frontline heroes during ongoing COVID-19 battle

By Lynda Charters; *Reviewed by Xiao Ying Liu, RN*

IN ONE OF the toughest times in modern history, heroes in the health care field have been emerging globally within the backdrop of the coronavirus disease 2019 (COVID-19) pandemic. Many such individuals are known for their undefeatable energy in caring for severely ill patients and for devising infection control practices that are applicable worldwide in clinical practice to protect staff and patients.

Orbis International specializes in providing training to local eye care teams in underserved areas of the world with the goal of improving the quality of eye care provided in their communities for the foreseeable generations. Sterilization and infection control skills now are more important than ever.

Four professionals engaging in teaching health care practices are Xiao Ying Liu, RN, a staff nurse, Orbis Flying Eye Hospital, Orbis International, New York; Yan Zhang, RN, associate director of nursing, Wuhan Aier Eye Hospital, Wuhan City, Hubei Province, China; Hai Xia Tu, from the Department of Infection Control and Quality Control, Wuhan Aier Eye Hospital, Wuhan City, Hubei Province, China; and Astrid Leck, a research fellow and microbiologist at the London School of Hygiene and Tropical Medicine. They are training health care professionals worldwide to arm themselves against the COVID-19 virus. They have compiled an article[1] on the role of nursing infection control in hospitals during COVID-19.

"Standard cleaning and disinfection protocols continue to apply during the pandemic but may have to take place more often," they emphasized. Their guidelines for cleaning and disinfection are a compilation of measures from the World Health Organization and current research, but they also advise following national guidelines.

> "Standard cleaning and disinfection protocols continue to apply during the pandemic but may have to take place more often."
>
> – Xiao Ying Liu, RN

CLEANING, DISINFECTION

The article by the quartet of nurses noted the importance of close monitoring of cleaning and disinfection practices and personnel involved in these activities having access to correct personal protective equipment (PPE) as well as proper training. Appropriate PPE includes heavy-duty gloves or durable disposable nonsterile gloves, face masks, safety goggles or face shields, gowns, and closed work shoes. All individuals involved in cleaning in the hospital setting, including matrons, domestic supervisors, and service managers, must be trained fully in safe disinfection preparation, cleaning methods and equipment used, standard precautions, and risk assessment and transmission-based precautions, the authors noted.

Importantly, heavy-duty gloves require disinfection, and disposable gloves must be changed when moving from one treatment area to another.

TAKE-HOME

- ***A cleaning protocol should begin in the cleanest areas and then move to the areas which have the highest risk of contamination. Even if a surface looks clean, it should be sanitized to ensure safety.***

DISINFECTANT PREPARATION

Fresh solutions of detergent and disinfection are ideally prepared for each individual cleaning shift, and fresh cloths are used. Continued use of the same disinfectant may result in transferring pathogens to surfaces as the disinfectant becomes less effective.

Disposable disinfectant wipes are preferred when cleaning equipment surfaces. Care must be exercised to prepare the correct concentration of the disinfectants, which must be left in contact with the contaminated surfaces for sufficient time to provide adequate disinfection.

"Concentrations with inadequate dilution during preparation (too low or too high) may reduce their effectiveness. High concentrations increase chemical exposure to users and may also damage surfaces," the authors cautioned.

If an area or piece of equipment has confirmed or suspected exposure to COVID-19, the solutions and cloths are discarded immediately.

Spraying and fumigating, the so-called nontouch methods, are not recommended for routine disinfection of indoor areas because of their associated health risks to exposed individuals.

Some disinfection solutions that are commonly and successfully used against the coronavirus are chlorine-containing disinfectants, alcohols, and hydrogen peroxide.

HOW TO CLEAN

The authors advised a cleaning protocol that begins in the cleanest areas and then moves to the most contaminated areas. All surfaces must be cleaned even if they appear unsoiled. "Scrubbing may be necessary to remove and reduce visible dirt, debris, and other organic matter such as blood, secretions, and excretions. Organic material or 'soil' may impede direct contact of a disinfectant with a surface and inactivate the germicidal properties or mode of action of a disinfectant," they warned.

High-traffic areas require more frequent cleaning, especially outpatient areas and rooms used by staff members to put on and remove PPE.

In addition to the frequency of cleaning, risk assessment is also a consideration. "Patient waiting areas are low risk, while operating areas are high risk," they said.

No surfaces should be overlooked. These include the reception/outpatient waiting area, the screening and triage areas, clinic rooms, inpatients rooms/wards, recovery room, and operating theater. Every surface in all of these areas should be cleaned at least twice daily, and the inpatient and recovery rooms should be cleaned at least 3 times daily.

"SARS-CoV-2 can remain viable for between 8 hours and several days, depending on the type of surface. Surfaces become contaminated when droplets that contain virus land on them or when hands that are contaminated touch these surfaces," Liu, lead author of the article, concluded. ■

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None of the study authors has a financial interest related to this subject matter.

*In some patients with continued daily use. One drop in each eye, twice daily (approximately 12 hours apart).[3]

†Xiidra is an LFA-1 antagonist for the treatment of dry eye disease. **Pivotal trial data:** The safety and efficacy of Xiidra were assessed in four 12-week, randomized, multicenter, double-masked, vehicle-controlled studies (N=2133). Patients were dosed twice daily. **Use of artificial tears was not allowed during the studies.** The study endpoints included assessment of signs (based on Inferior fluorescein Corneal Staining Score [ICSS] on a scale of 0 to 4) and symptoms (based on patient-reported Eye Dryness Score [EDS] on a visual analogue scale of 0 to 100).[3]

A larger reduction in EDS favoring Xiidra was observed in all studies at day 42 and day 84. Xiidra reduced symptoms of eye dryness at 2 weeks (based on EDS) compared to vehicle in 2 out of 4 clinical trials. Effects on signs of dry eye disease: ICSS (on a scale from 0-4; 0=no staining; 4=coalescent) was recorded at each study visit. At day 84, a larger reduction in inferior corneal staining favoring Xiidra was observed in 3 of the 4 studies.[3]

Indication

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

Important Safety Information

- Xiidra is contraindicated in patients with known hypersensitivity to lifitegrast or to any of the other ingredients.
- In clinical trials, the most common adverse reactions reported in 5-25% of patients were instillation site irritation, dysgeusia and reduced visual acuity. Other adverse reactions reported in 1% to 5% of the patients were blurred vision, conjunctival hyperemia, eye irritation, headache, increased lacrimation, eye discharge, eye discomfort, eye pruritus and sinusitis.
- To avoid the potential for eye injury or contamination of the solution, patients should not touch the tip of the single-use container to their eye or to any surface.
- Contact lenses should be removed prior to the administration of Xiidra and may be reinserted 15 minutes following administration.
- Safety and efficacy in pediatric patients below the age of 17 years have not been established.

For additional safety information about XIIDRA®, please refer to the brief summary of Full Prescribing Information on adjacent page.

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NOVARTIS

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East Hanover, New Jersey 07936-1080

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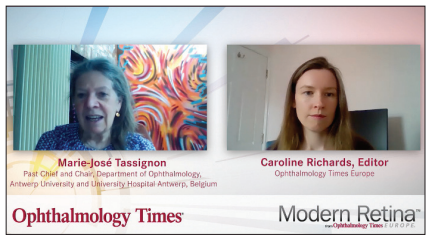
Headache paired with visual loss may require honing of detective skills

Kathleen B. Digre, MD, details how a headache in conjunction with visual loss is a scenario that requires an in-depth examination, including evaluation of the visual fields, pupils, and fundus to gather clues to the diagnosis.

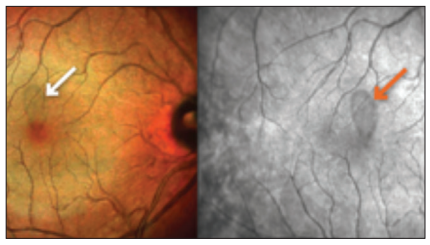
OphthalmologyTimes.com/view/aao-live-headache-with-visual-loss-requires-honing-of-detective-skills



How not to be afraid of performing a posterior capsulorhexis

Prof. Marie-José Tassingnon, past chief and chair, Department of Ophthalmology, Antwerp University and University Hospital Antwerp, Belgium, provides an overview of her novel technique in performing a risk-free posterior capsulorhexis.

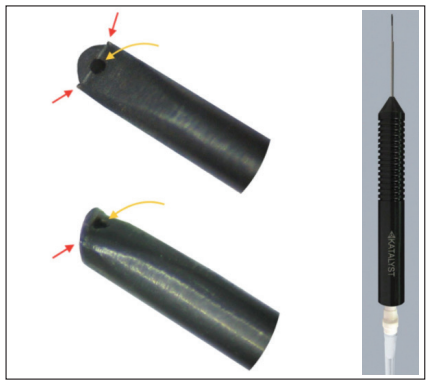
OphthalmologyTimes.com/view/aao-2020-how-not-to-be-afraid-of-performing-a-posterior-capsulorhexis



Fingolimod for MS offers disease control with no development of uveitis

Bradley Smith, MD, explains how fingolimod 0.5 mg, a first-line treatment for multiple sclerosis, may reduce both the number of relapses and disease progression in patients with relapsing-remitting MS as well as the incidence of uveitis.

OphthalmologyTimes.com/view/aao-fingolimod-for-ms-offers-disease-control-with-no-development-of-uveitis



Micro Vacuum Pick for use during vitreoretinal surgery proving to be a better mousetrap

Carl Awh, MD, discusses the Micro-Vacuum Pick, a device for peeling internal limiting membranes that's providing vitreoretinal surgeons an alternative to forceps during surgeries.

OphthalmologyTimes.com/view/aao-micro-vacuum-pick-for-vitreoretinal-surgery-may-be-a-better-mousetrap

Headache image courtesy of Tryfonov @Adobe Stock

The value of new diagnostics and personalized medicine

Emerging technology may facilitate individualized care, disease management

By Lynda Charters; *Reviewed by Justis P. Ehlers, MD*

There is a great need for precision medicine in retinal disease, and Justis P. Ehlers, MD, explained that precision medicine and image-guided metrics will help optimize diagnostic efficiency, risk stratify patients more quickly and accurately, and determine treatment risk and benefit.

Moreover, Ehlers said it also can enable an individualized therapeutic approach with targeted clinical trial enrollment as more therapeutics become available, the ability to understand treatment failures, and improve economic models.

Ehlers is the Norman C. and Donna L. Harbert Endowed Chair for Ophthalmic Research at the Cleveland Clinic's Cole Eye Institute, and director of the Tony and Leona Campane Center for Excellence in Image-Guided Surgery and Advanced Imaging Research at the Cleveland Clinic in Cleveland, Ohio.

While considering these needs, artificial intelligence (AI) often is considered as a solution. While AI could be a great asset to help in decision-making processes, caution must be exercised in the "black box" nature of some the algorithms.

As Ehlers pointed out, AI has the potential to be used nearly everywhere in patient care, "but more specifically, there is great opportunity for use of AI in automated detection of disease; automated disease characterization, such as in severity grading; big data assimilation for risk stratification or diagnostic accuracy; enabling next-generation disease interrogation, creating opportunities not possible previously; enhancing current analysis platforms to improve efficiency and accuracy of workflow; and opportunities in pattern recognition and phenotype classification using pharmacogenomics or imaging genomics to understand underlying diseases."

AI NEEDS

In order to train neural networks, he explained, datasets of sufficient sizes and quality are needed composed of either annotated or raw images.

"In understanding AI technology, I think that understanding the 'thought process' is important, that is, how is the computer actually evaluating a feature of interest, how is it interpreting a finding, and what happens when things go wrong with AI systems?" Ehlers said.

Al use in diabetic retinopathy (DR) image grading was found to be successful in detecting the stages of DR. The recognition of this capability paved the way for FDA approval of AI-based image assessment and diagnostics.

The role of AI in image analysis is being expanded by many research groups. The IDx Platform (Digital Diagnostics) is a companion piece to a standard fundus camera that uses software to detect DR that is worse than mild disease. The technology has 87% sensitivity and 90% specificity of identifying more than mild DR and was able to identify *all* patients with DR of level 43 or higher and therefore at higher risk.

The systemic features that AI can detect based on a very large dataset is the gender of the patient based on the fundus photo. The software may be picking up some information around the fovea to make that determination. The neural network also can look at the retinal vessels to predict the systolic blood pressure, which was more accurate than the predictions of the diastolic blood pressures.

PRACTICAL APPLICATION

Ehlers described how his laboratory is using multiple technologies in image assessment and higher order image characterization, including AI and radiomics-based feature extraction.

Ultra-widefield angiography is critical for retinal vascular disease to understand the disease burden. However, he explained, there is not currently an objective measure for treatment decision-making with antivascular endothelial growth factor therapy for DR that has been established as an optimal biomarker for treatment response. In his laboratory, the research team have been developing platforms to quantify multiple parameters, including microaneurysm counts, ischemic index, and leakage index in DR. His group has demonstrated that the leakage seen in ultra-widefield angiography is strongly correlated with the degree of DR, ranging from mild to moderate nonproliferative, severe, and proliferative DR.

When considering the next-generation analysis platforms, one advantage of integrating machine-learning technologies is the integration of multiple models into a single platform that provides enhanced performance or efficiency of assessment. In ultra-widefield angiography, examples of multiple model integration for platform development include region of interest detection, blood vessel segmentation, fovea/optic nerve identifier, image feature (eg, ischemia) segmentation, and artifact removal tools (eg, eyelid detector).

NEXT-GENERATION OCT ASSESSMENT

OCT is the backbone of diagnostic assessment of retinal diseases. Most current commercial systems provide some basic software for retinal thickness measurements. Generally, most clinical decisions are made based on subjective clinician interpretation of imaging features (eg, the presence of fluid). Higher-order OCT analysis, often using machine-learning augmentation, can provide new opportunities for targeted layer/zone specific interrogation and pathology-specific segmentation (eg, fluid volume assessment). These analysis systems enable new opportunities for disease characterization. One example is hydroxychloroquine (Plaquenil, Sanofi) toxicity, where detecting early subtle damage can be challenging. "Utilizing targeted mapping of the ellipsoid zone, this system has been able to generate visualization maps to detect signaling of retinopathy earlier in the disease stage that might have implications for future toxicity screening," he commented.

LOOKING AHEAD

OCT also can quantify the volumetric characteristics of intraretinal and subretinal fluid as well as therapeutic responses. These exudative metrics may provide greater understanding of therapeutic responses, the tempo of fluid resolution, and important features that provide disease insight.

"Computational image analysis, imaging biomarkers, and AI-based platforms are likely to play a major role in eye care in the future," Ehlers concluded. "Additional research is needed to better understand how to integrate these into practice. Emerging technology related to this field may provide a major inflection point in practice to facilitate individualized care and overall disease management." ■

JUSTIS P. EHLERS, MD

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Ehlers serves as a consultant for Novartis, Allegro, Allergan, Genentech, Regeneron, Aerpio, Roche, Alcon, Leica, and Zeiss. Ehlers receives research support from Novartis, Allergan, Regeneron, Aerpio, Boehringer-Ingelheim, and Genentech. Ehlers has intellectual property licensed to Leica and multiple patents in the image analysis space.

Panel discusses advancements in the management of dry eye

The disease is a public health concern in the United States

By Lynda Charters

Recently, experts from around the country got together virtually for an *Ophthalmology Times*® and *Optometry Times*® Viewpoints series to discuss dry eye disease (DED).

On the panel were **Marguerite B. McDonald, MD**, a clinical professor in the department of ophthalmology at NYU Robert I. Grossman School of Medicine in New York, New York, and the discussion moderator; **Eric D. Donnenfeld, MD**, a founding partner of Ophthalmic Consultants of Long Island and Ophthalmic Consultants of Connecticut, clinical professor of ophthalmology at New York University in New York, and trustee of the Audrey and Theodor Geisel School of Medicine at Dartmouth in Hanover, New Hampshire; **Tracy S. Swartz, OD, MS, FAAO**, who is in private practice in Madison, Alabama; and **Crystal Brimer, OD, FAAO**, who is in private practice in Wilmington, North Carolina.

DIAGNOSIS/PROGRESSION RISK

Brimer highlighted the under-recognized effects of DED.

"There is a correlation between dry eye and depression, anxiety, sleep quality, and diet," she said. "Multiple patients have reported wanting to commit suicide. The disease affects every aspect of life."

Swartz described the progressive cycle beginning with hyperosmolarity followed by damage to the ocular surface, goblet, and epithelial cells; increased inflammation; and tear film instability. Reduced tear film break-up time (TBUT) exacerbates hyperosmolarity, and physical symptoms increase with inflammation and discomfort. This scenario is complicated by ocular allergy, ocular surface disease (OSD), contact lens wear, preserved topical drops, and makeup and skin creams. Mask wearing during the coronavirus disease 2019 pandemic further reduces TBUT.

A cascade of events can ultimately cause severe keratopathy with reduced best-corrected vision, neovascularization, ulceration, and corneal melts.

DIAGNOSIS/TREATMENT

Donnenfeld advised paying close attention to patients' symptoms. Fluctuating vision is almost always due to OSD, he said. He evaluates both eyelids and eyes, because meibomian gland disease (MGD) is responsible for at least 75% of DED.

For testing in most patients, the basics are important. The panelists agree that diagnosis is not easy because DED can be subclinical and other symptoms can be misdiagnosed as dry eye. Early identification and formulation of a treatment plan are the goals to address this common disease. Brimer said positive testing will tailor a targeted treatment.

In addition to evaluating the patient's overall systemic appearance, Swartz said she evaluates the tear film for debris and allergic mucus. She assesses for conjunctivochalasis and lissamine green staining; examines the cornea using meibography, an aggressive tear film analysis of tear meniscus height and tear film dynamic, and interferometry; and determines a redness score.

