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VOL. 9, NO. 4 · JULY/AUGUST 2024

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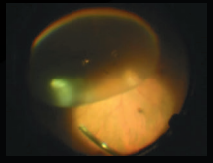
AI Screening for DIABETIC RETINOPATHY and DME

AI has the potential to make screening easier in various clinical settings.

Page 18

Also Inside

Online Video



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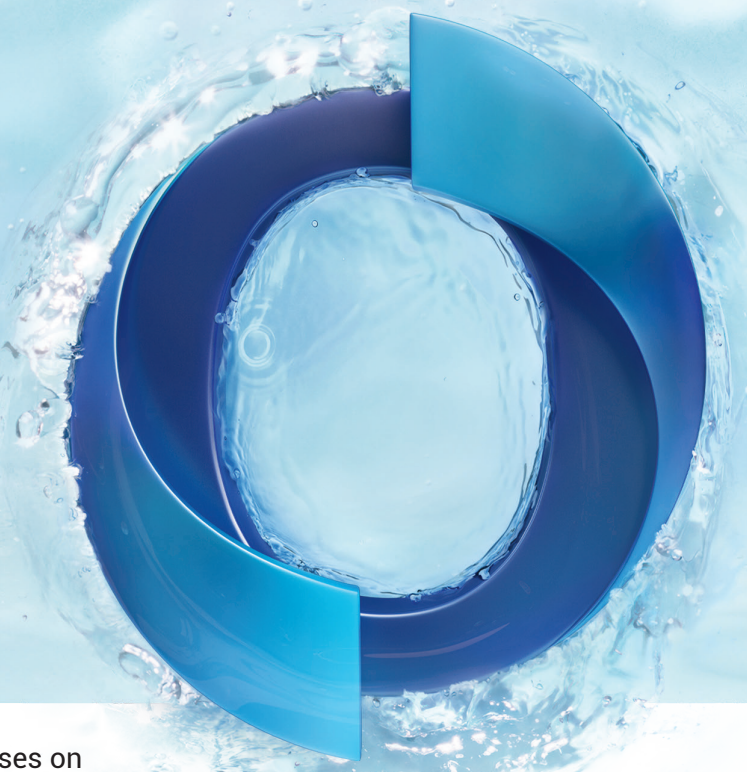
(chloroprocaine HCl ophthalmic gel) 3%

IHEEZO Gives You Nothing



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IHEEZO™ is the topical ocular anesthetic that compromises on nothing. Rapid onset and an established safety profile for your patients. No uncertainty with a sterile, single-use unit for you.

In a Phase III clinical study of IHEEZO,

NO supplemental treatment needed to maintain anesthesia*†[1]

NO serious adverse events with an established safety profile[2]

NO patients reported experiencing pain[2]

*In the clinical trial, no patient undergoing routine cataract surgery receiving IHEEZO required supplemental treatment to maintain anesthesia; this was not the case for patients receiving tetracaine. Supplemental treatment was defined as general anesthesia, intraoperative systemic analgesia, or local anesthesia. Though supplemental administration was not required by any patient in the clinical trial, IHEEZO may be reapplied as needed to maintain anesthesia.[1,2]

†Sufficient anesthesia with IHEEZO lasted an average of 21.5 minutes in the clinical trial, while mean total surgical time was 13.9 minutes.[2]

APPROVED USE

IHEEZO is indicated for ocular surface anesthesia.

IMPORTANT SAFETY INFORMATION

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

IHEEZO should not be injected or intraocularly administered.

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

Do not touch the dropper tip to any surface as this may contaminate the gel.

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

The most common adverse reactions in studies following IHEEZO administration (incidence greater than or equal to 5%) were mydriasis, conjunctival hyperemia, and eye irritation.

You are encouraged to report suspected adverse reactions to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

Please see Brief Summary of Full Prescribing Information for IHEEZO on adjacent page.

HARROW®

Your patients. Our purpose.

References: 1. Iheezo. Prescribing information. Harrow IP, LLC; 2022. **2.** Data on File. Harrow IP, LLC; 2023.

IHEEZO™

(chloroprocaine HCl ophthalmic gel) 3%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IHEEZO™ (chloroprocaine hydrochloride ophthalmic gel) 3% is a preservative-free ester anesthetic indicated for ocular surface anesthesia.

4 CONTRAINDICATIONS

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Injection or Intraocular Administration

IHEEZO should not be injected or intraocularly administered.

5.2 Corneal Injury Due to Insensitivity

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

5.3 Corneal Opacification

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

5.4 Risk of Contamination

Do not touch the dropper tip to any surface as this may contaminate the gel.

5.5 For Administration by Healthcare Provider

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

6 ADVERSE REACTIONS

6.1 Clinical Trials Experience

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

The data described below reflect 201 patients undergoing various surgical ocular procedures in two placebo-controlled trials (Study 1 and Study 2). Patients in Study 1 were randomized to receive a single instillation of 3 drops of IHEEZO or placebo. Patients in Study 2 were randomized to receive a single or multiple instillations of 1, 3, or 3+3 drops of IHEEZO or placebo.

The most common adverse reactions in these studies (incidence greater than or equal to 5%) following IHEEZO administration were mydriasis, conjunctival hyperemia, and eye irritation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of IHEEZO use in pregnant women to inform a drug-associated risk. There are no animal reproduction studies for chloroprocaine.

8.2 Lactation

Risk Summary

There are no data on the presence of chloroprocaine 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 IHEEZO and any potential adverse effects on the breastfed infant from IHEEZO.

8.4 Pediatric Use

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

8.5 Geriatric Use

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

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Chloroprocaine, like other local anesthetics, blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, slowing the propagation of the nerve impulse, and reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.3 Pharmacokinetics

The systemic exposure to chloroprocaine following topical ocular administration of IHEEZO has not been studied.

Elimination

Metabolism

Chloroprocaine is metabolized by plasma pseudocholinesterases and nonspecific esterases in ocular tissues. Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolysis of chloroprocaine results in the production of ß-diethylaminoethanol and 2-chloro-4-aminobenzoic acid, which inhibits the action of the sulfonamides.

Excretion

Chloroprocaine plasma half-life in vitro is approximately 25 seconds in adults and approximately 43 seconds in neonates. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate carcinogenic potential of chloroprocaine have not been conducted.

Mutagenesis

2-chloroprocaine and the main metabolite, ACBA, were negative in the in vitro bacterial reverse mutation test (Ames assay) and the in vitro chromosome aberrations assay.

Impairment of Fertility

Studies in animals to evaluate the impairment of fertility have not been conducted with chloroprocaine.