Donnenfeld commented on the need to identify new biomarkers of dry eye that will make diagnosis easier and more reproducible and treatment more effective.

The availability of anti-inflammatory agents for managing DED was a game-changer with cyclosporine (Restasis, Allergan), Donnenfeld noted. Lifitegrast (Xiidra, Novartis), a potent immunomodulator, different cyclosporine concentrations, and FDA-approved corticosteroids are also now available.

Donnenfeld said he uses loteprednol 0.25% (Eysuvis, Kala Pharmacueticals) for dry eye flares.

Nutrition in the management of dry eye is controversial, with results from clinical studies reaching opposite conclusions. All the panelists are firm believers in omega-3s and found them to be extremely helpful.

Antibiotics are useful for treating MGD and lipid-deficiency dry eye. Donnenfeld and Swartz said they prescribe oral doxycycline; he uses 100 mg twice daily for infections. Very low doses of 50 or 40 mg daily also work. Topical antibiotics and the macrolide family of antibiotics address dry eye in pregnant women and those with yeast infections and gastrointestinal intolerance. Topical azithromycin applied to the lid margin has an anti-inflammatory effect akin to doxycycline. Erythromycin has a similar effect.

Brimer prefers Tranquileyes (Eye Eco) for MGD for its better penetration. However, home lid hygiene has limitations. In-office, she and Swartz said they use thermal expression with LipiFlow (Johnson & Johnson Vision), the preferred product because of heating under the lid. Brimer and Swartz are both proponents of intense pulsed light for its multiple mechanisms of action and marked inflammation reduction. NuLids (NuSight Medical) provides excellent exfoliation on a daily basis. Swartz also relies on autologous serum 4 times daily for patients who are not covered for other treatments. For Donnenfeld, microblepharoexfoliation with BlephEx (BlephEx, LLC) works best because of its quick action and cost. Swartz uses punctal plugs for aqueous-deficient dry eye. She tests with InflammaDry (Quidel Corporation) before inserting the plug.

NEW DRUGS

A number of new products are working their way through the pipeline, according to the panelists.

BRM421 (BRIM Biotechnology) is a synthetic peptide derived from pigment epithelium factor that aids in corneal repair and enhances limbal epithelial stem cell proliferation in mice.

RGN-259 (RegeneRx) promotes corneal healing by reducing inflammation; promoting cell migration, angiogenesis, and stem cell recruitment; protecting against cytotoxicity; reducing apoptosis; accelerating collagen; upregulating production of laminin-5; and reducing scar formation.

One interesting drug is varenicline (OC-01, Oyster Point Pharma), a nicotinic acetylcholine receptor agonist being developed as a preservative-free nasal spray. When sprayed, it creates a reflex that causes tear production by activating the lacrimal glands, reducing dry eye signs and symptoms. The FDA trials are extremely promising for this new drug.

SKQ1 (Visomitin) is a cardiolipin peroxidation inhibitor that acts on the mitochondria to reduce oxidative stress and neutralize mitochondrial reactive oxygen species.

Tanfanercept (HanAll Biopharma) is a tumor necrosis factor (TNF) receptor 1 fragment that targets pro-inflammatory cytokines to reduce inflammation. In a phase 3 trial, it inhibited TNF activity, modulating inflammation and preventing corneal damage.

Reproxalap (Aldeyra Therapeutics) is a new inflammatory mediator that inhibits reactive aldehyde species that covalently bind to cellular biomolecules, disrupting their function and activating pro-inflammatory mediators that increase inflammation. Binding the free aldehydes improves ocular inflammation. It is in phase 2 clinical trials for allergic conjunctivitis.

For Swartz, NOVO3 (Novaliq) is the most interesting drug. It is 100% perfluorohexyloctane, which stabilizes the lipid layer to protect the tear film for extended periods and penetrates the meibomian glands. ■

It takes a village to beat visual system diseases in children

Community involvement, research continue to boost treatment in pediatric population

By Lynda Charters; *Reviewed by Richard W. Hertle, MD*

NEW STANDARDS HAVE emerged for treating visual diseases in pediatric populations during the previous 2 decades, thanks to community involvement and external funding of research, according to Richard W. Hertle, MD, who described the progress achieved in various diseases as a result of those factors.

Hertle

Hertle is chief of pediatric ophthalmology and director of the Vision Center at Akron Children's Hospital in Akron, Ohio. He also is director of the hospital's pediatric ophthalmology fellowship program and is the Dr Robert "Boomer" and Jill Burstine Chair in Pediatric Ophthalmology. He also is a professor of surgery at Northeast Ohio Medical University in Rootstown, Ohio.

RETINOPATHY OF PREMATURITY

Numerous studies of retinopathy of prematurity (ROP) have evaluated interventions such as cryotherapy, supplemental oxygen, light reduction, and early laser treatment that reduced blindness caused by abnormal development of blood vessels in thousands of infants annually to about 500.

The major findings included the following: (1) Cryotherapy (Cryotherapy for Retinopathy of Prematurity Study [NCT00000133]) decreased blindness by 50% in infancy and 17% by age 10. (2) Supplemental oxygen therapy (Supplemental Therapeutic Oxygen for Prethreshold Retinopathy of Prematurity Study [NCT01203436]) and reduction of ambient light (Light Reduction in Retinopathy of Prematurity Study [NCT00000156]) did not stop progression of ROP. (3) Early laser application reduced blindness by another 5% (Early Treatment for Retinopathy of Prematurity [ETROP] Study [NCT00027222]). (4) Artificial intelligence and use of telemedicine approaches for evaluating acute ROP decrease blindness worldwide.[1]

A more recent treatment is injection of intraocular bevacizumab (Avastin, Genentech), which, when compared with laser therapy, has been found by physicians to be equally efficacious, with the same long-term benefits and fewer adverse effects, Hertle said.[2]

STRABISMUS/AMBLYOPIA

The Pediatric Eye Disease Investigator Group, a collaborative that conducts multicenter clinical research in strabismus, amblyopia, and other diseases treated by pediatric ophthalmologists, functions internationally with hundreds of physicians. These trials, funded by more than $65 million raised since inception of the group in 1997, have developed new treatment protocols for strabismus, amblyopia, nasolacrimal duct obstruction, myopia, hyperopia, and uveitis.[3]

Hertle further recounted major findings of this group that were not the standard of care before the clinical trials, including the following: (1) Patching for 2 hours is as effective as patching for 6 or 8 hours in patients with moderate amblyopia; (2) Patching 6 hours works as well as full-time patching in patients with dense amblyopia; (3) Atropine use can be as effective as patching; (4) Spectacle use alone can treat amblyopia without patching or drops in strabismic amblyopia.[4]

"The changes in the current standards of practice in common eye diseases are the result of these large clinical trials," Hertle explained. "We are moving from anecdotes to the ability to practice rigorous ways to treat amblyopia and strabismus."

CONGENITAL CATARACT

The Infant Aphakia Treatment Study[5] (NCT00212134) evaluated the use of an intraocular lens (IOL) compared with a contact lens during the first 6 months of life to treat unilateral congenital cataract. The results showed equal vision with both.

CONVERGENCE INSUFFICIENCY

Children aged 9 to less than 18 years diagnosed with this disorder, which is present in 5% to 7% of children, were treated in a multicenter, randomized clinical trial[6] to determine the effectiveness of the 4 therapies: office-based vergence/accommodative therapy plus home reinforcement, home-based pencil push-ups, home-based computer vergence/accommodative therapy and pencil push-ups, and office-based placebo therapy.

"The results showed that doing therapy in the office with home reinforcement was better than any other type of therapy, including pencil push-ups," Hertle said.

A separate convergence trial that included 221 patients showed that convergence therapy to treat attention and reading was ineffective for attention and reading, and only helped convergence.[6]

TAKE-HOME

- ***Community support is the most important factor in ascertaining effective treatments for pediatric eye diseases.***

COMMUNITY SUPPORT

When considering all the studies performed in thousands of patients with a variety of visual diseases, the community support was the most consequential factor.

"By allowing the family and their children to participate in these trials and the grants, gifts, endowments, and time, we were able to progress in pediatric eye care," Hertle said. ■

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Hertle has no financial interest in this subject matter.

YOUR PATIENTS WITH DME ARE READY FOR A CHANGE

The power of EYLEA improved and sustained outcomes in the largest phase 3 anti-VEGF clinical trials completed to date in DME (N=862), with improved visual acuity at 52 and 100 weeks.[1]

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 with 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.
- 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.

EYLEA IMPROVED AND SUSTAINED VISION GAINS THROUGH 52 AND 100 WEEKS IN DME[1-3]

	EYLEA 2 MG EVERY 4 WEEKS[§]	EYLEA 2 MG EVERY 8 WEEKS[‖]	CONTROL
VISTA	(n=154)	(n=151)	(n=154)
MEAN CHANGE IN BCVA (52 WEEKS,* 100 WEEKS†)	**+12.5, +11.5 LETTERS**	**+10.7, +11.1 LETTERS**	**+0.2, +0.9 LETTERS**
PROPORTION GAINED ≥15 LETTERS (52 WEEKS,‡ 100 WEEKS†)	**41.6%, 38.3%**	**31.1%, 33.1%**	**7.8%, 13.0%**
VIVID	(n=136)	(n=135)	(n=132)
MEAN CHANGE IN BCVA (52 WEEKS,* 100 WEEKS†)	**+10.5, +11.4 LETTERS**	**+10.7, +9.4 LETTERS**	**+1.2, +0.7 LETTERS**
PROPORTION GAINED ≥15 LETTERS (52 WEEKS,‡ 100 WEEKS†)	**32.4%, 38.2%**	**33.3%, 31.1%**	**9.1%, 12.1%**

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received 1) EYLEA 2 mg administered every 8 weeks following 5 initial monthly doses; 2) EYLEA 2 mg administered every 4 weeks; or 3) macular laser photocoagulation (control) at baseline and then as needed. Protocol-specified visits occurred every 28 (±7) days. In both studies, the primary efficacy endpoint was the mean change from baseline in BCVA at week 52, as measured by ETDRS letter score.
Efficacy of both EYLEA groups was statistically superior vs control at 52 and 100 weeks ($P<0.01$).
*Primary endpoint.
† Prespecified exploratory endpoint.
‡ Secondary endpoint.
§ Last observation carried forward; full analysis set.
‖ Following 5 initial monthly doses.
The results of exploratory endpoints require cautious interpretation and could represent chance findings, as a multiplicity adjustment has not been applied.
anti-VEGF = anti–vascular endothelial growth factor; BCVA = best-corrected visual acuity; DME = Diabetic Macular Edema; ETDRS = Early Treatment Diabetic Retinopathy Study.

See more at HCP.EYLEA.US

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).

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EYLEA®
(aflibercept) Injection
For Intravitreal Injection

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

08/2020
EYL.20.07.0057

EYLEA® (aflibercept) Injection
For Intravitreal Injection

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

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	**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

	CRVO		BRVO	
Adverse Reactions	**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

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	**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

Issue Date: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.19.07.0306

Patient-physician trust and the COVID-19 vaccine

Without a source of primary care that patients turn to, a voice for vaccine legitimacy is lost

By Timothy Hoff, PhD

THE NEWS THAT several viable coronavirus disease 2019 (COVID-19) vaccines will soon be available is positive news. But the bad news is that significant percentages of people may have reservations about getting the COVID-19 vaccine.

At presstime, the Pfizer/BioNTech's vaccine received approval in the United States, and the first patients received an initial dose of the vaccine in early December.

The US Food and Drug Administration's advisory committee in mid-December was holding a key meeting to consider emergency use authorization for Pfizer/BioNTech's COVID-19 vaccine, and was expected to make a ruling. In December, Canada granted emergency approval for the vaccine after health officials determined it met safety, efficacy and quality requirements. Canada was expected to begin its immunization rollout as early as next the third week of December.

Groups that are at a disproportionately higher risk of greater morbidity and mortality from COVID-19, also are potentially even more likely to indicate a willingness to receive a COVID-19 vaccination.

Such findings imply that once a vaccine is available to people, some will choose either to delay getting it or decline to receive it altogether. Depending on how great these numbers become, it may negatively impact our collective ability to develop herd immunity to the illness and lessen its incidence in certain communities. This would mean additional lives lost and more time to recover socially, educationally, and economically from the devastating effects of the pandemic. It also would exacerbate existing health care disparities.

COMPLEX ISSUE

What influences people to be hesitant about receiving a COVID-19 vaccine appears to be a complex issue. A recent study found several different factors—gender, race/ethnicity, concerns about vaccine safety and efficacy, and the source for vaccine endorsements, e.g. public health experts versus politicians—may influence people's likelihood of getting a COVID-19 vaccine.

But the most important underlying cause is the lack of trust people have that a vaccine will do what it is supposed to do and will not result in any adverse health impacts for themselves or their children. The importance of trust in a vaccine is nothing new. Around the world, significant numbers of individuals remain less trusting in the safety and efficacy of vaccines generally.

GAINING TRUST

One important potential source for people gaining greater trust in the COVID-19 vaccine is the doctor, specifically a patient's primary care doctor, or a child's pediatrician. There is plenty of evidence that doctors are an important source of trust for all sorts of medical advice. This includes advice to patients about receiving different types of vaccines, either for themselves or family members. But many of us do not have these trusting, ongoing relationships with doctors.

In the United States, for example, the percentage of people without a regular source of primary care continues to increase. Particular groups such as males and, more specifically, non-White males have been shown to be disproportionately affected, with their percentages higher than the rest of the population.

TAKE-HOME

- ***With questions, concerns and anxieties about a COVID-19 vaccine rising in the US, it is important for patients to have access to a critical voice of legitimacy to ease their fears.***

ACCESS DISTRIBUTION AN ISSUE

Access to regular primary care is also maldistributed geographically, with one study showing census tracts with higher proportions of Black Americans 28 more times likely to be in a lower access area for primary care providers compared to census tracts with a low proportion of Black Americans. Higher percentages of younger millennials also state that they do not have a regular doctor to go to, compared with older generations.

Even where there is access to a regular primary care doctor, the ability to develop ongoing, trusting relationships is hindered by the lack of time available to spend with the doctor, heavy physician workloads that lead to burnout and less attentive physicians, and quality metrics that do not reward the establishment of doctor-patient trust.

Without a regular source of primary care that patients can turn to for expert advice, reassurance, listening, and empathy when it comes to questions, concerns, and anxieties about getting a COVID-19 vaccine, a critical voice of legitimacy is lost, making the loudest voices on the vaccine topic become those of politicians, who are less trusted, and public health agencies and experts, who also now increasingly suffer from public crises of confidence.

TIME TO VACCINATE

When the call comes to receive a COVID-19 vaccine, many of us would like to call up a doctor whom they have seen for a long time, who they believe on matters such as this, and help be convinced it is the right and necessary thing to do. The millions of people who have no regular source of physician-based primary care will be left having to convince themselves and be potentially more subject to influence by misinformation and half-truths.

Make no mistake, this will result in fewer people getting a COVID-19 vaccine.

For years now, we have continually downplayed the growing crisis that involves too many of us not having a regular and trusted source of primary care. We have downplayed the important role played by primary care doctors.

The health care system has encouraged episodic, fast-food sources of episodic primary care such as urgent care centers and retail clinics, where the potential for ongoing, trusting doctor-patient relationships is nonexistent.

It is during a time like this, in the middle of a global pandemic where the main way out of it is getting as many as possible vaccinated, when we see how much not trying to fix this problem may impact not just the health of individuals, but the public at large.

Timothy Hoff, PhD, is professor of management, healthcare systems, and health policy at Northeastern University in Boston; a visiting associate fellow at the University of Oxford, and author of Next in Line: Lowered Care Expectations in the Age of Retail- and Value-Based Health. ■

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

Transscleral laser therapy device simplifies procedure

Noninvasive option reduces IOP in patients with glaucoma

By Jella An, MD; *Special to* Ophthalmology Times®

MicroPulse Transscleral Laser Therapy (MicroPulse TLT) is a nonincisional procedure that substantially reduces IOP for a broad range of glaucoma patients.[1-2] Patient-friendly, safe, and effective, MicroPulse TLT is my preferred nonincisional procedure for glaucoma patients before proceeding to surgical interventions to potentially reduce the number of drop therapies or address drop failure. Recently, a revised MicroPulse P3 Delivery Device was introduced to the market, and it has made the delivery of MicroPulse TLT easier to administer.

An

MicroPulse laser is a treatment mode in the Cyclo G6 Laser System (IRIDEX) that works by "chopping" a continuous-wave laser beam into a series of short bursts of energy with longer off periods. The energy pauses allow the tissue to cool, thus minimizing damage to surrounding tissues.

Numerous studies have demonstrated the safety and efficacy of MicroPulse TLT for a variety of glaucoma types and severity.[1-4] The exact mechanism of action of MicroPulse TLT is still undetermined; however, there is research that suggests it is multifactorial in both trabecular and uveoscleral outflow.[3]

As with any surgery, MicroPulse TLT is subject to several variables, including surgeon technique and individual patient physiology. The revised MicroPulse P3 Device incorporates features that minimize treatment variables to improve consistency in surgeon technique.

THOUGHTFUL DESIGN

I have been using the revised device for more than 10 months, and the overall impression is an improved ease of use. This is due to a number of revised design elements.

- **A recessed fiber tip and an added fluid channel retain the gel, thus enabling consistent fiber immersion in fluid and improved light coupling to the tissue, which is necessary to effectively transmit the laser energy. With the original MicroPulse P3 Device, I had to create a "well" of lidocaine gel on the eye during the procedure; however, the amount of gel made it difficult to see the location of the clear probe when submersed in the gel. The revised design retains the gel within a recessed channel of the probe itself. I use less gel, which makes it cleaner and easier to visualize the probe during the procedure.**
- **A concave, scleral-matching footplate curvature improves probe stability and makes it easier to keep the probe angled to the scleral surface during treatment. In addition, a smaller tip makes the device more agile, makes positioning simpler, and allows for treating the smaller palpebral fissure.**
- **A limbal-matching curvature on the probe's footplate has "bunny ears" that match the curve of the limbus, making it more intuitive to determine correct positioning of the probe.**
- **An elongated stem improves visibility and functions as a speculum to hold back the eyelids during laser delivery. This eliminates the need to maneuver the eye with forceps and prevents subconjunctival hemorrhage.**

IMPROVED ERGONOMICS, IMPROVED RESULTS

I find the revised MicroPulse P3 Device to be simpler to handle. It allows for easier visualization of the treatment area than its predecessor. Even the junior residents at the teaching institution are able to perform MicroPulse TLT because the probe's design makes treatment straightforward and consistent. Repeat treatments can be administered as necessary if the initial reduction in IOP starts to rebound over time. While I still need to analyze my data with the revised probe, survival time was approximately 9 to 12 months with the original probe. I feel I am achieving excellent results while still maintaining a low-risk profile.

CASE EXAMPLE

I had a patient who was a Caucasian man, aged 75 years, with normal tension glaucoma in both eyes. His pressure was 14-15 mm Hg in both eyes on 2 classes of medication, yet he was demonstrating disc heme, a sign that pressures are not sufficiently controlled. This patient was not able to add additional topical therapies due to allergies, and he was not interested in filtering surgery, so I decided to treat the right eye with MicroPulse TLT in June 2019.

I saw him 1 month later and the pressure was 9 mmHg in the right eye. In May 2020, the pressure remained at 10 mm Hg. He has had a sustained response for close to 1 year with no recurrence of disc heme and a stable visual field. I also treated his left eye in August 2019. His preoperative IOP, which measured at 15 mm Hg, had reduced and remained stable at 11 mm Hg for 1 year following the procedure. Both eyes were treated with 2000 mW and 50 seconds per hemisphere (3 sweeps of 20 seconds each). IRIDEX recommends 2500 mW, 50 seconds, and 5 sweeps, so I have shifted to 2500 mW. I have seen no inflammatory complications or decreases in visual acuity with this patient or others.

I have treated my patients with MicroPulse TLT successfully for many years and find it an effective and flexible treatment. I am pleased with the enhancements made to the MicroPulse P3 Device and anticipate continuing to turn to this therapy frequently to treat my patients. ■

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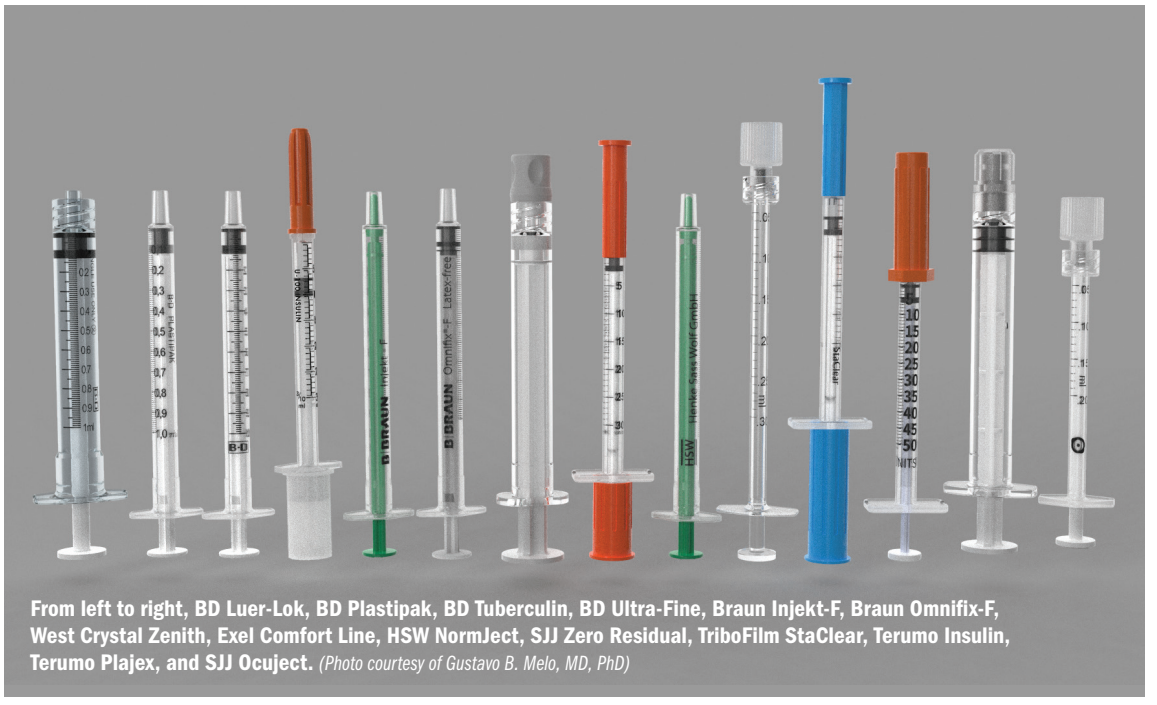
SYRINGE

(Continued from page 1)

"Available data show these droplets matter," he said. "In the 2018 American Society of Retina Specialists PAT [Preferences and Trends] survey, 5% of US retina specialists said they had done vitrectomy for symptomatic droplets and 2% have patients seeking legal action for their floaters. In addition, silicone droplets are linked to inflammatory reactions after aflibercept injection."



From left to right, BD Luer-Lok, BD Plastipak, BD Tuberculin, BD Ultra-Fine, Braun Injekt-F, Braun Omnifix-F, West Crystal Zenith, Exel Comfort Line, HSW NormJect, SJJ Zero Residual, TriboFilm StaClear, Terumo Insulin, Terumo Plajex, and SJJ Ocuject. *(Photo courtesy of Gustavo B. Melo, MD, PhD)*

DEFINING THE IDEAL SYRINGE

According to Melo, the ideal syringe for intravitreal injections would be silicone oil free; have negligible dead space to minimize expensive medication waste; use an attachable needle, giving physicians the option to choose their needle; and feature a Luer lock tip that allows for an attachable needle and prevents liquid leakage along with accidental needle removal.

Melo

"Preferably, it would also be designed for ophthalmic use," Melo said.

OUTLINING PROS AND CONS

Melo and Geoffrey G. Emerson, MD, PhD, an ophthalmologist in private practice at The Retina Center in Minnesota, reviewed the advantages and disadvantages of syringes used for intravitreal injections, including those most commonly used in the Americas and Europe, along with emerging products. They based their information on the silicone oil released by each syringe on scientific publications and personal research. Clinical and scientific experiences were the foundation for comments on additional features.

"Our review included the syringes that we are aware are being used for intravitreal injection. Other syringes, both good and bad, may be available," Melo said.

> "Our review included the syringes that we are aware of being used for intravitreal injection."
>
> – Gustavo B. Melo, MD, PhD

BEST OF THE BATCH

The OcuJect syringe (SJJ Solutions), which is expected to receive CE and FDA certification in mid 2021, seems to meet all the ideal criteria outlined by Melo. It is silicone oil free, has a low volume of dead space and a Luer lock tip, and is designed for ophthalmic use.

The StaClear syringe (TriboFilm Research) recently received FDA clearance for marketing for use in intravitreal injections. It has low dead space and low particulates, complying with USP Chapter 789 testing for ophthalmic solutions. The syringe is manufactured with a silicone lubricant, but the lubricant is fixed to the syringe's lumen.

The Zero Residual Luer Lock syringe (SJJ Solutions) is another syringe that has a lot of positive characteristics. It has a low volume of dead space and a Luer lock tip, can be prefilled air free, and is designed for ophthalmic use. It is not silicone oil free, as it is lubricated with a small amount of oil.

The Daikyo Crystal Zenith (West Pharmaceutical Services) and Plajex (Terumo) syringes have the advantages of being silicone oil free and having a Luer lock tip. In addition, the Daikyo Crystal Zenith complies with USP Chapter 789. However, both syringes have significant dead space and are not available to be filled at point of care.

The Injekt-F (B. Braun Medical Inc) and Norm-Ject (Henke-Sass Wolf) syringes have the advantage of being silicone free. However, they both have moderate dead space and a Luer slip tip.

"The protruding tip of the Injekt-F syringe helps to minimize dead space. However, the design of this syringe can lead to some confusion regarding the injected volume," Melo noted.

THE LONGER LIST

The BD Luer-Lok syringe (Becton, Dickinson and Company), which is distributed with aflibercept in some markets, has a Luer lock tip. On the downside, it is siliconized, albeit with a small amount of silicone oil. In addition, this syringe has a large dead space that wastes expensive drugs, and it is heavy.

Similarly, the company's BD Plastipak syringe, which is available worldwide, and BD Tuberculin syringe, which is more commonly used in the US, are also siliconized and have significant dead space. Another disadvantage is that they have a Luer slip tip.

Available in many markets, the BD Ultra-Fine syringe is an insulin syringe that has negligible dead space. However, it is siliconized with a large amount of oil.

"This syringe is notorious for its association with silicone oil droplets in the vitreous," Melo pointed out. "It has a fixed needle that cannot be substituted."

TAKE-HOME

- ***All syringes used for intravitreal injections have pros and cons. Some recently marketed and forthcoming products are coming closer to meeting "ideal" criteria.***

CONCLUSION

Distributed with ranibizumab (Lucentis, Genentech/Roche) in some markets, the Omnifix-F syringe (B. Braun Medical Inc) is siliconized but with just a small amount of silicone oil. However, it has significant dead space and a Luer slip tip.

The Comfort Point insulin syringe (Exel) is available in the US. It has negligible dead space but a fixed needle, and although it is also siliconized, it releases less oil than the BD Ultra-Fine syringe, according to Melo.

Available in many markets, the insulin syringe manufactured by Terumo Medical also has a low volume of dead space. However, it has a fixed needle and releases a large amount of silicone oil. ■

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This article is based on Melo's video presentation at the European Society of Retina Specialists 2020 Virtual meeting. Melo and Emerson have no financial interests to declare.

Power and Simplicity of ROCK Inhibition

Consistent IOP reduction, whether added to a PGA monotherapy or to a combination of therapies[1,2]

Only Rocklatan® demonstrated superior efficacy over latanoprost in registration trials at all time points[3,4]

IMPORTANT SAFETY INFORMATION FOR RHOPRESSA®

WARNINGS AND PRECAUTIONS

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

Contact Lenses: Contact lenses should be removed prior to instillation of Rhopressa® and may be reinserted 15 minutes following its administration.

IMPORTANT SAFETY INFORMATION FOR ROCKLATAN®

CONTRAINDICATIONS

None.

WARNINGS AND PRECAUTIONS

- Pigmentation changes
- Eyelash changes
- Intraocular inflammation
- Macular edema
- Herpetic keratitis
- Bacterial keratitis
- Contact lens wear

ONCE-DAILY rhopressa® (netarsudil ophthalmic solution) 0.02%

ONCE-DAILY rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%

Visit DISCOVaerieLive.com to learn more about these innovative IOP-lowering treatments

Please refer to Brief Summary on the reverse side.

IOP, intraocular pressure; PGA, prostaglandin analog.

ONCE-DAILY rhopressa® (netarsudil ophthalmic solution) 0.02%

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

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

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

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

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

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

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

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

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

For additional information, please refer to full Prescribing Information at Rhopressa.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-1088.

U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043; 9,931,336

ONCE-DAILY rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005%

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

INDICATIONS AND USAGE
Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% is indicated for the reduction of elevated intraocular pressure (IOP) in patients with open-angle glaucoma or ocular hypertension.

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

If one dose is missed, treatment should continue with the next dose in the evening. The dosage of Rocklatan® should not exceed once daily. Rocklatan® may be used concomitantly with other topical ophthalmic drug products to lower IOP. If more than one topical ophthalmic drug is being used, the drugs should be administered at least five (5) minutes apart.

CONTRAINDICATIONS
None.

WARNINGS AND PRECAUTIONS
Pigmentation
Rocklatan® contains latanoprost which has been reported to cause changes to pigmented tissues. The most frequently reported changes have been increased pigmentation of the iris, periorbital tissue (eyelid), and eyelashes. Pigmentation is expected to increase as long as latanoprost is administered.

The pigmentation change is due to increased melanin content in the melanocytes rather than to an increase in the number of melanocytes. After discontinuation, pigmentation of the iris is likely to be permanent, while pigmentation of the periorbital tissue and eyelash changes have been reported to be reversible in some patients. Beyond 5 years the effects of increased pigmentation are not known.

Iris color change may not be noticeable for several months to years. Typically, the brown pigmentation around the pupil spreads concentrically towards the periphery of the iris and the entire iris or parts of the iris become more brownish. Neither nevi nor freckles of the iris appear to be affected by treatment. While treatment with Rocklatan® can be continued in patients who develop noticeably increased iris pigmentation, these patients should be examined regularly.

Eyelash Changes
Rocklatan® contains latanoprost which may gradually change eyelashes and vellus hair in the treated eye; these changes include increased length, thickness, pigmentation, the number of lashes or hairs, and misdirected growth of eyelashes. Eyelash changes are usually reversible upon discontinuation of treatment.

Intraocular Inflammation
Rocklatan® contains latanoprost which 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 because it may exacerbate inflammation.

Macular Edema
Macular edema, including cystoid macular edema, has been reported during treatment with latanoprost. Rocklatan® 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
Reactivation of herpes simplex keratitis has been reported during treatment with latanoprost. Rocklatan® should be used with caution in patients with a history of herpetic keratitis. Rocklatan® should be avoided in cases of active herpes simplex keratitis because it may exacerbate inflammation.

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

Use with Contact Lenses
Contact lenses should be removed prior to the administration of Rocklatan® and may be reinserted 15 minutes after administration.

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

Rocklatan®
The most common ocular adverse reaction observed in controlled clinical studies with Rocklatan® was conjunctival hyperemia which was reported in 59% of patients. Five percent of patients discontinued therapy due to conjunctival hyperemia. Other common ocular adverse reactions reported were instillation site pain (20%), corneal verticillata (15%), and conjunctival hemorrhage (11%). Eye pruritus, visual acuity reduced, increased lacrimation, instillation site discomfort, and blurred vision were reported in 5-8% of patients.

Other adverse reactions that have been reported with the individual components and not listed above include:

Netarsudil 0.02%
Instillation site erythema, corneal staining, increased lacrimation and erythema of eyelid.

Latanoprost 0.005%
Foreign body sensation, punctate keratitis, burning and stinging, itching, increased pigmentation of the iris, excessive tearing, eyelid discomfort, dry eye, eye pain, eyelid margin crusting, erythema of the eyelid, upper respiratory tract infection/nasopharyngitis/influenza, photophobia, eyelid edema, myalgia/arthralgia/back pain, and rash/allergic reactions.

DRUG INTERACTIONS
In vitro drug interaction studies have shown that precipitation can occur when eye drops containing thimerosal are mixed with Rocklatan®. If such drugs are used, they should be administered at least five (5) minutes apart.

The combined use of two or more prostaglandins or prostaglandin analogs including latanoprost ophthalmic solution 0.005% is not recommended. It has been shown that administration of these prostaglandin drug products more than once daily may decrease the IOP lowering effect or cause paradoxical elevations in IOP.

For additional information, refer to the full Prescribing Information at Rocklatan.com.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

U.S. Patent Nos.: 8,450,344; 8,394,826; 9,096,569; 9,415,043; 9,931,336; 9,993,470; 10,174,017; 10,532,993; 10,588,901; 10,174,017

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

References: 1. Rhopressa® (netarsudil ophthalmic solution) 0.02% Prescribing Information. Aerie Pharmaceuticals, Inc., 2019. **2.** Data on file. Aerie Pharmaceuticals, Inc. **3.** Rocklatan® (netarsudil and latanoprost ophthalmic solution) 0.02%/0.005% Prescribing Information. Aerie Pharmaceuticals, Inc., 2020. **4.** Asrani S, Bacharach J, Holland E, et al. Fixed-dose combination of netarsudil and latanoprost in ocular hypertension and open-angle glaucoma: pooled efficacy/safety analysis of phase 3 MERCURY-1 AND -2. *Adv Ther*. 2020;37(4):1620-1631.

Research is unfolding the proteins in retinitis pigmentosa

Investigators focus on biophysical method to study protein-protein interactions

By Lynda Charters; *Reviewed by Paul Park, PhD*

Investigations into how retinitis pigmentosa (RP) occurs are being conducted at the molecular level in the laboratory of Paul Park, PhD, where researchers study the processes occurring in the photoreceptor cells in the retina. A promising technology used in this research is Förster resonance energy transfer (FRET), a biophysical method to study protein-protein interactions.