14 CLINICAL STUDIES

14.1 Study 1 and Study 2

Study 1 (NCT04779606) and Study 2 (NCT04753710) were randomized, double-blinded, placebo-controlled studies conducted to evaluate the efficacy, safety, and local tolerability of IHEEZO in 145 healthy volunteers.

In Study 1, 85 healthy males and females were randomized in a 4:1 ratio to receive a single ocular instillation of IHEEZO (n=68) or placebo (n=17). The double-blinded treatment included an IHEEZO or a placebo dose of 3 drops instilled at 1-minute (±15 seconds) intervals in the right eye of each volunteer. The median age was 39 years (range 19 to 55 years); 59% female and 41% male.

In Study 2, 60 healthy males and females were randomized (40:20) to receive single or multiple ocular instillations of an IHEEZO dose of 3 drops in the right eye. The median age was 25 years (range 18 to 59 years); 54% female and 46% male.

The efficacy in Study 1 and Study 2 was determined by proportion of patients achieving full conjunctival anesthesia evaluated by conjunctival pinching 5 minutes after administration.

Efficacy results of Study 1

The proportion of subjects with successful anesthesia was 90% in the IHEEZO group and 12% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 14.3 minutes.

Efficacy results of Study 2

The proportion of subjects with successful anesthesia was 95% in the IHEEZO group and 20% in the placebo group (P<0.01). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 19.3 minutes.

14.2 Study 3

Study 3 (NCT04685538) was a randomized, prospective, multicenter, active-controlled, observer-masked study conducted to evaluate the efficacy and safety of IHEEZO (n=166) versus tetracaine ophthalmic solution 0.5% (n=172) in patients undergoing cataract surgery.

The primary endpoint was defined as the proportion of patients in each treatment group gaining successful anesthesia without any supplementation. On average, patients needed 1 to 1.5 minutes to obtain sufficient anesthesia to successfully perform the surgical procedure, which lasted on average 22 minutes.

No patient treated with IHEEZO required supplemental treatment to complete the intended surgical procedure.

17 PATIENT COUNSELING INFORMATION

Eye Care Precaution

Do not touch the dropper tip to any surface as this may contaminate the gel. Advise patients that their eyes will be insensitive for up to 20 minutes due to the effect of the anesthetic, and that care should be taken to avoid accidental injuries.

For Full Prescribing Information, please visit www.iheezo.com/prescribinginformation.

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EDITORIAL

By Jason Hsu, MD

The TermEYEnator: AI and the future of retina

I recently had the pleasure of sharing the podium with Judy Kim, MD, and hearing her give a fantastic talk on how artificial intelligence is impacting ophthalmology. The speed with which AI has entered the mainstream is perhaps only rivaled by the dramatic rise in Nvidia stock.

We now hear about generative AI and large language models doing incredible things from writing programs to screen for diabetic retinopathy[1] to giving explanations and recommendations that are on par with specialists.[2] For years, we've seen how deep learning can detect subtleties that even we retina specialists can't, such as detecting gender based on fundus photos or optical coherence tomography.[3] Is this the beginning of the end for us as a specialty?

I would argue this is the beginning of the next stage in our evolution. AI is already being deployed to assist with screening for retinal diseases, especially DR. It's being incorporated into home OCT to assist with fluid detection and clinician alerts. AI-based scribes are being developed within electronic medical records systems, which will improve charting efficiency. AI platforms to aid in patient education are being developed.

The confluence of AI advancements with the epidemic of diabetes and the aging population couldn't have come at a better time. It's estimated that 10,000 people are turning 65 years old in the United States every day. The number of people with diabetes worldwide is projected to nearly double to 700 million in the next two decades.

As it is, our clinics are bursting at the seams, leading to thinking that we're not training enough retina specialists to carry the oncoming load. This is where AI could step in.

Imagine a future where an AI call center schedules patients in the most efficient manner. AI techs do the intake and testing. AI captures imaging and provides preliminary interpretations with any pathology already highlighted for us.

During our exam and discussion with the patient, the AI scribe listens and documents the salient parts into a complete chart note, which it then rewrites automatically in layman's terms when patients go online to access their records. AI assistants are available 24/7 to answer questions and triage calls.

The further development of low-cost home retinal imaging with AI monitoring decreases the need for regular visits, allowing patients to only come in when they need treatment. Coupled with long-lasting therapeutics, it's conceivable that our clinics will be transformed for the better.

So let's not fear the TermEYEnator but rather embrace the future. *Hasta la vista*, baby. RS

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RETINA SPECIALIST

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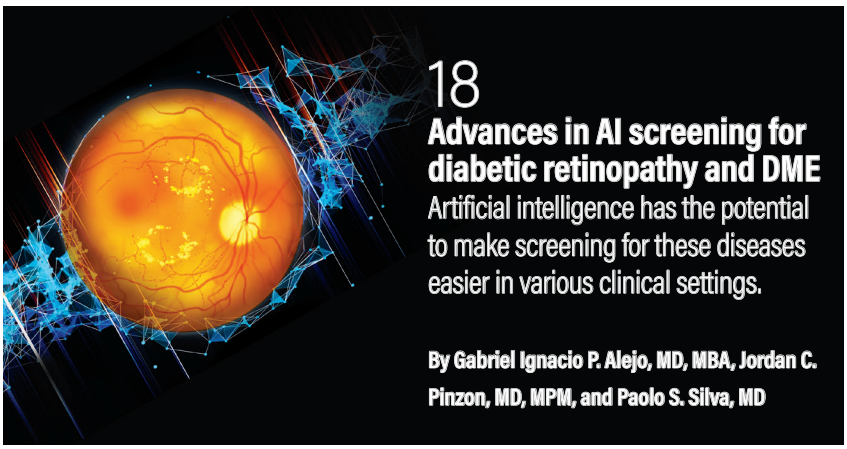
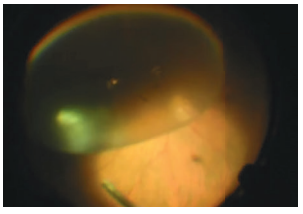
FEATURES



DEPARTMENTS



Susvimo Implant to Return to the Market

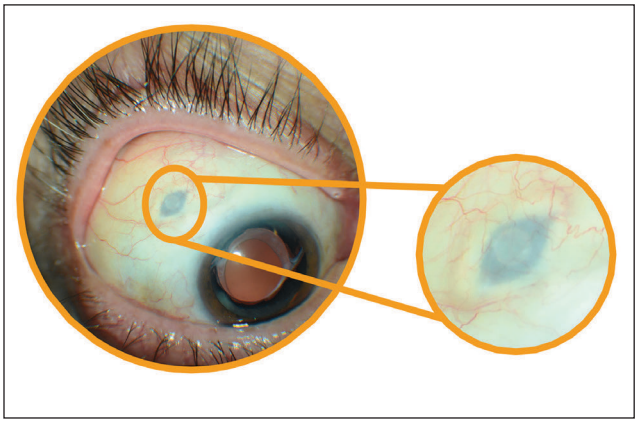
Genentech recently announced that it will be reintroducing its sustained-release ranibizumab implant, Susvimo (ranibizumab injection), onto the market for the treatment of wet age-related macular degeneration. This comes following a voluntary recall of the device in October of 2022.

Susvimo is implanted surgically and refilled once every six months with a needle designed specifically for the implant. It was initially approved by the FDA in 2021 for the treatment of wet AMD in eyes with at least two prior anti-vascular endothelial growth factor injections.

Genentech took the implant and tool assembly kit, including the drug vial and initial fill needle, off the market after it investigated reports of septum dislodgement in the port delivery system in patients during the Phase III trial program. The recall didn't include the Susvimo 100 mg/ml drug vial or refill needle in order to allow retina specialists to continue refill-exchange procedures in those patients with an existing implant.

In a letter sent to health-care providers first announcing the recall, Genentech stated, "During an investigation into septum dislodgement cases in the port delivery system with ranibizumab Phase III clinical trial program, we identified a need for additional testing of the commercial implant supply. This additional testing of our commercial supply involved repeatedly puncturing Susvimo implants with a needle, to evaluate performance of the septum of the implant over the long-term via multiple refills. The results showed that some implants did not perform to our standards. Hence, a pause in all new implantations is required."[1]

According to Jason Hsu, MD, *Retina Specialist's* chief medical editor and in practice at Wills Eye Hospital in Philadelphia, who was part of the Phase III trials for Susvimo, as the company alluded to in its statement, the implant includes a septum for the needle to penetrate.



"The septum creates a barrier to prevent any efflux of the drug into the subconjunctival space," he explains. "However, in the reports of dislodgement, the glue of the septum wasn't holding, essentially causing the septum to drop into the tip of the implant and prevent any refills."

Among the changes to the implant were the doubling of the bonding strength of the septum component, as well as lubrication of the refill needle, which allows it to be inserted more smoothly and reduces the insertion force, notes Dr. Hsu.

"In my experience inserting these devices, septum dislodgement wasn't a major issue," he says. "We did see it happen in a couple of patients, but we witnessed dislodgement of the entire implant into the eye during the refill procedures. Some of that had to do with the amount of pressure it took to insert the needle into the device for refills. The changes made to the refill needle add a little bit more reassurance that it won't require as much pressure, so this should hopefully make it much safer for the long term."

The U.S. Food and Drug Administration has given a post-approval supplement to the Biologics License Application for Susvimo, reflecting these updates. Genentech also said it will work to make Susvimo available in the United States in the coming weeks.

"As for those who did have the original Susvimo implant, now that a new device is Food and Drug Administration approved, they'll need to have it exchanged at some point, which is a bit of an inconvenience to undergo another surgery," continues Dr. Hsu. "But I think these long-lasting, anti-VEGF options are a huge benefit to everyone, patients and clinicians, in terms of burden of care. I'm happy to see it's back on the market because I think it will allow us to have another option for patients who need very frequent treatments. This potentially means they don't need to come back to the office as often for repeated intravitreal injections."

REFERENCE

1. Voluntary recall of the SUSVIMO Ocular Implant. https://www.gene.com/download/pdf/Susvimo_DHCP_Important_Prescribing_Information_2022-10-18.pdf. Accessed July 18, 2024.

FDA Approves First OCT Device for At-home Use

Patients with neovascular AMD are often subject to frequent office visits so that eye care providers can monitor anatomical changes and signs of disease progression on OCT—but what if physicians could perform this imaging remotely? This is now possible with the recent FDA approval of the first at-home OCT from Notal Vision, marketed as "Scanly," which uses artificial intelligence software to evaluate various imaging biomarkers in nAMD. By analyzing scans remotely between scheduled visits, eye doctors may be able to gain additional insight into patients' disease status, while also cutting back on their travel time.

The company explains in its press release that the device captures spectral-domain OCT images in a

10x10-degree area centered on the point of fixation. Once scans are complete, the AI software is used to segment and estimate the volume of hypo-reflective spaces. All images are automatically transmitted via a built-in wireless connection and stored in the Notal Health Cloud for analysis. There, physicians can review data and set eye-specific notification criteria (including a volume threshold for total retinal hypo-reflective spaces), as well as receive notifications via a web portal.

Two pivotal U.S. trials involving more than 500 patients with nAMD (mean age: 77) were completed to assess the accuracy and user-friendliness of the home OCT device. Notal Vision reports that 97 percent of the total 5,426 scans performed by patients in the study eye were successful. The company further noted an adherence rate of 5.9 scans/week, and on average, patients took 48 seconds to self-image.

To have a Scanly Home OCT device shipped to a patient's home, the patient must first enroll in what Notal Vision calls the "Scanly Home OCT Monitoring Program."

For more information on the program or device itself, go to notalvision.com/services/scanly-oct.

Warfarin May Increase Risk of Wet AMD Conversion

A recent study published in *Ophthalmology* highlighted the delicate balancing act of preventing life-threatening cardiac events and sight-threatening diseases when it reported that warfarin significantly increased the risk of conversion to neovascular AMD.[1]

A newer class of blood thinners called direct oral anticoagulants (DOACs) have proven superior in several studies compared with traditional warfarin and are preferred first-line agents for stroke prevention in certain cases. However, all anticoagulants are associated with bleeding risks, and DOACs' intraocular complications aren't clear yet. Researchers sought to understand the risks in patients with higher bleeding risk such as those with AMD.

The study included patients with non-neovascular AMD initiated on DOACs (n=20,300) or warfarin (n=13,387). Researchers found that at six months and at one year, patients treated with warfarin had a higher risk of developing neovascular AMD compared with those who were treated with DOACs. They also reported that warfarin-treated patients had an increased risk of requiring intravitreal anti-VEGF therapy and pars plana vitrectomy.

Additionally, patients with AMD and atrial fibrillation had an increased risk of ocular complications and need for anti-VEGF therapy over a five-year period. The researchers reported no significant difference in the development of major systemic hemorrhagic events in the two groups over five years.