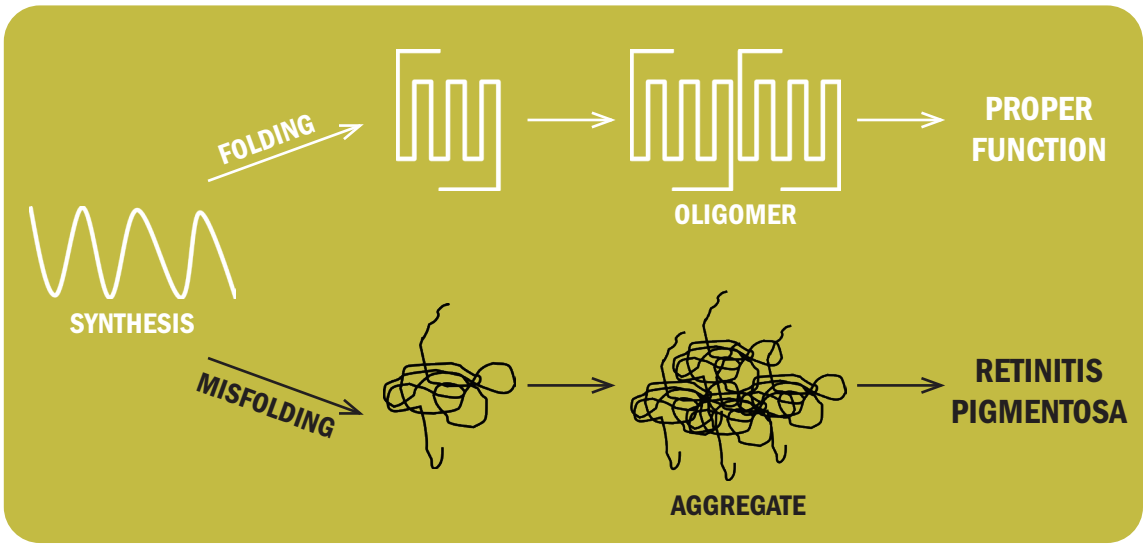
"The disruptions of these cells cause various dysfunctions ranging from mild problems with night blindness to severe ones that result in retinal degenerations and complete blindness," said Park, associate professor at Case Western Reserve University's Department of Ophthalmology and Visual Sciences in Cleveland, Ohio.

Rhodopsin, a protein that detects photons of light that start biochemical reactions, is involved in the initial events of vision and the focus of their work, specifically in relation to factors that maintain the health of the photoreceptor cells.

Rhodopsin's light-sensing activity is mediated by a vitamin A derivative conjugated to the protein. Dysfunctions in rhodopsin cause RP, congenital night blindness, and Leber's congenital amaurosis, and rhodopsin activity can have secondary effects in the pathogenesis of diabetic retinopathy and age-related macular degeneration.

Proper production of rhodopsin with proper 3-dimensional conformation to form higher order structures is paramount for functioning in the eye; protein misfolding results in RP. Using atomic force microscopy, Park and colleagues can visualize the clusters of rhodopsin in the disc membranes in the photoreceptor cells.

When the proper structure of rhodopsin cannot be attained, the consequent misfolding results in toxic complexes (aggregates), with RP as the product.



Investigators are examining retinitis pigmentosa on a molecular level. *(Photo courtesy of Paul Park, MD)*

RP AND FRET

RP is a group of diseases that begin with rod photoreceptor degeneration, leading to eventual cone photoreceptor degeneration and blindness. Mutations in more than 40 genes can cause this process. Among them are mutations in rhodopsin.

"Mutations in the rhodopsin gene are among the leading cause of autosomal-dominant RP, and more than 100 mutations have been identified, a majority [of] which cause protein misfolding and aggregation," Park said.

The mechanism by which the misfolding and aggregation occur and lead to deterioration of the healthy retina is unclear. The misfolding and aggregation of different proteins also are common to Alzheimer disease, Parkinson disease, and prions disease.

The goal now is to gain an understanding of the malignant processes in the eye and to devise strategies to disrupt the aggregation, Park said.

"The challenge that we have is how to study the aggregates of rhodopsin," he said. His laboratory is using FRET to detect protein-protein interactions. He said this is an artificial system devised in his laboratory that facilitates manipulation of rhodopsin DNA to genetically engineer a fluorescent protein that can be fused to the receptor. This can then be expressed in cultured cells for study using FRET.

"FRET allows us to determine if 2 protein molecules are far apart from each other or forming complexes," he said. The investigators look at aggregates by treating the cells with detergents that can disrupt complexes formed by normal rhodopsin but cannot disrupt aggregated rhodopsin.

Park said FRET is being used on a range of different rhodopsin mutations that cause RP, including the *P23H* mutation, and characterizing the aggregation properties. The investigators also are testing various pharmacologic agents.

Investigators have learned that there is variability in the severity of misfolding and aggregation depending on specific mutations. The autosomal-dominant phenotype does not result from physical interactions between mutations and wild-type receptors, useful information to aid in development of medications. Proposed pharmacologic therapies are predicted to be ineffective for some mutations and detrimental for others. Finally, the species background of rhodopsin mutations can affect aggregation properties and the effects of pharmacologic therapies.

The plan is for investigators to correlate the biophysical studies with those in animal models and to formulate strategies to disrupt the mutant aggregates that can then be tested by biophysics and in animal models, Park said. ■

TAKE-HOME

- ***The puzzle surrounding misfolding of proteins in retinitis pigmentosa is being unraveled.***

PAUL PARK, PHD

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Park has no financial interest in this subject matter.

Investigators see link between inflammation, diabetic retinopathy

Study examining the role of IL-17A in patients with diabetes

By Lynda Charters; *Reviewed by Patricia R. Taylor, PhD*

THE FACT THAT many patients with type I diabetes and most with Type II diabetes will develop diabetic retinopathy (DR) during their lifetimes underscores the importance for investigations to preserve vision.

Taylor

DR is now the leading cause of blindness in working-age patients with diabetes worldwide, according to Patricia R. Taylor, PhD, who is working to determine how diabetes-mediated low-grade, chronic inflammation induces DR. Taylor is an assistant professor in the Department of Ophthalmology and Visual Sciences at Case Western Reserve University in Cleveland, Ohio, and a research health scientist at the Louis Stokes Cleveland VA Medical Center.

In 1 scenario, inflammatory proteins, such as cytokines, are produced continuously and the chemical signaling does not turn off. This chronicity can become toxic and induce vascular damage leading to DR, she explained during her presentation at the Cleveland Eye Bank Foundation's virtual Vision Research Symposium in October. Taylor's research is supported by the Cleveland Eye Bank Foundation.

In patients without diabetes, IL-17A is induced during the course of an infection and turned off at the end of the infection. However, in many diabetics, production of IL-17A continues unabated. This is also true in other immune disorders in which IL-17A induces tissue and vascular damage. Taylor took her studies a step further to determine if IL-17A is involved in the development of DR.

She described the results of a pilot study of blood collected from individuals without diabetes and patients with type I diabetes who have or do not have DR. The results indicated that almost no IL-17A was found in the blood of patients without diabetes, but was detected in the blood of all diabetics. Additionally, levels of IL-17A were significantly higher ($P < 0.01$) in patients with diabetes with DR than those without DR.

In another pilot study, Taylor and colleagues investigated vitreous samples from cadaver eyes of individuals without diabetes and diabetics with DR, and they then quantified levels of IL-17A. The investigators found that only the vitreous samples of diabetics with DR had detectable levels of IL-17A.

To achieve a close look at the mechanism of IL-17A in the development of DR, Taylor used a streptozotocin (STZ)-induced diabetes murine model, in which animals were injected into the intraperitoneal with STZ for 5 days. Seventeen days after the final injection, the development of diabetes was confirmed. During the 17-day period, STZ binds to GLUT-2, which transports STZ into the pancreatic β cell, inhibits glucose metabolism, damages the β cell DNA, and inhibits release of insulin.

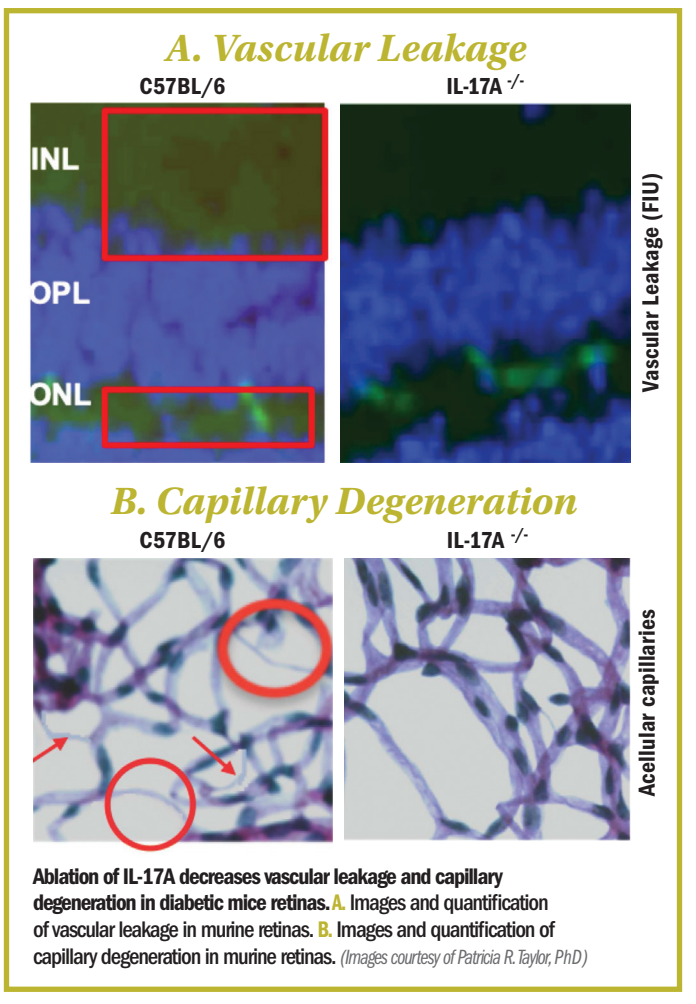
This mechanism caused Type I diabetes 22 days after the first injection. Two months after diabetes was confirmed, retinal inflammation, oxidative stress, and cytokine production were present. Early-stage DR developed by 8 months, which was characterized by vascular permeability and leakage and capillary degeneration. At 2 months, IL-17A was detected in the retinas of diabetic mice but not in the nondiabetic controls.[1]

Eight months following confirmation of diabetes, nondiabetic and diabetic wild-type mice (C57BL/6), were compared with nondiabetic and diabetic IL-17A transgenic-knockout mice to determine if there was a difference in retinal vascular impairment. To examine vascular leakage, mice were injected with fluorescein isothiocyanate-bovine serum albumin, and the retinas were collected post mortem.

Histopathology showed retinal vascular leakage in the inner and outer nuclear layers and in the outer plexiform layer of the diabetic C57BL/6 mice, but no vascular leakage was present in the IL-17A knockout mice. Further, capillary degeneration was significantly higher in the diabetic C57BL/6 mice than in the diabetic IL-17A knockout mice.[2-3]

The investigators concluded that the IL-17A detected in diabetic retinas induces the onset of DR in murine models. Similarly, IL-17A was detected only in the vitreous of cadaver eyes of diabetics with DR, whereas IL-17A was detected in the blood of all diabetic donors and was significantly increased in the diabetics with DR.

To further examine the role of IL-17A in the progression of DR, Taylor and colleagues are carrying out a 4-year clinical study at Louis Stokes Cleveland VA Medical Center in collaboration with Case Western Reserve University's School of Medicine and University Hospitals. ■



Ablation of IL-17A decreases vascular leakage and capillary degeneration in diabetic mice retinas. A. Images and quantification of vascular leakage in murine retinas. **B.** Images and quantification of capillary degeneration in murine retinas. *(Images courtesy of Patricia R. Taylor, PhD)*

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1. Sigurdardottir S, Zapadka TE, Lindstrom SI, et al. Diabetes-mediated IL-17A enhances retinal inflammation, oxidative stress, and vascular permeability. *Cell Immunol.* 2019;341(7):103921. doi:10.1016/j.cellimm.2019.04.009

2. Lindstrom SI, Sigurdardottir S, Zapadka TE, et al. Diabetes induces IL-17A-Act1-FADD-dependent retinal endothelial cell death and capillary degeneration. *J Diabetes Complications.* 2019;33(9):668-674. doi:10.1016/j.jdiacomp.2019.05.016

3. Zapadka TE, Lindstrom SI, Taylor BE, et al. RORγT inhibitor-SR1001 halts retinal inflammation, capillary degeneration, and the progression of diabetic retinopathy. *Int J Mol Sci.* 2020;21(10):3547. doi:10.3390/ijms21103547

PATRICIA R. TAYLOR, PHD

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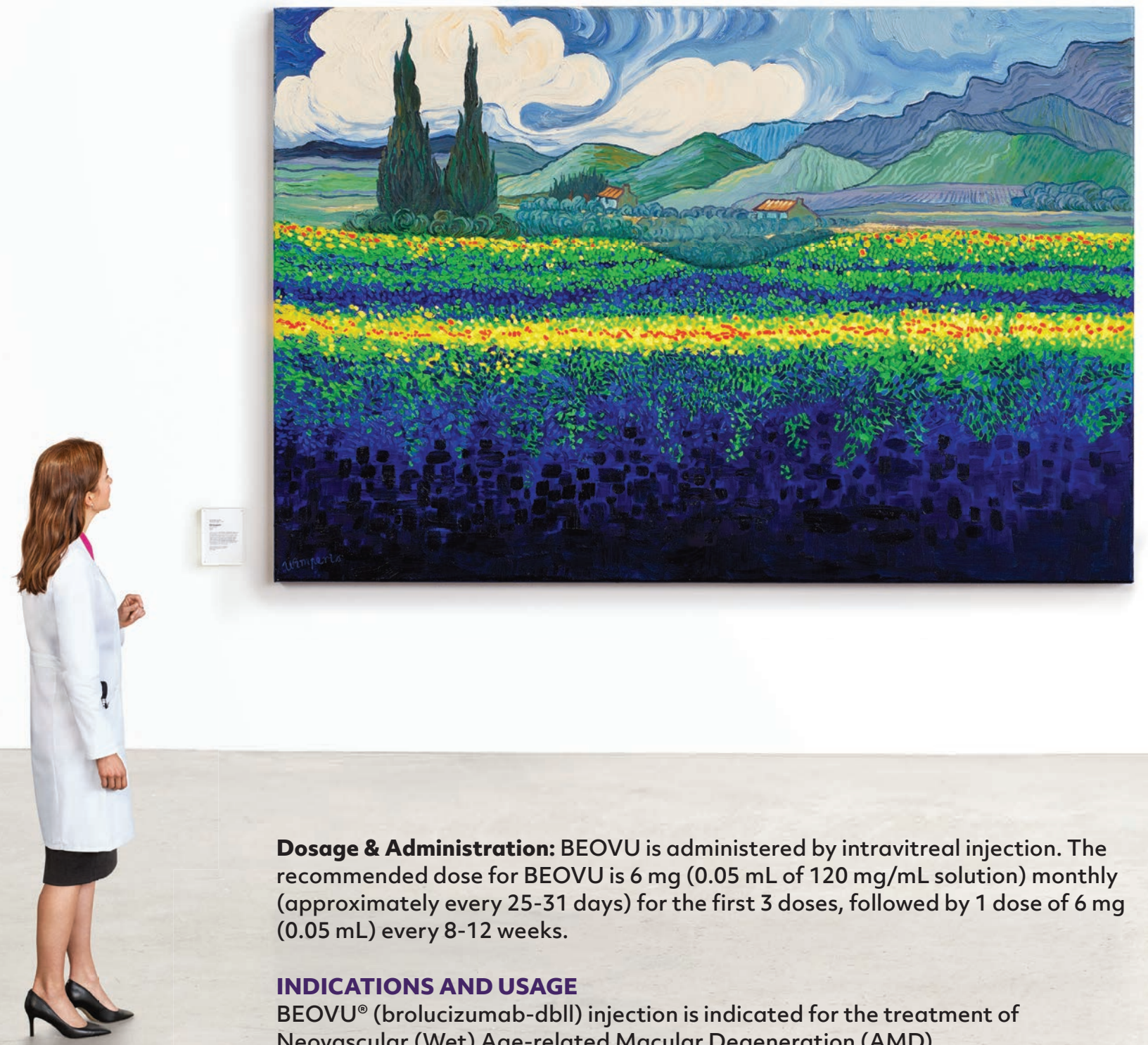
Taylor has no financial interest in this subject matter.

Beovu®
(brolucizumab-dbll)
Injection



Dosage & Administration: BEOVU is administered by intravitreal injection. The recommended dose for BEOVU is 6 mg (0.05 mL of 120 mg/mL solution) monthly (approximately every 25-31 days) for the first 3 doses, followed by 1 dose of 6 mg (0.05 mL) every 8-12 weeks.

INDICATIONS AND USAGE
BEOVU® (brolucizumab-dbll) injection is indicated for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS
BEOVU is contraindicated in patients with ocular or periocular infections, active intraocular inflammation or known hypersensitivity to brolucizumab or any of the excipients in BEOVU. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

AMD=age-related macular degeneration; BCVA=best corrected visual acuity; CST=central subfield thickness; ETDRS=Early Treatment Diabetic Retinopathy Study; IRF=intraretinal fluid; Q8=treatment every 8 weeks; Q12=treatment every 12 weeks; SRF=subretinal fluid.

Contact your local Novartis Sales Specialist or learn more at **BEOVUhcp.com**

THIS WAY TO
BEOVU DATA →

For patients with wet AMD[1]

THEIR VISION IS A WORK OF ART

In 2 head-to-head trials vs aflibercept, BEOVU[1,2]:

- **Achieved** similar mean change in BCVA at Week 48[1]*
- **Started** eligible patients on Q12 immediately after loading, and **maintained** over half at Week 48 (56% and 51%)[1,2†]
- **Demonstrated** greater CST reductions and fewer patients with IRF and/or SRF as early as Week 16, and at Week 48[2‡]

In HAWK, superior CST reductions and reductions in the percentage of patients with IRF and/or SRF were achieved at Week 16 and Week 48. In HARRIER, *P* values are nominal and not adjusted for multiplicity.[2] Clinical significance has not been established. No conclusions of efficacy may be drawn.

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachment

Intravitreal injections, including those with BEOVU, have been associated with endophthalmitis and retinal detachment. Proper aseptic injection techniques must always be used when administering BEOVU. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

Retinal Vasculitis and/or Retinal Vascular Occlusion

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of BEOVU. Patients should be instructed to report any change in vision without delay.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following pages.