Based on the real-world study findings, the researchers wrote that patients with non-neovascular AMD on warfarin are at an increased risk for developing ocular complications such as neovascular disease, macular hemorrhage and vitreous hemorrhage, and are more likely to require anti-VEGF therapy or surgical vitrectomy than patients on DOACs.

"Furthermore, there was an observed increased risk of these same events when evaluated over an extended continuous five-year period in a cohort of individuals with dry AMD

(Continued on page 10)

Vanishing Vascular Tumors

The role of belzutifan for patients with von Hippel-Lindau syndrome.

By Alyssa C. Bonnell, MD, Nathan Agi, MD, and Andrew W. Stacey, MD, MSc

Alyssa C. Bonnell, MD

Nathan Agi, MD

Andrew W. Stacey, MD, MSc

A 44-year-old woman with von Hippel-Lindau syndrome presented for follow-up with the ocular oncology service at the University of Washington Medicine Eye Institute. She has a history of two peripheral retinal capillary hemangioblastomas (RCHs) in the left eye and has previously undergone successful laser photocoagulation of these vascular tumors. She also has a history of juxtapapillary RCHs in both eyes. Half-fluence photodynamic therapy was trialed for the left juxtapapillary RCH five years prior to presentation with minimal response. Since then, the juxtapapillary tumors in both eyes have been monitored without treatment. At follow-up, the patient denied a change in vision.

Examination and Findings

Best corrected visual acuity was 20/20 in both eyes. Her pupils were equal and reactive without a relative afferent pupillary defect. Intraocular pressures were within normal limits in each eye. Dilated fundus examination revealed interval growth of the juxtapapillary RCH in the right eye compared to one year prior. The juxtapapillary RCH in the left eye was stable.

Imaging and Workup

Optos fundus photography and fluorescein angiography demonstrated the juxtapapillary vascular tumors in both eyes (*Figure 1*). The patient is also followed closely by the neurosurgery and urology services for monitoring and treatment of her central nervous system and renal tumors.

Management

Given the growth of the right juxtapapillary tumor, this case was discussed with the medical oncology service for consideration of belzutifan treatment. Belzutifan is a hypoxia-inducible factor 2-alpha (HIF-2α) inhibitor medication that was approved by the U.S. Food and Drug Administration in 2021 for the treatment of CNS, neuro-endocrine and renal tumors associated with von Hippel-Lindau syndrome.[1] It's an oral medication taken daily.[1] It's generally well-tolerated by most patients. Common side effects of the medication include anemia, fatigue, headache and nausea.[1] After discussing the potential risks and benefits of therapy, the patient elected to trial belzutifan treatment.

Follow-up

The patient followed up with the ophthalmology service three months after starting belzutifan. At follow-up, there was notable regression of the juxtapapillary tumors in both eyes (*Figure 1* and *Figure 2*). She was tolerating the medication well.

Von Hippel-Lindau Syndrome

Von Hippel-Lindau syndrome is a rare, autosomal dominant disease characterized by many systemic tumors, including retinal and CNS hemangioblastomas, pheochromocytomas and clear cell renal carcinomas.[2] These tumors form due to a mutation or loss of the *VHL* tumor suppressor gene on chromosome 3.[2]

Ophthalmologists are often the first specialists to diagnose patients with von Hippel-Lindau syndrome because retinal capillary hemangioblastomas are most commonly the first presenting sign of disease, followed by central nervous system hemangioblastomas.[3] The lifetime risk of developing RCHs for all patients with von Hippel-Lindau syndrome is about 70 percent.[3] The average age of onset of retinal capillary hemangioblastomas is 25 years.[3]

Close surveillance of patients is essential to reduce morbidity and mortality in this patient population, including vision loss. Renal cell carcinoma is the most common cause of mortality for patients.[2]

BIOS

Dr. Fortenbach is an assistant professor of ophthalmology at the University of Washington, Seattle, where **Dr. Stacey** is an associate professor, **Dr. Bonnell** is an ophthalmology resident and **Dr. Agi** is a retina fellow.

DISCLOSURES: The authors have no relevant disclosures.

UW Medicine EYE INSTITUTE

Retinal Capillary Hemangioblastomas

RCHs can be diagnosed and monitored through dilated fundoscopic examination of the retina and widefield imaging, including widefield fluorescein angiography. While small peripheral vascular tumors may be asymptomatic, tumors with exudation affecting the macula can lead to vision loss.[4] Less common sequelae of these retinal tumors include neovascularization leading to vitreous hemorrhage and glaucoma, large exudative retinal detachment, or tractional retinal detachment due to glial cell proliferation on the retinal surface.[4]

Ablative therapy is preferred for extrapapillary and extramacular vascular tumors. Tumors smaller than 1.5 mm can often be effectively treated with laser photocoagulation.[4] Larger tumors may require other ablative modalities, such as cryotherapy or brachytherapy. Rarely, with advanced disease, vitreoretinal surgery may be indicated.

Juxtapapillary and Macular Tumors

Treatment for juxtapapillary and macular RCHs is particularly challenging. In these cases, ablative therapy may lead to permanent vision loss. Full- or half-fluence PDT has been reported to be successful in some cases, but it was unsuccessful for our patient.[5]

A New Treatment: Belzutifan

Belzutifan is a novel HIF-2α inhibitor taken as an oral medication.[1] The dose is 120 mg daily.[1] This report and others have demonstrated regression of RCHs with belzutifan use.[6-9] This medication may be most beneficial for juxtapapillary or macular tumors, where typical ablative treatment is challenging. Belzutifan may also be helpful in eyes with large peripheral tumors. Tumor regression with treatment may allow for greater success with laser photocoagulation, as opposed to more invasive and destructive treatments.

While belzutifan therapy is generally well-tolerated, about one-third of patients will discontinue the medication due to side effects, like fatigue.[10] The potential for RCH recurrence after discontinuing treatment must be considered for these patients. Reduced medication dose to 80 mg daily has been reported to control the retinal tumors in one case with short-term follow-up.[9]

Bottom Line

Ophthalmologists are often the first specialists to diagnose von Hippel-Lindau syndrome. Prompt and appropriate referral for close systemic surveillance with appropriate subspecialists is essential. Common extraocular tumors include CNS hemangioblastomas, pheochromocytomas and renal cell carcinomas. Early treatment of RCHs

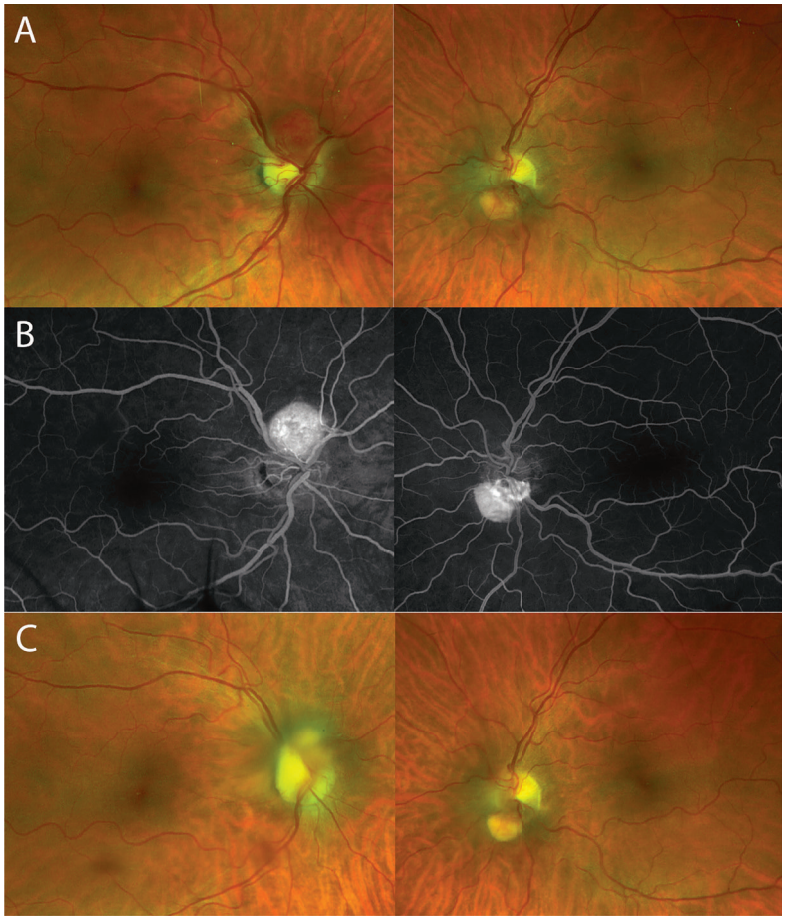


Figure 1. Optos fundus photography (A) and fluorescein angiography (B) of the juxtapapillary RCHs in both eyes at presentation. Follow-up Optos fundus photography (C) three months after starting belzutifan.

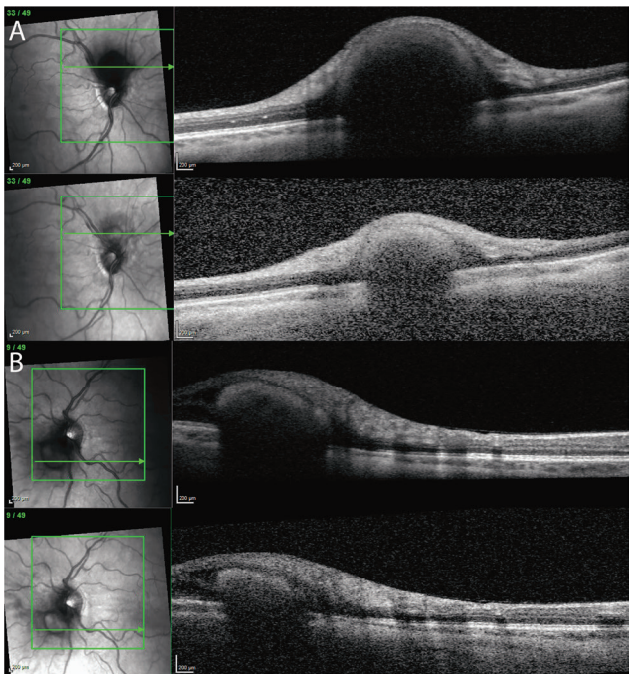


Figure 2. Optical coherence tomography imaging of the juxtapapillary tumors at baseline (top) and three months after initiating daily belzutifan treatment (bottom) in the (A) right and (B) left eyes.

may improve visual outcomes for patients. For challenging lesions near the optic nerve and macula, the novel HIF-2α inhibitor, belzutifan, may be an effective treatment. However, the potential for recurrence of these vascular tumors after discontinuation of treatment must be considered.

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Warfarin and Wet AMD Conversion
(Continued from page 7)

receiving the anticoagulation for the indication of chronic atrial fibrillation," the researchers added in their paper.

They concluded that "switching oral anticoagulation from warfarin to select FDA approved DOACs in patients with subsequent neovascular AMD and/or history of neovascular AMD must be considered carefully, given the improved bleeding profile highlighted in the present study."

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The Pandemic's Effect on DR Screening

Researchers have found that the number of patients being screened for diabetic retinopathy continues to lag behind pre-pandemic levels.[1]

Investigators analyzed health claims in central Massachusetts from 2018 to 2022 to compare the number of DR screenings from the years before and after the COVID-19 virus became widespread. The data showed that post-pandemic weekly DR screenings in the region decreased by 15.1 percent compared to pre-pandemic rates. Adjusting for seasonal variation, the study authors reported a post-lockdown screening rate that was 12 percent lower than the mean weekly DR screening rate during the pre-pandemic period. Established patient DR screenings saw a significant decline after the pandemic while no differences were seen for new patients.

The driving forces behind DR screening rates remain unclear, but the researchers wrote in their paper that "it is likely a combination of factors, such as patient behavior and health care resource availability."

As to why established patients were disproportionately impacted, the researchers wrote in *Ophthalmic Epidemiology* that "health-care providers may have prioritized new patients for DR screening appointments after the pandemic." It's also possible, they add, that established patients with longer duration of diabetes "may have had more advanced diabetes, which is associated with increased comorbid conditions."