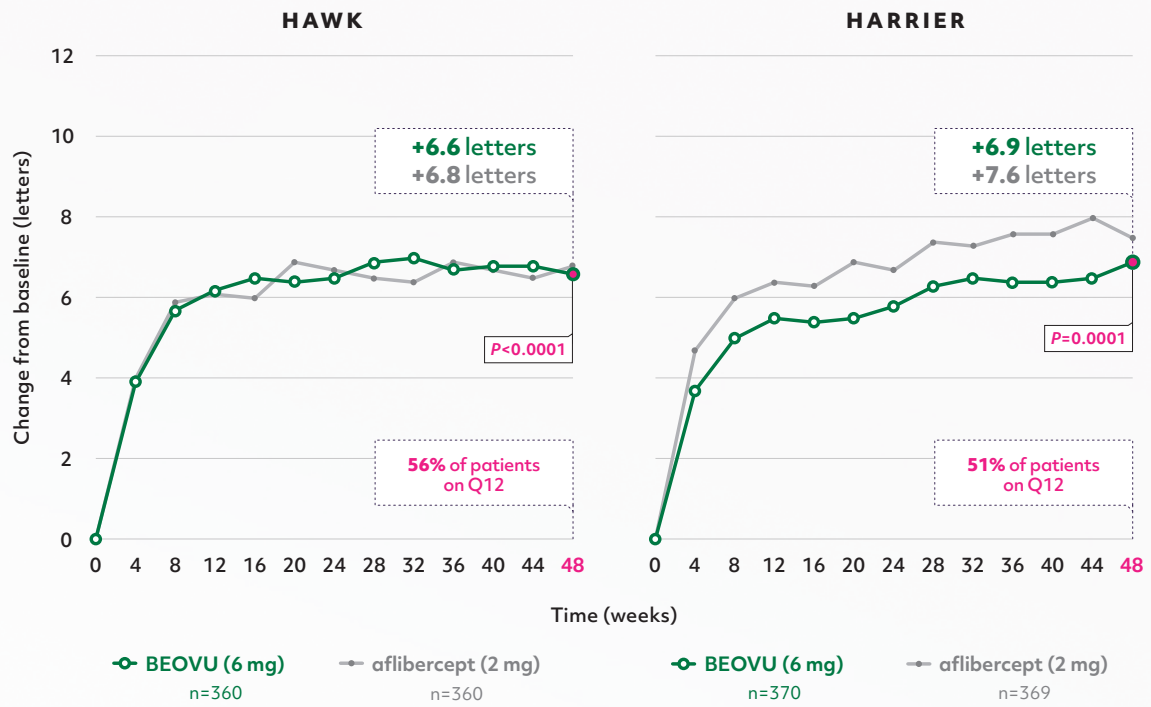
*The primary endpoint was to demonstrate efficacy in mean change in BCVA from baseline at Week 48, measured by ETDRS letters. BEOVU (Q8/Q12) demonstrated noninferiority in BCVA to aflibercept 2 mg (fixed Q8).[1]

†In HAWK and HARRIER, respectively. All remaining patients were on Q8. Patients on BEOVU could be adjusted from Q12 to Q8 at any disease activity assessment.[1,2]

‡CST reductions in patients on BEOVU vs aflibercept at Week 16 in HAWK (P=0.0008): -161.4 µm vs -133.6 µm; Week 48 (P=0.0012): -172.8 µm vs -143.7 µm. CST reductions in patients on BEOVU vs aflibercept at Week 16 in HARRIER (P<0.0001): -174.4 µm vs -134.2 µm; Week 48 (P<0.0001): -193.8 µm vs -143.9 µm. Percentage of patients with IRF and/or SRF on BEOVU vs aflibercept at Week 16 in HAWK (P<0.0001): 34% vs 52%; Week 48 (P=0.0001): 31% vs 45%. Percentage of patients with IRF and/or SRF on BEOVU vs aflibercept at Week 16 in HARRIER (P<0.0001): 29% vs 45%; Week 48 (P<0.0001): 26% vs 44%.[2-4]

Visual gains achieved with BEOVU were similar to aflibercept[1,2]

Primary endpoint: Mean change in BCVA with BEOVU vs aflibercept from baseline to Week 48[1,3,4]



The primary endpoint was to demonstrate efficacy in mean change in BCVA from baseline at Week 48, measured by ETDRS letters. Both studies confirmed the hypothesis of noninferiority at Week 48 with a margin of 4.0 letters.[1,2]

RESULTS SEEN WITH

over half of patients on Q12 at Week 48 (56% and 51%)[1]

Study design: The safety and efficacy of BEOVU were assessed in 2 randomized, multicenter, double-masked, active-controlled, 2-year, Phase III studies in patients with wet AMD (N=1459). The primary endpoint demonstrated noninferiority in mean change in BCVA from baseline to Week 48 vs aflibercept as measured by ETDRS letters. Patients were randomized to receive either BEOVU 6 mg or aflibercept 2 mg (Q8 per label). Disease Activity Assessments (DAAs) were conducted throughout the trial at prespecified intervals. After 3 initial monthly doses, treating physicians decided whether to treat each patient on a Q8 or Q12 interval guided by visual and anatomical measures of disease activity, although the utility of these measures has not been established. Patients with disease activity at Week 16 or at any DAA could be adjusted to Q8 for the remainder of the study.[1,2]

IMPORTANT SAFETY INFORMATION (cont)

WARNINGS AND PRECAUTIONS

Increase in Intraocular Pressure

Acute increases in intraocular pressure (IOP) have been seen within 30 minutes of intravitreal injection including with BEOVU. Sustained IOP increases have also been reported. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately.

Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the BEOVU clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The ATE rate in the two controlled 96-week neovascular AMD studies (HAWK and HARRIER) during the first 96-weeks was 4.5% (33 of 730) in the pooled brolucizumab arms compared with 4.7% (34 of 729) in the pooled aflibercept arms.

ADVERSE REACTIONS

Serious adverse reactions including endophthalmitis, retinal detachment, retinal vasculitis and/or retinal vascular occlusion, increases in intraocular pressure, and arterial thromboembolic events have occurred following intravitreal injections with BEOVU.

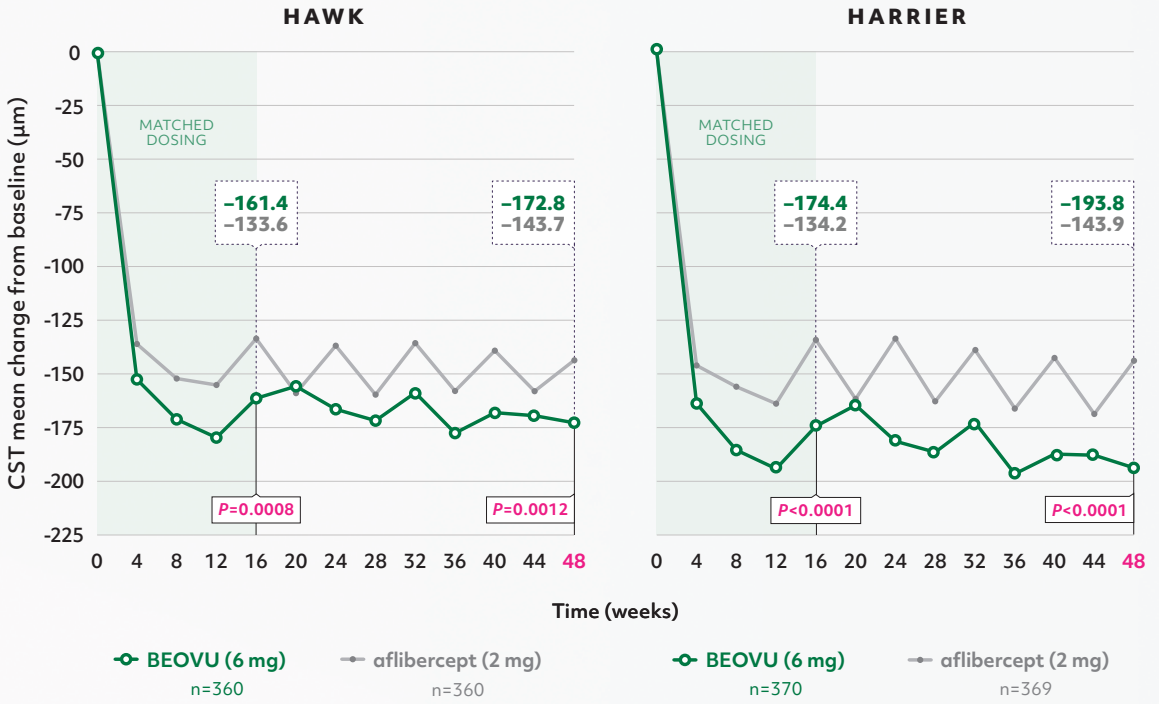
The most common adverse events (≥5% of patients) with BEOVU were vision blurred, cataract, conjunctival hemorrhage, vitreous floaters and eye pain.

REFERENCES: 1. Beovu [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corp; June 2020. **2.** Dugel PU, Koh A, Ogura Y, et al, on behalf of the HAWK and HARRIER Study Investigators. HAWK and HARRIER: Phase 3, multicenter, randomized, double-masked trials of brolucizumab for neovascular age-related macular degeneration. *Ophthalmology*. 2020;127(1):72-84. **3.** Data on file. RTH258-C001 Clinical Study Report. Novartis Pharmaceuticals Corp; December 2018. **4.** Data on file. RTH258-C002 Clinical Study Report. Novartis Pharmaceuticals Corp; December 2018. **5.** Data on file. RTH258-C001 & RTH258-C002 CST. Novartis Pharmaceuticals Corp; September 2019.

Learn more at **BEOVUhcp.com**

Greater CST reductions[2]

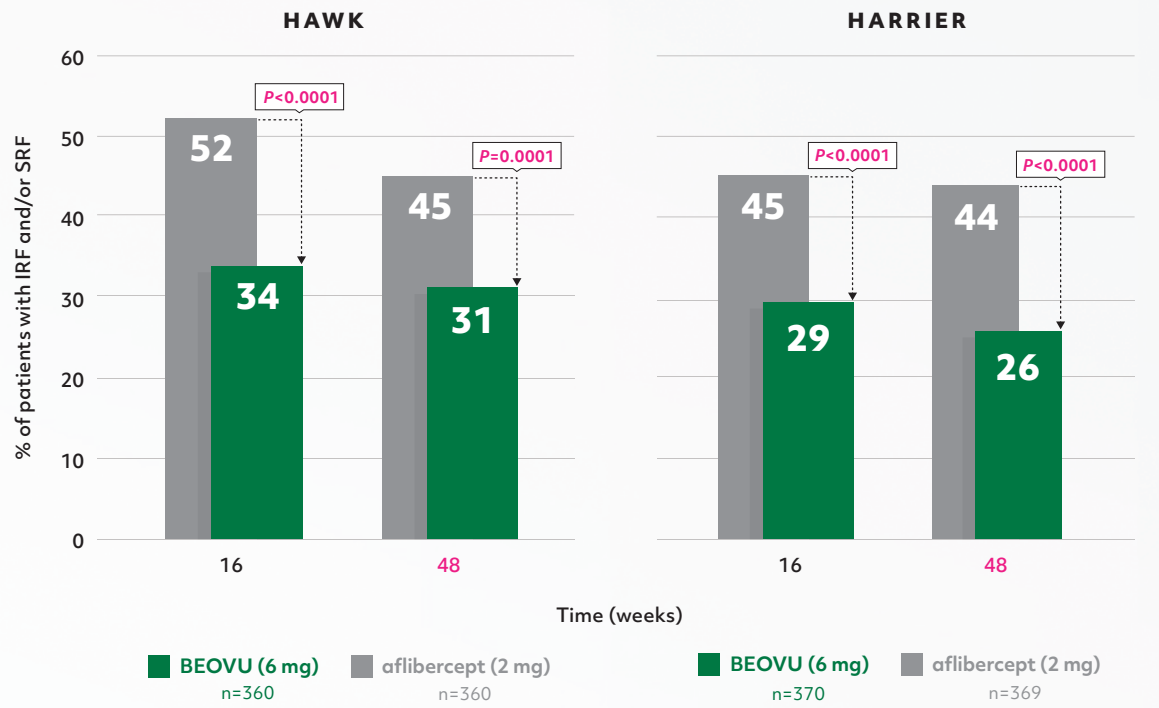
Secondary endpoint: CST reductions with BEOVU vs aflibercept from baseline to Week 48[2-5]



In HAWK, superior CST reductions were achieved at Week 16 and Week 48. In HARRIER, *P* values are nominal and not adjusted for multiplicity.[2] Clinical significance has not been established. No conclusions of efficacy may be drawn.

Fewer patients with IRF and/or SRF[2]

Secondary endpoint: % of patients on BEOVU with IRF and/or SRF vs aflibercept at Weeks 16 and 48[3,4]



In HAWK, superior reductions in the percentage of patients with IRF and/or SRF were achieved at Week 16 and Week 48. In HARRIER, *P* values are nominal and not adjusted for multiplicity.[2] Clinical significance has not been established. No conclusions of efficacy may be drawn.

IMPORTANT SAFETY INFORMATION (cont)

ADVERSE REACTIONS (cont)

As with all therapeutic proteins, there is a potential for an immune response in patients treated with BEOVU. Anti-brolucizumab antibodies were detected in the pre-treatment sample of 36% to 52% of treatment naive patients. After initiation of dosing, anti-brolucizumab antibodies were detected in at least one serum sample in 53% to 67% of patients treated with BEOVU. Intraocular inflammation was observed in 6% of patients with anti-brolucizumab antibodies detected during dosing with BEOVU. The significance of anti-brolucizumab antibodies on the clinical effectiveness and safety of BEOVU is not known.

Please see additional Important Safety Information and Brief Summary of full Prescribing Information on the following page.

NOVARTIS

Novartis Pharmaceuticals Corporation
East Hanover, New Jersey 07936-1080

12/20

BVU-1397760

Beovu® (brolucizumab-dbll) Injection

BEOVU® (brolucizumab-dbll) injection, for intravitreal use
Initial U.S. Approval: 2019

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

1 INDICATIONS AND USAGE

BEOVU® is indicated for the treatment of Neovascular (Wet) Age-related Macular Degeneration (AMD).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections

BEOVU is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation

BEOVU is contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity

BEOVU is contraindicated in patients with known hypersensitivity to brolucizumab or any of the excipients in BEOVU. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, erythema, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachment

Intravitreal injections, including those with BEOVU, have been associated with endophthalmitis and retinal detachment *[see Contraindications (4.1) and Adverse Reactions (6.1)]*. Proper aseptic injection techniques must always be used when administering BEOVU. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately *[see Dosage and Administration (2.4) and Patient Counseling Information (17) in the full prescribing information]*.

5.2 Retinal Vasculitis and/or Retinal Vascular Occlusion

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of BEOVU *[see Contraindications (4.2) and Adverse Reactions (6.1)]*. Patients should be instructed to report any change in vision without delay.

5.3 Increase in Intraocular Pressure

Acute increases in intraocular pressure (IOP) have been seen within 30 minutes of intravitreal injection, including with BEOVU *[see Adverse Reactions (6.1)]*. Sustained IOP increases have also been reported. Both IOP and perfusion of the optic nerve head must be monitored and managed appropriately *[see Dosage and Administration (2.4) in the full prescribing information]*.

5.4 Thromboembolic Events

Although there was a low rate of arterial thromboembolic events (ATEs) observed in the BEOVU clinical trials, there is a potential risk of ATEs following intravitreal use of VEGF inhibitors. Arterial thromboembolic events are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

The ATE rate in the two controlled 96-week neovascular AMD studies (HAWK and HARRIER) during the first 96-weeks was 4.5% (33 of 730) in the pooled brolucizumab arms compared with 4.7% (34 of 729) in the pooled aflibercept arms *[see Clinical Studies (14.1) in the full prescribing information]*.

6 ADVERSE REACTIONS

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

- Hypersensitivity *[see Contraindications (4.3)]*
- Endophthalmitis and Retinal Detachment *[see Warnings and Precautions (5.1)]*
- Retinal Vasculitis and/or Retinal Vascular Occlusion *[see Warnings and Precautions (5.2)]*
- Increase in Intraocular Pressure *[see Warnings and Precautions (5.3)]*
- Thromboembolic Events *[see Warnings and Precautions (5.4)]*

6.1 Clinical Trials Experience

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

A total of 1088 patients, treated with brolucizumab, constituted the safety population in the two controlled neovascular AMD Phase 3 studies (HAWK and HARRIER) with a cumulative 96 week exposure to BEOVU, and 730 patients treated with the recommended dose of 6 mg *[see Clinical Studies (14.1) in the full prescribing information]*.

Adverse reactions reported to occur in ≥ 1% of patients who received treatment with BEOVU pooled across HAWK and HARRIER, are listed below in Table 1.

Table 1: Common Adverse Reactions (≥ 1%) in the HAWK and HARRIER wet AMD Clinical Trials

Adverse Drug Reactions	BEOVU (N = 730)	Active Control (aflibercept) (N = 729)
Vision blurred[a]	10%	11%
Cataract	7%	11%
Conjunctival hemorrhage	6%	7%
Vitreous floaters	5%	3%
Eye pain	5%	6%
Intraocular inflammation[b]	4%	1%
Intraocular pressure increased	4%	5%
Retinal hemorrhage	4%	3%
Vitreous detachment	4%	3%
Conjunctivitis	3%	2%
Retinal pigment epithelial tear	3%	1%
Corneal abrasion	2%	2%
Hypersensitivity[c]	2%	1%
Punctate keratitis	1%	2%
Retinal tear	1%	1%
Endophthalmitis	1%	< 1%
Blindness[d]	1%	< 1%
Retinal artery occlusion	1%	< 1%
Retinal detachment	1%	< 1%
Conjunctival hyperemia	1%	1%
Lacrimation increased	1%	1%
Abnormal sensation in eye	1%	2%
Detachment of retinal pigment epithelium	1%	< 1%

[a]Including vision blurred, visual acuity reduced, visual acuity reduced transiently, and visual impairment.
[b]Including anterior chamber cell, anterior chamber flare, anterior chamber inflammation, chorioretinitis, eye inflammation, iridocyclitis, iritis, retinal vasculitis, retinal vascular occlusion, uveitis, vitreous haze, vitritis.
[c]Including urticaria, rash, pruritus, erythema.
[d]Including blindness, blindness transient, amaurosis, and amaurosis fugax.

6.2 Immunogenicity

As with all therapeutic proteins, there is a potential for an immune response in patients treated with BEOVU. The immunogenicity of BEOVU was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to BEOVU 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 BEOVU with the incidence of antibodies to other products may be misleading.

Anti-brolucizumab antibodies were detected in the pre-treatment sample of 36% to 52% of treatment naive patients. After initiation of dosing, anti-brolucizumab antibodies were detected in at least one serum sample in 53% to 67% of patients treated with BEOVU. Intraocular inflammation was observed in 6% of patients with anti-brolucizumab antibodies detected during dosing with BEOVU.

The significance of anti-brolucizumab antibodies on the clinical effectiveness and safety of BEOVU is not known.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of BEOVU administration in pregnant women.

Based on the anti-VEGF mechanism of action for brolucizumab *[see Clinical Pharmacology (12.1) in the full prescribing information]*, treatment with BEOVU may pose a risk to human embryo-fetal development. BEOVU should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

All pregnancies have a background risk of birth defect, loss, and 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 is 2%-4% and of miscarriage is 15%-20% of clinically recognized pregnancies.

Data

Animal Data

VEGF inhibition has been shown to cause malformations, embryo-fetal resorption, and decreased fetal weight. VEGF inhibition has also been shown to affect follicular development, corpus luteum function, and fertility.

8.2 Lactation

Risk Summary

There is no information regarding the presence of brolucizumab 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 transferred in human milk and because of the potential for absorption and adverse reactions in the breastfed child, breastfeeding is not recommended during treatment and for at least one month after the last dose when stopping treatment with BEOVU.

8.3 Females and Males of Reproductive Potential

Contraception

Females

Females of reproductive potential should use highly effective contraception (methods that result in less than 1% pregnancy rates) during treatment with BEOVU and for at least one month after the last dose when stopping treatment with BEOVU.

Infertility

No studies on the effects of brolucizumab on fertility have been conducted and it is not known whether brolucizumab can affect reproductive capacity. Based on its anti-VEGF mechanism of action, treatment with BEOVU may pose a risk to reproductive capacity.

8.4 Pediatric Use

The safety and efficacy of BEOVU in pediatric patients has not been established.

8.5 Geriatric Use

In the two Phase 3 clinical studies, approximately 90% (978/1089) of patients randomized to treatment with BEOVU were ≥ 65 years of age and approximately 60% (648/1089) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is required in patients 65 years and above.

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Study: Innovative dexamethasone formulation shows efficacy, safety

Once-daily corticosteroid treats pain, inflammation after surgery

By Cheryl Guttman Krader, BS Pharm; *Reviewed by Eric D Donnenfeld, MD*

Results of a phase 2 trial suggest that OCS-01 (dexamethasone cyclodextrin nanoparticle ophthalmic suspension 1.5% mg/mL, Oculis), a novel topical formulation of dexamethasone, has the potential to become the first once-daily and preservative-free topical corticosteroid for treating pain and inflammation after ocular surgery, according to Eric D. Donnnenfeld, MD.

Donnenfeld reported results from the SKYGGN study, which randomly assigned 153 patients 1:1:1 to treatment with OCS-01 once daily, OCS-01 twice daily, or vehicle for 14 days. The study met its primary end points analyzing absence of anterior chamber cells at postoperative (postop) day 15 and absence of ocular pain at postop day 4. There were no efficacy differences between the two OCS-01 dosing regimens and both were safe and well tolerated.

"Inflammation and pain remain expected consequences of ocular surgery. Although available topical steroids are effective for treating these sequelae, potency and compliance with products that need to be used several times a day are major issues," said SKYGGN investigator Donnenfeld, a clinical professor of ophthalmology at New York University Langone Medical Center, New York, and a founding partner at Ophthalmic Consultants of Connecticut.

> "The overall adverse event rate was higher in the vehicle group than in the OCS-01 groups, probably because the adverse events were procedure related rather than treatment related."
>
> – Eric D. Donnenfeld, MD

"[With a] novel and proprietary nanoparticle formulation, OCS-01 was developed to deliver a potent anti-inflammatory effect and excellent safety profile with once-a-day dosing," he said.

Donnenfeld noted that the concentration of dexamethasone in OCS-01 is 15-fold greater than that found in commercially available topical dexamethasone suspension. In addition, the novel vehicle used for OCS-01 increases ocular surface residency time to hours compared with the minutes using conventional dexamethasone 0.1% suspension. Furthermore, the proprietary nanoparticle technology enhances penetration of the active ingredient. As another benefit, the formulation is preservative-free.

TAKE-HOME

- ***A vehicle-controlled phase 2 study investigating once- and twice-daily administration of a novel, preservative-free topical formulation of dexamethasone as treatment for pain and inflammation after cataract surgery met its primary end points.***

SKYGGN DESIGN AND OUTCOMES

A total of 20 US centers participated in the SKYGGN study. Patients were eligible for enrollment if they had an anterior chamber cell score of 2 or greater at their first postop visit 18 to 30 hours post uncomplicated cataract surgery. In addition, they had to have a pin-hole Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity without any other correction that was greater than 20 letters (approximately 20/400) in the operative eye and greater than 35 letters (approximately 20/200) in the fellow eye. Follow-up visits were scheduled at post-op days 4, 8, 15, and 22.

The 3 study groups were similar at baseline in their demographic characteristics, and 148 patients completed the study. The mean age of patients across the 3 groups ranged from 66 to 68 years, approximately two-thirds of participants were female, and the majority were Caucasian.

The percentage of patients with absence of anterior chamber cells on day 15 in the OCS-01 once-daily, OCS-01 twice-daily, and vehicle group was 51.0%, 66.7%, and 45.1%, respectively ($P < .0001$ for both OCS-01 groups vs vehicle). Absence of pain on day 4 was achieved by 72.5% of patients treated with OCS-01 once daily and by 19.6% of controls ($P < .005$). In the OCS-01 twice-daily group, 62.7% of patients were pain-free on day 4 ($P = .074$ vs vehicle).

"Data on [the] percentage of patients with absence of anterior chamber cells from earlier postoperative visits show [that] a statistically significant difference favoring the once-daily OCS-01 group versus vehicle was achieved on day 8," Donnenfeld said. "The results for the pain assessment showed the proportion of patients who were pain-free increased in all groups as follow-up continued, but the difference was statistically significant between both OCS-01 groups and vehicle at days 8 and 15."

One patient in the vehicle group and 1 patient treated with OCS-01 twice daily withdrew from the study because of an adverse event. However, there were no significant ocular or systemic adverse events. Importantly, IOP of 30 mm Hg or greater was not observed in any patients at any follow-up visits nor did any patient have a 10 mm Hg or greater increase from baseline IOP.

"The overall adverse event rate was higher in the vehicle group than in the OCS-01 groups, probably because the adverse events were procedure related rather than treatment related," Donnenfeld said.

CONCLUSION

Donnenfeld noted that the potent activity, safety, and tolerability of OCS-01 observed in SKYGGN are consistent with results of another phase 2 trial investigating the novel steroid formulation as a treatment for diabetic macular edema. The latter study enrolled 144 patients and found a statistically significantly greater decrease in central macular thickness in patients treated with OCS-01 compared with vehicle-treated controls. There were no significant ocular adverse events in the OCS-01 group. ■

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Physicians discuss advancements in the treatment of wet AMD

The current treatments are good, but the best is yet to come

By Lynda Charters

LEADING RETINA SPECIALISTS focusing on the treatment of wet age-related macular degeneration (AMD) gathered for a discussion in the *Ophthalmology Times*® and *Modern Retina*® Viewpoint series to discuss the disease diagnosis and clinical manifestations, with an emphasis on treatment and new technologies in the pipeline.

The panel was moderated by **Caroline R. Baumal**, MD, a professor of ophthalmology at Tufts University School of Medicine in Boston. The panel also included **Thomas Albini**, MD, professor of ophthalmology at Bascom Palmer Eye Institute, Miami; **Aleksandra Rachitskaya**, MD, assistant professor of ophthalmology at the Cole Eye Center in Cleveland, Ohio; and **Michael Singer**, MD, professor of ophthalmology at University of Texas San Antonio.

Baumal pointed out a hallmark of wet macular degeneration is choroidal neovascularization and the pathophysiology of AMD is multifactorial.

"This makes for a really complex mechanism involving metabolic, functional, genetic, and environmental factors," she said. "There is so much that we need to know about AMD and why wet AMD develops in some people and dry AMD in others."

A few trends in AMD are becoming more apparent, the first being the increasing prevalence in the aging population.

Albini pointed out that AMD is "exploding" and may double over the next 2 decades. The current estimates are that between 10-11 million Americans are affected with all forms of AMD, with wet AMD accounting for probably 10% of that, he explained.

Rachitskaya said she is seeing older patients who present with more advanced disease, such as neovascular AMD or even more geographic atrophy than ever before. People with a history of smoking or who are active smokers are at a higher risk. Her typical patients usually have 20/40-20/60 vision and the current treatments are very effective. She also noted that she sees older patients who present with very advanced wet AMD, and despite effective treatments, their vision is not restorable as effectively as with early presentation. Singer reported that other trends are shot fatigue and compliance issues.

TREATMENT

The basic treatment approaches are monthly regimens, as-needed injections, and treat-and-extend. Rachitskaya prefers treat-and-extend to keep retinas as dry as possible, while Albini said his treatment decisions are patient-specific considerations that he combines with treat-and-extend. Singer said he tends toward patient-specific decisions, adding that he finds that in many cases he is hampered by insurance coverage demanding step therapy. He prefers using the branded drugs because of better retinal drying, which is an objective measure on optical coherence tomography (OCT). When a retina is dry, he said he extends the treatment interval.

The anti-vascular endothelial growth factor (VEGF) drug used most often to treat AMD is bevacizumab (Avastin, Genentech Inc), as an off-label intravitreal injection. The advantages, Albini said, are that it is aliquoted, cheaper that other FDA-approved agents, and is not inferior to ranibizumab (Lucentis, Genentech Inc), the first FDA-approved agent still used; no differences are seen between them when administered as-needed. Aflibercept (Eylea, Regeneron), also noninferior to ranibizumab, is perhaps the most commonly used FDA-approved drug in the US; many physicians may favor aflibercept because of its slightly better drying potential, resulting in longer treatment intervals.

Brolucizumab (Beovu, Novartis) was approved recently for wet AMD, but a downside is the higher overall inflammation rate compared with aflibercept, which has affected its widespread acceptance. Albini noted that brolucizumab may have even better drying power and even better durability; it is a smaller molecule, which permits more molecules to be injected thus extending the half-life and decreasing the injection burden.

Rachitskaya said she appreciates the availability of these drugs, but is looking ahead to newer technologies to alleviate injection burden, such as new injectables, combination therapies, or a therapy such as a core delivery system or gene therapy. Until these technologies arrive, she said she encourages patients about their treatment status to bolster compliance.

Safety is always a concern with intravitreal injections. For Albini, one consideration is the risk of endophthalmitis, despite the low incidence. Discussions with patients are important and should include retinal detachments and vitreous hemorrhages. Intraocular inflammation is often being discussed because of the occurrence of severe cases with occlusive vasculitis with brolucizumab. OCT has added to the safety of injections and facilitates guided injections based on the anatomy visible on the scans, he said.

Some physicians administer bilateral injections to treat AMD. Rachitskaya said she does so to ease the patient travel burden. Regarding bevacizumab, Albini noted that physicians should trust the source of the drug because of cluster outbreaks of *Streptococcus* endophthalmitis cases.

NEW TECHNOLOGIES

Development of biosimilar drugs is a new technologic spin that is envisioned to eventually play a larger role in the US. The concept of biosimilar formulations has come to the fore because the patents on the drugs currently used to treat are expiring, which raises the question about new biosimilars coming to market and their costs.

According to Rachitskaya, current AMD drugs are biologics, i.e., derived from living organisms.

"Biosimilars are not intended to be carbon copies of aflibercept or ranibizumab; they are similar and provide the same therapeutic endpoint, in contrast to generic drugs that are carbon copies of the original drugs," she said.

Singer mentioned faricimab (Roche), an Ang-2 blocker that is combined with ranibizumab in 1 molecule for vessel stabilization. This drug has shown good results in the STAIRWAY, TENAYA, and LUCERNE trials.

The Port Delivery System with ranibizumab (Genentech) provides continuous drug release over time, with the vast majority of patients did not need refills before 6 months. Results show less macular atrophy than monthly injections.

KSI-301 (Kodiak Sciences), is an antibody biopolymer conjugate, that uses a large molecular structure to bind to and inhibit VEGF; in a Phase I study about 44% of patients had an extended duration of action out to 6 months.

Albini said he is looking forward to upcoming gene therapies that use various vectors to manipulate the retinal pigment epithelial cells, photoreceptors, or other ocular cells to make the drug continuously perhaps as the result of a 1-time delivery.

Singer looks forward to at-home OCT monitoring, which he envisions will facilitate longer periods between injections and patients will be able to advise physicians when an injection is needed. The Notal OCT Analyzer (Notal Vision) is 1 such device.

Generally speaking, the consensus is that the future for neovascular AMD is promising.

"There is an amazing group of drugs from which to choose compared with a decade ago and they improve over time. It is an amazing era and has been a huge change for ophthalmology," Albini concluded. ■

Harnessing 1-2 punch of KAMPs for corneal infection, inflammation

Peptides offering ophthalmologists a potential treatment option for keratitis

By Lynda Charters; *Reviewed by K.P. Connie Tam, PhD*

KERATITIS IS A common presentation in clinics, and some cases can threaten vision. For the most serious cases, keratin 6A (*KRT6A*)-derived antimicrobial peptides (KAMPs) may answer the need for adequate therapy, an effective option against various bacterial pathogens that cause keratitis.

Tam

A second benefit of KAMPs that was recently discovered is that they can inhibit production of cytokines from white blood cells and suppress pathologic cell recruitment to the inflamed cornea, according to K.P. Connie Tam, PhD. It also underscored the need for effective antimicrobial therapies in cases that are unresponsive to antibiotics.

Part of the problem is the reduction of the effectiveness of classic antibiotics because of resistance by the 2 most common pathogens, *Pseudomonas aeruginosa* and *Staphylococcus aureus*, she said. The resistance will not abate until new antibiotics are clinically available. The other part of the problem is that the drugs are too similar to existing ones.

Tam also underscored the importance of moving away from traditional ophthalmic steroids because of their adverse effects, although they do have a use in certain cases. She is associate staff at the Cleveland Clinic Cole Eye Institute and Lerner Research Institute, and an assistant professor of ophthalmology at the Cleveland Clinic Lerner College of Medicine of Case Western Reserve University, Cleveland.

HUMAN KAMPS

One area Tam and colleagues have focused on is developing novel anti-infective and anti-inflammatory drugs. KAMPs are fragments that belong to the keratin 6A protein, a building block that forms a filament network that helps maintain structure in epithelial cells.

The investigators found that when KAMPs are added to corneal epithelial cells infected with bacteria, the bacteria become inactivated. Tam demonstrated the severe damage that KAMPs inflicted on *P aeruginosa* and *S aureus* bacterial cell envelopes in scanning and transmission electron microscopy images.

The investigators also showed, in an in vitro study, the decreased inflammation that KAMPs can achieve by suppressing cytokine secretion from murine neutrophils and macrophages in a dose-dependent manner. Addition of KAMPs to these cells under stimulation with lipopolysaccharide (LPS) and lipoteichoic acid (LTA) significantly reduced quantities of cytokines, such as tumor necrosis factor alpha (TNFα), interleukin 6, and chemokine ligands 1 and 2.

When KAMPs were instilled in human corneal epithelial cell culture and live mouse corneas, no toxicity was observed, compared with samples bearing the damage caused by a common antimicrobial preservative benzalkonium chloride.

"Overall, KAMPs appear to be nontoxic to the eye," Tam said.

In a mouse model of corneal disease, KAMPs were found to suppress noninfectious inflammation induced by inactivated *P aeruginosa* and *S aureus*. In this model, the KAMP eye drops were administered before or after the induction. After 24 hours, corneal cytokines were measured and the same effect was seen as in vitro.

"KAMP eye drops reduced inflammation in vivo by suppressing cytokine production and immune cell infiltration," Tam said.

In a wound-healing model, KAMP eye drops suppressed inflammation and accelerated the epithelial wound closure compared to the control peptide.

In a mouse model of corneal infection, the groups were infected with *P aeruginosa* and *S aureus*. After 24 hours, 1 group was untreated as control and the other group was treated with KAMP drops 3 times daily for 3 days. KAMPs eliminated most bacteria and reduced disease severity for the infected corneas, controlling the infection.

Tam summarized the key points in this line of investigation. The global increase in antibiotic resistance poses a serious risk of vision loss in patients with ocular infections. Development of a new class of antibiotics is critical. In a mouse model of sterile corneal inflammation, topical KAMPs suppressed LPS- and LTA-induced releases of cytokines accompanied by neutrophil and macrophage infiltration.