REFERENCE

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EYLEA® HD
(aflibercept) Injection 8 mg

Permanent J-code
J0177

Approved for Wet AMD

Long-Lasting Control, Fewer Injections[1]

As demonstrated by vision outcomes in PULSAR at Week 48 —fewer injections vs EYLEA® (aflibercept) Injection 2 mg

EYLEA HD is the first and only anti-VEGF treatment approved in Wet AMD for immediate dosing at Q8W and up to Q16W intervals following 3 initial monthly doses[1]

PULSAR primary endpoint: Mean change in BCVA (ETDRS letters) from baseline at Week 48 was 6.2 letters gained for EYLEA HD Q16W, 6.7 letters for EYLEA HD Q12W, and 7.6 letters for EYLEA 2 mg Q8W.* LS mean differences were noninferior to EYLEA 2 mg using a margin of 4 letters: -1.1 letters (95% CI, -3.0 to 0.7) for EYLEA HD Q16W and -1.0 letters (95% CI, -2.9 to 0.9) for EYLEA HD Q12W. Patients received 3 initial monthly doses.[1]

- Fewer mean number of injections: 5.2 for EYLEA HD Q16W and 6.1 for EYLEA HD Q12W vs 6.9 for EYLEA 2 mg Q8W†[1]

*FAS at baseline: EYLEA HD Q16W (n=338), EYLEA HD Q12W (n=335), EYLEA 2 mg Q8W (n=336). FAS; observed values (censoring data post ICE) at Week 48: EYLEA HD Q16W (n=289), EYLEA HD Q12W (n=299), EYLEA 2 mg Q8W (n=285).[1,2]

†Patients who completed Week 48: EYLEA HD Q16W (n=312), EYLEA HD Q12W (n=316), EYLEA 2 mg Q8W (n=309).[1]

See the outcomes at EYLEAHDhcp.us

IMPORTANT SAFETY INFORMATION FOR EYLEA HD AND EYLEA

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis and retinal detachments and, more rarely, retinal vasculitis with or without occlusion. Proper aseptic injection technique must always be used when administering EYLEA HD or EYLEA. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis, retinal detachment, or retinal vasculitis without delay and should be managed appropriately.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA HD and 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 HD and EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).
  - EYLEA HD: The incidence of reported thromboembolic events in the wet AMD study (PULSAR) from baseline through week 48 was 0.4% (3 out of 673) in the combined group of patients treated with EYLEA HD compared with 1.5% (5 out of 336) in patients treated with EYLEA 2 mg. The incidence in the DME study (PHOTON) from baseline to week 48 was 3.1% (15 out of 491) in the combined group of patients treated with EYLEA HD compared with 3.6% (6 out of 167) in patients treated with EYLEA 2 mg.
  - EYLEA: The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- EYLEA HD:
  - The most common adverse reactions (≥3%) reported in patients receiving EYLEA HD were cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage.
- EYLEA:
  - 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.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA HD or EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® HD (aflibercept) Injection 8 mg is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

EYLEA® (aflibercept) Injection 2 mg 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).

Please see Brief Summary of Prescribing Information for EYLEA HD and EYLEA on the following page.

anti-VEGF, anti-vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set; ICE, intercurrent event; LS, least squares; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks.

References: 1. EYLEA HD full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. December 2023. **2.** Brown DM; PULSAR Study Investigators. Aflibercept 8 mg in patients with nAMD: 48-week results from the phase 3 PULSAR trial. Presented at: Angiogenesis, Exudation, and Degeneration 2023; February 11, 2023; virtual.

REGENERON®

03/2024
US.EHD.24.02.0071

EYLEA® HD (aflibercept) Injection 8 mg, for intravitreal use AND EYLEA® (aflibercept) Injection 2 mg, for intravitreal use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

4. CONTRAINDICATIONS

4.1 Ocular or Periocular Infections EYLEA HD and EYLEA are contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation EYLEA HD and EYLEA are contraindicated in patients with active intraocular inflammation.

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis, Retinal Detachments, and Retinal Vasculitis with or without Occlusion Intravitreal injections including those with aflibercept have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]* and, more rarely, retinal vasculitis with or without occlusion *[see Adverse Reactions (6.2)]*. Proper aseptic injection technique must always be used when administering EYLEA HD or EYLEA. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis, retinal detachment or retinal vasculitis without delay and should be managed appropriately [*see Dosage and Administration (2.6 EYLEA HD, 2.4 EYLEA) in the full Prescribing Information and 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 HD and 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 [*see Dosage and Administration (2.6 EYLEA HD, 2.4 EYLEA) in the full Prescribing Information*].

5.3 EYLEA HD, 5.4 EYLEA Thromboembolic Events There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA HD and EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

- **EYLEA HD:** The incidence of reported thromboembolic events in the wet AMD study (PULSAR) from baseline through week 48 was 0.4% (3 out of 673) in the combined group of patients treated with EYLEA HD compared with 1.5% (5 out of 336) in patients treated with EYLEA 2 mg. The incidence of reported thromboembolic events in the DME study (PHOTON) from baseline to week 48 was 3.1% (15 out of 491) in the combined group of patients treated with EYLEA HD compared with 3.6% (6 out of 167) in patients treated with EYLEA 2 mg.
- **EYLEA:** 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, retinal detachments and retinal vasculitis with or without occlusion [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3 for EYLEA HD, 5.4 for EYLEA)*]

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.

- **EYLEA HD:** A total of 1164 patients were treated with EYLEA HD and 503 patients were treated with EYLEA 2 mg in two clinical studies. The most common adverse reactions reported in ≥3% of patients treated with EYLEA HD were cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage.
- **EYLEA:** A total of 2980 adult 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 (Wet AMD)

EYLEA HD: The data described below reflect exposure to EYLEA HD or EYLEA 2 mg in 1009 patients with Wet AMD, in 1 double-masked, controlled clinical study (PULSAR) for 48 weeks [*see Clinical Studies (14.1) in the full Prescribing Information*].

EYLEA: 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 (VIEW 1 and VIEW 2) for 24 months (with active control in year 1) [*see Clinical Studies (14.1) in the full Prescribing Information*].

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

	PULSAR ARs (≥1%) in at least one group			VIEW 1 and VIEW 2 Baseline to Week 52		VIEW 1 and VIEW 2 Baseline to Week 96	
Adverse Reactions	**EYLEA HD q12 (n=335)**	**EYLEA HD q16 (n=338)**	**EYLEA 2q8 (n=336)**	**EYLEA (n=1824)**	**Active Control (ranibizumab) (n=595)**	**EYLEA (n=1824)**	**Control (ranibizumab) (n=595)**
Conjunctival hemorrhage[a]	3%	2%	1%	25%	28%	27%	30%
Eye pain	-	-	-	9%	9%	10%	10%
Ocular discomfort/eye pain/eye irritation[a]	3%	3%	2%	-	-	-	-
Cataract[a]	4%	4%	4%	7%	7%	13%	10%
Vitreous detachment[a]	2%	3%	2%	6%	6%	8%	8%
Vitreous floaters[a]	1%	4%	3%	6%	7%	8%	10%
Intraocular pressure increased[a]	4%	4%	2%	5%	7%	7%	11%
Ocular hyperemia[a]	-	-	-	4%	8%	5%	10%
Corneal epithelium defect[a]	2%	2%	3%	4%	5%	5%	6%
Retinal pigment epithelial detachment[a]	1%	1%	2%	3%	3%	5%	5%
Injection site pain	-	-	-	3%	3%	3%	4%
Foreign body sensation in eyes[a]	1%	1%	2%	3%	4%	4%	4%
Lacrimation increased	-	-	-	3%	1%	4%	2%
Vision blurred[a]	4%	6%	7%	2%	2%	4%	3%
Intraocular inflammation[a]	1%	1%	1%	2%	3%	3%	4%
Retinal pigment epithelial tear	-	-	-	2%	1%	2%	2%
Retinal pigment epithelial tear/ epitheliopathy[a]	2%	1%	2%	-	-	-	-
Injection site hemorrhage	-	-	-	1%	2%	2%	2%
Eyelid edema	-	-	-	1%	2%	2%	3%
Corneal edema	-	-	-	1%	1%	1%	1%
Retinal detachment[a]	1%	<1%	0%	<1%	<1%	1%	1%
Retinal hemorrhage	3%	3%	4%	-	-	-	-
Vitreous hemorrhage	<1%	1%	1%	-	-	-	-

Reported terms differ between the PULSAR and VIEW 1 and VIEW 2 studies, as indicated by dashes in the table.

[a]Represents grouping of related terms in PULSAR

Adverse drug reactions (ADRs) reported in <1% of participants treated with EYLEA HD were ocular hyperemia (includes adverse events of conjunctival hyperemia, conjunctival irritation, ocular hyperemia), lacrimation increased, eyelid edema, hypersensitivity (includes adverse events of rash, urticaria, pruritus), retinal tear, and injection site hemorrhage.

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA in VIEW 1 and VIEW 2 were hypersensitivity, retinal tear, and endophthalmitis.

6.2 Postmarketing Experience The following adverse reactions have been identified during postapproval use of aflibercept. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders: retinal vasculitis and occlusive retinal vasculitis related to intravitreal injection with aflibercept (reported at a rate of 0.6 and 0.2 per 1 million injections, respectively, based on postmarketing experience from November 2011 until November 2023).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary Adequate and well-controlled studies with EYLEA HD and 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 exposure (based on AUC for free aflibercept) was approximately 0.9-fold of the population pharmacokinetic estimated exposure in humans after an intravitreal dose of 8 mg for EYLEA HD and approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose of 2 mg for EYLEA [*see Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA HD or EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1) in the full Prescribing Information*], treatment with EYLEA HD or EYLEA may pose a risk to human embryofetal development. EYLEA HD and 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 0.9-fold of the population pharmacokinetic estimated systemic exposure (AUC) in humans after an intravitreal dose of 8 mg for EYLEA HD and approximately 6 times higher than systemic exposure (AUC) observed in adult patients after a single intravitreal dose of 2 mg for EYLEA.

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 HD and EYLEA are not recommended during breastfeeding. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA HD or EYLEA and any potential adverse effects on the breastfed child from EYLEA HD or 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 4 and 3 months after the last intravitreal injection of EYLEA HD or EYLEA, respectively.

Infertility There are no data regarding the effects of EYLEA HD or EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose 91 times higher (based on AUC of free aflibercept) than the corresponding systemic level estimated based on population pharmacokinetic analysis in humans following an intravitreal dose of 8 mg for EYLEA HD and at a dose approximately 1500 times higher than the systemic level observed in adult patients with an intravitreal dose of 2 mg for EYLEA. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1) in the full Prescribing Information*].

8.4 Pediatric Use The safety and effectiveness of EYLEA HD in pediatric patients have not been established.

The safety and effectiveness of EYLEA have been demonstrated in two clinical studies of pre-term infants with Retinopathy of Prematurity. These two studies randomized pre-term infants between initial treatment with EYLEA or laser. Efficacy of each treatment is supported by the demonstration of a clinical course which was better than would have been expected without treatment [*see Dosage and Administration (2.9), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.6) in the full Prescribing Information for EYLEA*].

8.5 Geriatric Use In PULSAR, approximately 90% (604/673) of the patients in the HDq12 and HDq16 groups were 65 years of age or older and approximately 51% (343/673) were 75 years of age or older.

In PHOTON, approximately 44% (214/491) of the patients in the HDq12 and HDq16 groups were 65 years of age or older and approximately 10% (50/491) were 75 years of age or older.

In the clinical studies for EYLEA 2 mg, 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.

10 OVERDOSAGE Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

17 PATIENT COUNSELING INFORMATION In the days following EYLEA HD or EYLEA administration, patients are at risk of developing endophthalmitis, retinal detachment or retinal vasculitis with or without occlusion. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients and/or caregivers to seek immediate care from an ophthalmologist [*see Warning and Precautions (5.1)*]. Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA HD or 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 10591-6707

US.EHD.23.12.0092 12/2023

PFO for pars plana lensectomy

Tips for using perfluoro-n-octane to protect the macula from unintentional trauma that dropped intraocular foreign bodies may cause.

By Rodney C. Guiseppi, MD, and Mikelson MomPremier, MD

Rodney C. Guiseppi, MD,

Mikelson MomPremier, MD

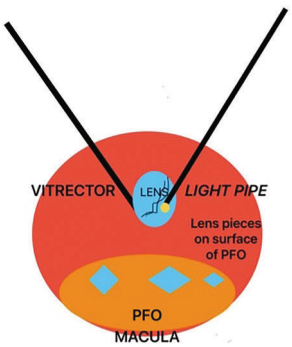
A partial perfluoro-n-octane (PFO) fill before performing lensectomy is a useful tool to protect the macula and peripheral retina from unintentional trauma during lensectomy, because the large mobile irregular lens pieces may fall at a high velocity onto the macula multiple times.

Perfluorocarbon liquids have been shown to potentially shield the macula from the impact of dropped intraocular foreign bodies by deflecting the trajectory on the perfluorocarbon liquid-balanced salt solution interface.[1]

Our case

In the accompanying video, we operate on a middle-aged man who had a subluxed lens after blunt force trauma. We used a 23-gauge vitrector set for pars plana lensectomy with a bimanual technique to break the lens into smaller pieces, which helped to make the lensectomy more efficient *(Figure)*.

We used the light pipe to directly apply mechanical pressure onto the lens surface and feed it into the vitrector and break it into smaller pieces. Smaller pieces were easier to remove, sometimes with just aspiration from the vitrector.



We do bimanual pars plana lensectomy using the vitrector and light pipe. The light pipe can help to feed larger lens pieces into the vitrector. The perfluoro-n-octane bubble protects the macula from mobile lens pieces during the procedure.