A mouse model of corneal wound healing indicated that topical KAMPs accelerate epithelial wound closure. A mouse model of corneal infection showed that topical KAMPs blocked infection by killing the bacteria and suppressed inflammation by reducing cytokine production and immune cell infiltration. ■

TAKE-HOME

- ***Keratin 6A-derived antimicrobial peptides fight corneal infection and inflammation.***

This image shows cells with no peptide, left, and then after KAMPs have been added. *(Photo courtesy of K.P. Connie Tam, PhD)*

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Tam is an inventor designated on a patent for KAMPs.

Anti-VEGF medications may cause systemic complications in ROP

Investigators examine long-term effects of therapeutics in infants

By Lynda Charters; *Reviewed by Kamiar Mireskandari, PhD, MBCHB, FRCSEd, FRCOphth*

ANTI-VEGF DRUGS ARE being used with increasing frequency for treatment of retinopathy of prematurity (ROP) in an off-label capacity, and they have been reported to be effective.[1,2]

However, concerns exist about the absorption of these drugs resulting in systemic complications in babies with ROP, according to Kamiar Mireskandari, PhD, MBCHB, FRCSEd, FRCOphth.

Mireskandari

Mireskandari is the John and Melinda Thompson Chair in Vision Research at The Hospital for Sick Children, which is affiliated with the University of Toronto in Ontario.

Evidence supports the effects of systemic absorption of anti-VEGF drugs. Intravitreally injected bevacizumab (Avastin, Genentech) is systemically absorbed and causes a reduction of VEGF in serum levels for about 8 weeks.[3]

The same investigators also conducted a study in which they compared aflibercept (Eylea, Regeneron Pharmaceuticals) with bevacizumab and reported that both drugs reduced the serum levels of VEGF for 12 weeks.[4]

In contrast, the RAINBOW study (NCT02375971) reported that ranibizumab (Lucentis, Genentech), even at high doses, does not have a significant effect on serum VEGF levels. [2]

RELEVANCE OF DECREASED VEGF

Despite its relative isolation, the eye is connected to the rest of the body. When the VEGF in the vitreous decreases in response to treatment, so does the VEGF in the serum.

"The retina, the organ most affected by intravitreal injections, goes on to vascularize and function well," Mireskandari said. "Why are remote bodily tissues affected by a relatively small change?"

To find out, he and his colleagues used a rat model in which rat pups were given a high dose of anti-VEGF, weighed for 14 days, and then killed on the last day to examine the organs.

Mireskandari reported that the anti-VEGF antibody was present in the systemic circulation 2 weeks after the injection. Evaluation of the whole body indicated that 1 anti-VEGF injection did not significantly affect the weights of the body, brain, lungs, liver, or kidneys.

However, the injection caused cardiac hypertrophy and pulmonary hypertension. The investigators also found the mRNA expression for VEGF was elevated in the lung and kidney but not the brain or liver.[5]

"These findings indicate that even though the whole body and organ weights did not change markedly as the result of the systemic VEGF levels at 14 days at the molecular levels, there was a signaling change for the lung and kidney, [which possibly affected] these organs," Mireskandari explained. "It is important to note that pulmonary hypertension is a potential problem and that there were no effects on the liver and brain."

The long-term systemic effects of VEGF are important to consider. Bronchopulmonary dysplasia is a problem in premature babies and may be affected by injection of bevacizumab. In the BEAT-ROP study (NCT00622726), 5 deaths occurred among the babies who received bevacizumab due to respiratory issues compared with the death of 2 babies treated with laser thereapy.[1] In the kidney, glomerular filtration is VEGF-dependent and may be a factor over time. The effects of VEGF on the brain and liver are inconclusive and require more study, Mireskandari concluded. ■

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Mireskandari is a consultant to Santen Canada and AbbVie. Use of anti-VEGF agents is off-label in ROP.

CATARACT PATIENTS

(Continued from page 1)

particularly if initiated in the preoperative period. Noting that DED can lead to biometric errors and adversely affect patient comfort and vision after surgery, they stated that the findings highlight the importance of improving the homeostasis of the ocular surface not only in patients with established DED but also in those without frank disease or evident DED risk factors.

STUDY DESIGN

The study identified patients who had undergone unilateral cataract surgery across 17 centers in Italy. A total of 419 patients met the inclusion criteria that required eligible patients to be aged at least 50 years and have undergone an uncomplicated procedure with a clear corneal incision, IOL implantation in the capsular bag, and postoperative treatment with dexamethasone and tobramycin 4 times a day for 10 days and nepafenac 0.1% 3 times a day for 1 month.

In addition, patients needed to have data from DED diagnostic tests conducted between 30 and 7 days before surgery and at 1, 4, and 8 weeks postoperatively. Patients were excluded if they had preexisting DED, which was diagnosed based on a Schirmer test without anesthesia less than 7 mm/5 min, TBUT less than 10 seconds, SPEED score greater than 4, and CFS score greater than

1, or if they had any other findings that could confound the results.

Preoperatively, the 3 study groups were well matched with respect to mean age (~ 72 years), mean Schirmer test score (~ 13 mm/5 min), mean TBUT (~ 12 sec), and percentage of eyes with a CFS score equal to 0 (65% to 76%). The postoperative data from all groups were consistent with previous reports showing that cataract surgery can induce signs and symptoms of DED.

Mean SPEED questionnaire scores did not change significantly in groups that were using artificial tears but increased significantly (worsened) at week 4 in the untreated patients. The differences in mean SPEED scores were statistically significant favoring both groups using the artificial tears versus the untreated group at all follow-up visits. The investigators noted that 25% of the patients in the untreated group had SPEED scores corresponding to mild-moderate dry eye symptoms at 8 weeks after surgery.

In addition, a statistically significant difference favoring the group starting artificial tear use preoperatively compared with the group treated only postoperatively was noted at postoperative weeks 1 and 4.

The TBUT was significantly higher in both groups using the artificial tears compared with the controls at all follow-up visits, and mean TBUT fell to below 10 seconds postoperatively only in the control group. In addition, TBUT recovered faster in the group using artificial tears preoperatively compared with the group that was treated only after surgery. At the week 4 postoperative visit, the TBUT was higher in the group that started artificial tear use preoperatively compared with the group treated only postoperatively.

The investigators noted the difference was statistically significant, but it was not clinically significant.

The results for CFS showed that patients using artificial tears had less corneal damage after surgery than their untreated counterparts. Among patients who used the artificial tears preoperatively and postoperatively, a small minority had CFS scores of 2 (7.2%) or 3 (0.7%) at the week 1 postoperative visit. In this same group by week 4, more patients had a CFS score of 0 compared with baseline, and the percentage was increased further at week 8.

A similar pattern of early worsening in CFS scores and subsequent progressive improvement was noted in the group that used artificial tears postoperatively only and in the untreated group.

However, among patients who used the artificial tears after surgery, approximately 6% of patients had a CFS score greater than 1 at week 4, whereas in the untreated group a CFS score greater than 1 was found in 20% of eyes at week 1, 13% at week 4, and 6.4% at week 8. ■

TAKE-HOME

- ***In a retrospective study including 419 patients without dry eye disease, perioperative use of artificial tears reduced ocular discomfort, tear instability, and ocular surface damage after cataract surgery. Initiating the treatment preoperatively was associated with better outcomes than if the artificial tears were used only after the procedure.***

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DEVELOPMENTS IN GLAUCOMA OFFERING HOPE, OPTIONS

Consider ideas about outflow pathways, neuroprotection

By Lynda Charters; *Reviewed by John R. Samples, MD*

NEW UNDERSTANDING OF GLAUCOMA

Research has provided a fuller understanding of the role of Schlemm's canal, tissue stiffness, and specifically the importance of flow beyond Schlemm's canal through the ostia into the collector channels and ultimately the episcleral veins. The recognition that uveoscleral outflow is now greater than previously thought, ie, it may exceed 50% of all outflow in some patients and the process works for 360 degrees in contrast to the segmental trabecular meshwork (TM) outflow of a few clock hours in most adults. The goal is to modify this limitation with drugs, laser, surgery in the form of minimally invasive glaucoma surgeries or other therapies, according to John R. Samples, MD.

Beta-blockers, alpha-adrenergic receptor agonists, and carbonic anhydrase inhibitors have been the mainstays to manage intraocular pressure (IOP). The popular beta-blockers, however, come with a lot of baggage in the form of systemic adverse effects, low nighttime efficacy, cardiac slowing, and high tachyphylaxis, and their prominence as a treatment of choice has started to wane with the growing prominence of and increased use of prostaglandin analogs and rho kinase inhibitors.

In an ideal world, glaucoma therapy would always be highly efficacious, have the ability to be combined with other therapies, have infrequent dosing, be low cost, have 24-hour IOP control, and provide neuroprotection. "We also hope that future therapies may structurally alter the retinal ganglion

Image courtesy of romaset @Adobe Stock

cells [RGCs] and Schlemm's canal and enhance the trabecular cells. Therapies are destined to become disease altering. That we can actually alter the disease process is the hope given to us by recent advances in cell biology and molecular biology. It is the reason that we have integrated the Trabecular Meshwork Study Club with the American Society for Cell Biology for the past 20 years," added Samples, a clinical professor at Washington State University's Elson S. Floyd School of Medicine, in Olympia, Washington.

NEW MEDICAL THERAPIES

New anti-glaucoma drugs that include the Rho-associated protein kinase (ROCK) inhibitors Rhopressa (netarsudil ophthalmic solution) and Rocklatan (netarsudil and latanoprost ophthalmic solution) (both from Aerie Pharmaceuticals) have been on the US market for over a year, Glanatec (riparsadil, Kowa Company) is in the Japanese market, and the RNAi beta-blocker Bamosiran (Sylentis) is in a phase 2 study. The highly anticipated adenosine-a1 agonist trabodenoson (INO-8875, Inotek Pharmaceuticals), disappointingly failed at the end of phase 3 trials.

Vyzulta (latanoprostene bunod combined with nitric oxide [NO], Bausch + Lomb), is one of the new prostaglandin analogs already available. Bimatoprost with a NO group attached (NCX 470, Nicox) is making its way through the pipeline, and DE-117 (Santen Pharmaceuticals) is already in a phase 3 trial. While the combination of NO and beta-blockers has not panned out, positive effects have been seen when NO was added to travoprost and bimatoprost.

NEW DRUGS WITHIN REACH

Tie2 drugs attach to the Tie2 transmembrane receptor on the endothelial cells. Tie2 functions include maintaining the endothelial cell junctions, inhibiting vascular inflammation, working downstream to activate rho kinase; it also have endothelial NO synthase activity. Aerpio Pharmaceuticals is developing one such drug, AKB-9778, that is administered subcutaneously, and in addition to activating Tie2, also
is a small molecule inhibitor of vascular endothelial protein tyrosine phosphatase, can elicit signal transduction pathways to mimic netarsudil and latanoprost with NO added.

Another and perhaps an even more promising area of research is examining the proteins in the perfused and non-perfused areas of the TM. This research has the potential for a large number of very interesting drug candidates in work done by Drs Janice Varanka and Ted Acott at Oregon Health and Sciences University, Samples pointed out.

Mayo Clinic researchers are exploring potassium-channel openers for modulating IOP. These drugs affect the episcleral venous system, are additive to timolol and prostaglandins, and may provide neuroprotection for RGCs.

Endogenous NO regulates conventional outflow and IOP, which results in relaxation of the TM, opens the extracellular matrix (ECM), and may affect vacuoles in the walls of Schlemm's canal The latanoprost marketed with NO has a higher concentration of latanoprost alone. This in no way detracts from its increased efficacy over routinely used generic latanoprost and prostaglandin than generic latanoprost and may have a possible longer presence in the sclera, which could theoretically act as a reservoir.

Adenosine-a1 agonists lower IOP; adenosine is distributed throughout the body, especially in the central nervous system and heart. Importantly, the A1 agonists can be neuroprotective if they can access RGCs. Trabodenoson was the first such drug studied, but it failed as mentioned previously in a phase 3 trial. However, the adenosine agonists and antagonists are one of many classes that may be beneficial to the RGCs.

FUTURE OF NEURO PROTECTION

All All of the previously mentioned therapies have varying potential to be neuroprotective. This can happen through means other than simply the lowering of IOP, which many still believe is the greatest neuroprotection of all. The rho kinase inhibitors are already used systemically to treat stroke; adenosine drugs, now failed for the purpose of lowering pressure in a phase III trial access the RGCs; and silencing RNA therapy for caspase 2 has been seen to be very promising in small clinical trials.

Neuroprotection (NO), Samples explained, is an umbrella term that ranges from neuroprotection to neurorescue to neurorejuvenation.

"In glaucoma, a central dogma is that synaptic changes release glutamate leading to excitotoxicity and cellular events that trigger depression of the visual fields leading to cell death," he said.

NO seems to have a bright future in the area of neuroprotection.

"It is exciting because it activates the TOR genes, which are associated with longevity," he explained.

There are convincing findings that suggest that manipulating the TOR genes may be associated with canine longevity. In the diet, NO, which is contained in fruit, dark chocolate, and red wine, relaxes the trabecular cells and increases the conventional trabecular outflow.

ROCK inhibitors block secretion of ECM and possibly act on the ECM in other ways. "It looks as if rho kinase inhibitors can produce long-lasting structural alterations in the TM that extend beyond what one might think," Samples commented.

Thus far, it has been shown that ROCK inhibitors protect RGCs and prevented fibrosis in cultured human TM cells. Netarsudil was found to reduce elevated IOP caused by steroids in a recent study,[1] and Stanford investigators have demonstrated that topical ROCK inhibitors increase RGC survival after trauma to the optic nerve.[2]

In light of research results with these drugs, which have been used for a long time to treat primary open-angle glaucoma, new uses seem to be in the offing.

Improvements in imaging technologies may be able to demonstrate the neuroprotective effects of these drugs. Moreover, drugs have subtle and potentially disease-altering biologic effects.

Samples noted that IOP-lowering RCG potential is available with some medications already in use, and cautioned that it is still unknown if they are able to penetrate and reach the optic nerve. Another promising class of drugs is the growth factors, especially ciliary neurotrophic factor, which is the most promising of these; recombinant human nerve growth factor, and brain-derived growth factor.

"Developments in drug delivery to the optic nerve are coming and should allow us to finally reach the nerve with a new level of certainty," Samples said.

take-home

- ***Ophthalmologists should be critical of claims forwarded about drugs, and cost remains a high barrier to device approval.***

SUSTAINED-RELEASE PELLET

Finally, a sustained-release pellet (bimatoprost implant, Durysta, Allergan) recently became available that is placed directly into the anterior chamber to lower open-angle glaucoma and works over several months. It is a great example of sustained drug delivery, which may have substantial new benefits from smoothing out IOP fluctuations, Dr. Samples explained.

Long-term studies will hopefully provide reassurance about the corneal endothelium with this exciting new class of implant.

"The future is very bright. We need to be critical of claims forwarded about drugs. Cost is a very high barrier to device approval. Effective devices are available and the other perceived barrier is regulation," Samples concluded. ■

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Samples consults and works for Kugler Publications as content architect. He receives royalties from Springer and Healio and for running GlaucomaCME.com, and holds patents with Allergan/Abbvie and Refocus.

Combination drops may help patients challenged by multiple glaucoma meds

They can simplify dosing, improving adherence and ocular surface health

By Jesse Richman, MD; *Special to* Ophthalmology Times®

MANAGEMENT OF GLAUCOMA aims to keep eye pressure reduced, without frequent or significant fluctuation. To meet these goals, we need patients to maintain a consistent pattern with their eye drop medications. That can be especially challenging when patients need to use more than 1 medication. Glaucoma drops typically are effective in optimal conditions, but some real-life barriers affect adherence and, as a result, pressure control. Compounded combination drops can help patients overcome those barriers.


Richman

BARRIERS TO SUCCESS WITH MULTIPLE GLAUCOMA DROPS

Patients who take 2 or more glaucoma drop medications are, unfortunately, less adherent than those who just take 1.[1] It is common to see several potential barriers to adherence for these patients.

First, it is tougher to take multiple eye drops every day, whether someone is older and perhaps has trouble keeping track or the patient is younger and busy with work and children.

We ask some patients to use drops 3, 4, or 5 times daily. That is a very challenging routine—some patients can manage, but many cannot. As a result, they will not maintain consistent IOP control.

Ocular surface toxicity is also a problem for many patients taking chronic glaucoma drops. Preservatives are known to contribute to this problem, particularly benzalkonium chloride (BAK). The problem is multiplied when patients take several doses a day.

Naturally, when the drops cause chronic irritation, adherence decreases. This is an important challenge to address because all the benefits of glaucoma drops are invisible, but the adverse effects (AEs) can be glaring. We need to minimize those AEs for long-term comfort and adherence.

COST CAN BE AN ISSUE

Cost can be problematic with multiple medications as well. The amount patients pay for their medications varies—some have a $5 copayments, whereas others might pay hundreds of dollars. Physicians usually do not know how much a patient is paying, but if someone is on the higher end, adding a second medication can be a financial burden, which is a potential adherence problem.

Finally, with multiple medications, issues can arise with refills. Some patients finish their bottles too early because it is hard for them to get only 1 drop at a time out of the bottle. States have different rules about whether ocular medications can be refilled early. If patients cannot get their medication, then they have gaps in therapy. Shortages of drugs such as dorzolamide can also disrupt the patients' pattern of continuous adherence to therapy.

SIMPLICITY OF COMPOUNDED COMBINATION DROPS

Combination drops can resolve some of the barriers to consistent long-term IOP control associated with taking multiple medications independently. While most of my patients still use traditional drops, compounded combination drops can be more affordable for some patients, and they offer a greater range of combinations.

Certainly, easier is better, and combination drops allow patients to take the same bottle of drops just once or twice a day, depending on the situation.

For example, I typically will prescribe a compounded timolol-brimonidine-dorzolamide drop (Tim-Brim-Dor; ImprimisRx) that allows patients to take 2 doses a day instead of 4. My patients who take timolol in the morning and latanoprost in the evening can take those same medications as a single compounded drop (Tim-Lat; ImprimisRx) once a day.

take-home

- ***With a flexible option, ophthalmologists can make patients' lives easier, in terms of taking medications, achieving better health outcomes and avoiding problems linked to preservatives.***

USED INDEPENDENTLY

In the past, I sometimes hesitated to prescribe a combination drop because the drops may be more effective when used independently. That is only true when they are used exactly as prescribed, however. Because patients can be less accurate with multiple drops, I think the effect is largely the same with less frequent dosing of a combination drop.

All compounded drops I prescribe are free of preservatives, so they are much less likely than drops with BAK to cause ocular surface toxicity. If we can minimize dry eye while effectively managing glaucoma, patients are more likely to adhere to their medications because the treatment is not making them miserable.

CONVENIENCE FOR PATIENTS

For most patients, compounded combination drops cost the same or a little less than they would for multiple bottles.

With the compounding pharmacy I use, there is also a bit more clarity related to the true costs, so patients know exactly what they are paying each month. That is because patients pay the compounding pharmacy directly.

The auto-refill program will set up recurring shipments to ensure that there are no gaps in therapy, which can happen with other medications when patients delay going to the pharmacy.

Patients like the convenience that an auto-refill program offers. In addition, patients also can adjust the delivery frequency depending upon how quickly they finish their bottles of drops.

QUALITY MATTERS

As with anything that we prescribe to our patients, we want compounded medications to meet very high standards for safety and quality. The compounding pharmacy also should be accredited so it meets rigorous standards. It is nice to offer patients convenience and perhaps lower cost, but it is essential that the medications are coming from a place with a reputation for producing safe, quality products. ■

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Richman specializes in medical and surgical treatment of glaucoma and cataracts at Wills Eye Hospital in Philadelphia, Pennsylvania, and Kremer Eye Center in Cherry Hill, New Jersey.

INDISPENSABLE

(FIGURE 1) **Patients view frames at Mittleman Eye, a West Palm Beach, Florida, clinic. The clinic works with Vision Associates, a dispensary management firm.** *(Photos courtesy of Mittleman Eye)*

Partnering with dispensary management firm boosts practice's business

Move to streamline operation has great payoff during COVID-19 pandemic

By Hugh Glatts; *Special to* Ophthalmology Times®

When the leadership team of Mittleman Eye, an ophthalmological practice with 2 locations in Palm Beach County, Florida, made the decision to engage an optical dispensary management firm, we had no way of knowing something unprecedented was coming.

That was March 2019, and the "something unprecedented" would occur in March 2020—coronavirus disease 2019 (COVID-19) spurred the most dramatic, "everything changed" moment in recent world history.

When we initially partnered with Vision Associates, we were looking to streamline the operation of the optical dispensaries at both of our offices.

Vision Associates is one of the country's most prominent optical dispensary management companies. Designed to provide a turnkey experience while utilizing accrued best practices to increase profit margins, the firm's services include inventory management of manufactured eye-

INDISPENSABLE

wear, training and development of staff, lab facility integration, point-of-sale software, organization of third-party billing, and in-house marketing.

As the nostalgically normal year of 2019 progressed, business was…well, business as usual. As leaders of a busy eye care practice in a densely populated area, we had trusted an expert's promise to strengthen our dispensary performance. Vision Associates reconfigured our eyewear centers' inventory based on demographic assessments, adjusted pricing in certain instances, and—with Mittleman Eye's oversight—conducted staff training exercises and made a few key hires.

Profits rose as promised. Our dispensaries began fulfilling their potential as a reliable source of secondary income. And then, everything changed.

As the worst pandemic in a century began to wreak medical and economic havoc across the country, no person or industry was left unaffected. Like the vast majority of eye care practices, Mittleman Eye deemed it necessary to all but close. Emergency patients still were seen, and others were consulted via teleconference, but business was anything but usual.

As a health care provider, Mittleman Eye fell into the essential services category, meaning any local lockdown orders did not apply. We decided to reopen 4 weeks later, sooner than many other eye care practices in South Florida. Mittleman Eye's reopening was typical of many businesses emerging from COVID-19: our patient load was lighter at first, as many patients postponed appointments out of an understandable abundance of caution.

And then came the deluge. Through July 2020, business at Mittleman Eye—all but shuttered for a full month and, upon reopening, unsurprisingly slow for another—is *up* compared with the same period in 2019.

That is a lot of appointments in not a lot of time. Fortunately, in addition to providing a surge of patients with the attentive eye care they deserved, we also were able to give our optical dispensaries an appropriate amount of attention. That is, none at all.

It was wonderful. We did not have to worry about the dispensaries during a time when we literally had no time to worry about them.

take-home

The partnership with an optical dispensary management firm offers smoother operation and maximizes customer service, sales, and profit margin, even during the national health crisis.

BUSINESS AS UNUSUAL

What Mittleman Eye experienced is a common crunch due to the pandemic. Many ophthalmologist offices around the country were closed for an extended period due to COVID-19 concerns. The resulting pent-up demand has left practices playing catch-up with long-postponed appointments, often pushing optical dispensaries further down the internal management priorities list.

Coupled with the swell of patients is a pandemic-related, 1-stop-shop consumer mentality. With the virus still prevalent in much of the country, consumers are increasingly looking to accomplish chores—including eye doctor visits and prescription eyewear procurement—in 1 fell swoop rather than "shop around." This lends itself to increased purchasing interest for optical dispensaries at many ophthalmologists' offices, oftentimes revealing the need for a smoother dispensary operation toward the goal of maximizing customer service, sales, and profit margin.

While there is never a right time for a tragedy as devastating and disruptive as the COVID-19 pandemic, Mittleman Eye found itself in the prescient position of having already addressed any concern over the rush of new interest at our dispensaries.

While the surrounding circumstances were anything but satisfactory, the pandemic presented an unforeseen opportunity to convert satisfied long-time eye care patients into satisfied first-time eyewear customers. Patients who may have merely browsed the in-office eyewear were suddenly motivated buyers.

"Thankfully, the eye care sector is starting to see some bright spots in what, by anyone's measure, has been a difficult, abnormal year," said Joe Casorio, president of Vision Associates. "Many industries, including ours, are recalibrating to a 'new normal' that brings opportunities as well as challenges."

Another anomaly also worked to Mittleman Eye's advantage. While our dispensaries were open, the majority of standalone optical dispensaries were not. Many didn't open for weeks or even months after patients began returning to Mittleman Eye.

However, Mittleman Eye's optical dispensaries were far from the only game in town. Our patients easily could have browsed our eyewear section then resorted to online shopping.

We still had to close the deal. From an eyewear standpoint, we needed to take patients from perusing to purchasing.

Like any set of professionals operating in an unprecedented and therefore unpredictable situation, the Vision-Mittleman team ran the dispensary leaning on combined expertise while adapting on the fly to extenuating circumstances. According to Casorio, 1 thing, of course, was paramount:

"Safety first," he said. "Mask wearing was mandated, sanitizing protocols were put into place, and a workflow was designed to assist 1 customer at a time without making those waiting feel ignored—a tricky pandemic 2-step that businesses across the country continue to hone."

Vision Associates also worked with Mittleman Eye to make finished eyewear prescriptions available by curbside pickup and mail, which kept in-person customer waiting to a minimum.

> "Thankfully, the eye care sector is starting to see some bright spots in what, by anyone's measure, has been a difficult, abnormal year." - Joe Casorio

(FIGURE 2) Amid the COVID-19 pandemic, Mittleman Eye has instituted a mask mandate, and sanitizing protocols have been put in place. *(Photos courtesy of Mittleman Eye)*

And once those decidedly unusual challenges were met, it was business as usual. The executive team at Mittleman Eye treated Vision Associates as an extension of itself, and the dispensary management crew at Vision Associates converted eye care patients into eyewear purchasers—ones more likely to become repeat customers thanks to our careful-yet-comprehensive service during the COVID-19 crisis. ■

HUGH GLATTS
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Glatts is CEO of Mittleman Eye, a West Palm Beach, Florida, ophthalmology clinic.

Artwork by Jon Carter

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EYSUVIS (loteprednol etabonate ophthalmic suspension) 0.25%, for topical ophthalmic use

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

INDICATIONS AND USAGE

EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Delayed Healing and Corneal Perforation—Topical corticosteroids have been known to delay healing and cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. The initial prescription and each renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining.

Intraocular Pressure (IOP) Increase—Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Corticosteroids should be used with caution in the presence of glaucoma. Renewal of the medication order should be made by a physician only after examination of the patient and evaluation of the IOP.

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

Bacterial Infections—Use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions of the eye, corticosteroids may mask infection or enhance existing infection.

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

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

Risk of Contamination—Do not to allow the dropper tip to touch any surface, as this may contaminate the suspension.

Contact Lens Wear—The preservative in EYSUVIS may be absorbed by soft contact lenses. Contact lenses should be removed prior to instillation of EYSUVIS and may be reinserted 15 minutes following administration.

ADVERSE REACTIONS

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

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

The most common adverse reaction observed in clinical trials with EYSUVIS was instillation site pain, which was reported in 5% of patients.

USE IN SPECIFIC POPULATIONS

Pregnancy—Risk Summary: There are no adequate and well controlled studies with loteprednol etabonate in pregnant women. Loteprednol etabonate produced teratogenicity at clinically relevant doses in the rabbit and rat when administered orally during pregnancy. Loteprednol etabonate produced malformations when administered orally to pregnant rabbits at doses 1.4 times the recommended human ophthalmic dose (RHOD) and to pregnant rats at doses 34 times the RHOD. In pregnant rats receiving oral doses of loteprednol etabonate during the period equivalent to the last trimester of pregnancy through lactation in humans, survival of offspring was reduced at doses 3.4 times the RHOD. Maternal toxicity was observed in rats at doses 347 times the RHOD, and a maternal no observed adverse effect level (NOAEL) was established at 34 times the RHOD. The background risk in the U.S. general population of major birth defects is 2 to 4%, and of miscarriage is 15 to 20%, of clinically recognized pregnancies.

Data—*Animal Data:* Embryofetal studies were conducted in pregnant rabbits administered loteprednol etabonate by oral gavage on gestation days 6 to 18, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations at 0.1 mg/kg (1.4 times the recommended human ophthalmic dose (RHOD) based on body surface area, assuming 100% absorption). Spina bifida (including meningocele) was observed at 0.1 mg/kg, and exencephaly and craniofacial malformations were observed at 0.4 mg/kg (5.6 times the RHOD). At 3 mg/kg (41 times the RHOD), loteprednol etabonate was associated with increased incidences of abnormal left common carotid artery, limb flexures, umbilical hernia, scoliosis, and delayed ossification. Abortion and embryofetal lethality (resorption) occurred at 6 mg/kg (83 times the RHOD). A NOAEL for developmental toxicity was not established in this study. The NOAEL for maternal toxicity in rabbits was 3 mg/kg/day.

Embryofetal studies were conducted in pregnant rats administered loteprednol etabonate by oral gavage on gestation days 6 to 15, to target the period of organogenesis. Loteprednol etabonate produced fetal malformations, including absent innominate artery at 5 mg/kg (34 times the RHOD); and cleft palate, agnathia, cardiovascular defects, umbilical hernia, decreased fetal body weight and decreased skeletal ossification at 50 mg/kg (347 times the RHOD). Embryofetal lethality (resorption) was observed at 100 mg/kg (695 times the RHOD). The NOAEL for developmental toxicity in rats was 0.5 mg/kg (3.4 times the RHOD). Loteprednol etabonate was maternally toxic (reduced body weight gain) at 50 mg/kg/day. The NOAEL for maternal toxicity was 5 mg/kg.

A peri-/postnatal study was conducted in rats administered loteprednol etabonate by oral gavage from gestation day 15 (start of fetal period) to postnatal day 21 (the end of lactation period). At 0.5 mg/kg (3.4 times the clinical dose), reduced survival was observed in live-born offspring. Doses ≥ 5 mg/kg (34 times the RHOD) caused umbilical hernia/incomplete gastrointestinal tract. Doses ≥ 50 mg/kg (347 times the RHOD) produced maternal toxicity (reduced body weight gain, death), decreased number of live-born offspring, decreased birth weight, and delays in postnatal development. A developmental NOAEL was not established in this study. The NOAEL for maternal toxicity was 5 mg/kg.

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

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

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

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility—Long-term animal studies have not been conducted to evaluate the carcinogenic potential of loteprednol etabonate. Loteprednol etabonate was not genotoxic *in vitro* in the Ames test, the mouse lymphoma thymidine kinase (tk) assay, in a chromosome aberration test in human lymphocytes, or *in vivo* in the single dose mouse micronucleus assay. Treatment of male and female rats with 25 mg/kg/day of loteprednol etabonate (174 times the RHOD based on body surface area, assuming 100% absorption) prior to and during mating caused pre-implantation loss and decreased the number of live fetuses/live births. The NOAEL for fertility in rats was 5 mg/kg/day (34 times the RHOD).

For a copy of the Full Prescribing Information, please visit www.EYSUVIS.com.

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INDICATION

EYSUVIS is a corticosteroid indicated for the short-term (up to two weeks) treatment of the signs and symptoms of dry eye disease.

IMPORTANT SAFETY INFORMATION

Contraindication:

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

Warnings and Precautions:

Delayed Healing and Corneal Perforation: Topical corticosteroids have been known to delay healing and cause corneal and scleral thinning. Use of topical corticosteroids in the presence of thin corneal or scleral tissue may lead to perforation. The initial prescription and each renewal of the medication order should be made by a physician only after examination of the patient with the aid of magnification, such as slit lamp biomicroscopy, and, where appropriate, fluorescein staining.

Intraocular Pressure (IOP) Increase: Prolonged use of corticosteroids may result in glaucoma with damage to the optic nerve, as well as defects in visual acuity and fields of vision. Corticosteroids should be used with caution in the presence of glaucoma. Renewal of the medication order should be made by a physician only after examination of the patient and evaluation of the IOP

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

Bacterial Infections: Use of corticosteroids may suppress the host response and thus increase the hazard of secondary ocular infections. In acute purulent conditions, corticosteroids may mask infection or enhance existing infection

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

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

Adverse Reactions:

The most common adverse drug reaction following the use of EYSUVIS for two weeks was instillation site pain, which was reported in 5% of patients.

Please see Brief Summary of Prescribing Information for EYSUVIS on the next page.

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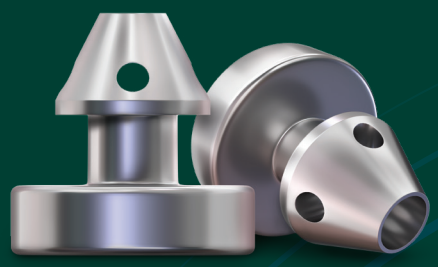

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Featuring a wide flange at its base, the new precision-engineered iStent *inject*® W is designed to:

- Safely and effectively control your patient's glaucoma[1]
- Optimize stent visualization while maintaining a truly micro-scale footprint
- Streamline implantation
- Deliver procedural predictability

Don't miss the opportunity to make a once-in-a-lifetime difference for your cataract patients with mild-to-moderate glaucoma.

TransformMIGS.com | 800.GLAUKOS (452.8567)

REFERENCE:

1. Samuelson TW, Sarkisian SR, Lubeck DM, et al. Prospective, randomized, controlled pivotal trial of an ab interno implanted trabecular micro-bypass in primary open-angle glaucoma and cataract. *Ophthalmology.* Jun 2019;126(6):811-821.

INDICATION FOR USE. The iStent *inject*® W Trabecular Micro-Bypass System Model G2-W is indicated for use in conjunction with cataract surgery for the reduction of intraocular pressure (IOP) in adult patients with mild to moderate primary open-angle glaucoma. **CONTRAINDICATIONS**. The iStent *inject* W is contraindicated in eyes with angle-closure glaucoma, traumatic, malignant, uveitic, or neovascular glaucoma, discernible congenital anomalies of the anterior chamber (AC) angle, retrobulbar tumor, thyroid eye disease, or Sturge-Weber Syndrome or any other type of condition that may cause elevated episcleral venous pressure. **WARNINGS.** Gonioscopy should be performed prior to surgery to exclude congenital anomalies of the angle, PAS, rubeosis, or conditions that would prohibit adequate visualization of the angle that could lead to improper placement of the stent and pose a hazard. **MRI INFORMATION.** The iStent *inject* W is MR-Conditional, i.e., the device is safe for use in a specified MR environment under specified conditions; please see Directions for Use (DFU) label for details. **PRECAUTIONS.** The surgeon should monitor the patient postoperatively for proper maintenance of IOP. The safety and effectiveness of the iStent *inject* W have not been established as an alternative to the primary treatment of glaucoma with medications, in children, in eyes with significant prior trauma, abnormal anterior segment, chronic inflammation, prior glaucoma surgery (except SLT performed > 90 days preoperative), glaucoma associated with vascular disorders, pseudoexfoliative, pigmentary or other secondary open-angle glaucomas, pseudophakic eyes, phakic eyes without concomitant cataract surgery or with complicated cataract surgery, eyes with medicated IOP > 24 mmHg or unmedicated IOP < 21 mmHg or > 36 mmHg, or for implantation of more or less than two stents. **ADVERSE EVENTS.** Common postoperative adverse events reported in the iStent *inject*® randomized pivotal trial included stent obstruction (6.2%), intraocular inflammation (5.7% for iStent *inject* vs. 4.2% for cataract surgery only), secondary surgical intervention (5.4% vs. 5.0%) and BCVA loss ≥ 2 lines ≥ 3 months (2.6% vs. 4.2%). **CAUTION:** Federal law restricts this device to sale by, or on the order of, a physician. Please see DFU for a complete list of contraindications, warnings, precautions, and adverse events.

GLAUKOS®