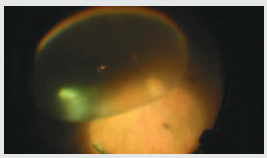
Intraoperative trouble-shooting

In patients with a medium-density lens, we recommend initiating the lensectomy with the larger vitrector and reserving the phacofragmatome for very dense lenses.

A core vitrectomy, posterior vitreous detachment induction and a good peripheral vitrectomy before starting the pars plana lensectomy are also key. During lensectomy, a loss in aspiration suggests that lens pieces may be occluding the vitrector, so it's important to flush the vitrector line outside the eye.

View the Video

Dr. Guiseppi and Dr. MomPremier perform a bimanual technique to remove a subluxed lens after blunt force trauma. Go to: https://bit.ly/VideoPearl-41 or scan the QR code.



Using PFO

We applied intraoperatively about 2 to 3 mLs of PFO (Perfluron, Alcon) to cover the posterior pole to the arcades, including the macula. Once we aspirated the large lens pieces, we safely removed the PFO and placed a secondary intraocular lens.

A scleral depressed exam at the end of the case ensured that no peripheral retinal breaks were present.

PFO may be costly and isn't necessary for all cases of pars plana lensectomy, but we recommend considering it in cases when the lens is dense and may fall multiple times onto the macula during surgery

Bottom line

Instilling and removing PFO is an additional but useful step in pars plana lensectomy by preventing iatrogenic damage to the macula during these cases. We recommend taking these additional steps for the entire lens or large lens pieces. RS

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BIOS

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Tyrosine Kinase Inhibitors in the Pipeline

Impressive early results may raise the bar for efficacy and durability.

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Take-home points

- Tyrosine kinase inhibitors (TKIs) are small molecules capable of inhibiting all VEGF receptor isoforms as well as other tyrosine kinase receptors intracellularly.
- Multiple TKIs are being investigated in clinical trials, utilizing varied modes of administration and innovative delivery platforms/vehicles.
- Results thus far display maintenance of visual acuity and anatomic stability with substantial and clinically meaningful reductions in the need for supplemental injections.
- The advent and potential future approval of TKIs may usher in a new era for wet AMD and DME patients, with the potential for reduced treatment burdens and improved long-term outcomes.

Treatments for exudative age-related macular degeneration and diabetic retinopathy and diabetic macular edema have advanced tremendously since the era of blasting the macula with thermal laser and full fluence photodynamic therapy. The current generation of anti-vascular endothelial growth factor agents have worked remarkably well in both preserving visual acuity and improving vision in a majority of our patients. These improvements have allowed our patients to continue to read, drive and work. While we retina specialists and our patients have had access to an improving array of anti-VEGF treatment options, vision can quickly be lost if patients don't adhere to the prescribed long-term treatment plans. Innovative options such as the Port Delivery System for ranibizumab (Genentech) have been helpful for a small subset of patients, but the voluntary recall has kept many patients from receiving this valuable long term therapy.

Recent additions to the marketplace such as high-dose aflibercept (Eylea HD; Regeneron) and faricimab (Vabysmo; Genentech) have offered improved anatomic effects and durability for many patients via higher molar doses and concentrations or dual mechanism inhibition of VEGF and Angiopoietin-2, respectively. While these new options have been excellent additions to our armamentariums, numerous companies and investigators continue to search for even more durable treatments to reduce the burden on our patients, potentially circumventing or at least alleviating, the challenges of patient noncompliance and treatment fatigue. This article will discuss the promising class of molecules known as tyrosine kinase inhibitors.

TKIs in Development

Whereas anti-VEGF medications primarily inhibit VEGF-A receptor binding extracellularly, TKIs are smaller molecules capable of diffusing into cells and

Bios

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inhibiting all VEGF receptor isoforms as well as other tyrosine kinase receptors such as FGFR and PDGFR.[1,2] This versatility in terms of target inhibition allows the potential for enhanced durability and disease control. Below we'll summarize the TKIs currently in development for wet AMD and DR (in alphabetical order).

• ***AIV007 (AiViva BioPharma)***. Relatively early in development, AIV007 is an injectable, broad-spectrum TKI that uses a proprietary technology that transitions to a biodissolvable gel depot at body temperature for prolonged drug release. A Phase I trial is enrolling 24 subjects with DME and wet AMD who'll receive one periocular injection with monthly evaluation for up to six months. Study completion is set for 2025.

• ***Axpaxli (Ocular Therapeutix)***. Axpaxli (previously OTX-TKI) is the TKI axitinib delivered by Ocular Therapeutix's Elutyx drug delivery platform. Elutyx technology is a completely bioresorbable, programmable hydrogel matrix that encapsulates axitinib to provide sustained and localized delivery lasting nine to 12 months with a single implant injected via a 25-gauge needle.[3] Axitinib is a highly selective, pan-VEGF inhibitor offering the potential for higher potency and ocular cell biocompatibility than other TKIs.[4] A Phase Ib randomized, double-masked trial evaluating wet AMD subjects with controlled retinal fluid compared 15 patients receiving 0.6 mg Axpaxli to five patients receiving aflibercept.[5] Despite needing a mean of eight intravitreal injections in the year prior to initiation, Axpaxli patients enjoyed an 89-percent reduction in anti-VEGF treatment burden at 12 months, while vision and central subfield thickness (CST) values were comparable to standard-of-care aflibercept dosed every eight weeks. Seventy-three percent of patients needed no supplemental injections in the first six months, and 33 percent needed no injections at 12 months.

The HELIOS trial is a Phase Ib trial evaluating Axpaxli in moderate to severe NPDR patients without DME.[6] This 12-month study should be releasing results very soon.

The SOL trial is a multicenter, double-masked, parallel-group, Phase III pivotal trial with 300 U.S. subjects comparing a reformulated, higher-dose Axpaxli to aflibercept in treatment-naïve wet AMD subjects with excellent visual acuity.[7,8]

• ***AXT107 (AsclepiX Therapeutics)***. AXT107 is a microparticulate suspension for intraocular injection that targets VEGF receptor 2 and activates the vessel-stabilizing receptor tyrosine kinase (TIE2). Fifteen patients are being recruited for a Phase I/IIa trial in wet AMD evaluating 40-week outcomes of three dose levels of a single injection.

• ***CLS-AX (Clearside Biomedical)***. CLS-AX is a proprietary formulation of the TKI axitinib that's delivered via suprachoroidal administration using Clearside's SCS Microinjector.[9] As described above, Axitinib may have potency up to 10 times higher than other TKIs. Suprachoroidal administration offers a favorable safety and efficacy profile due to compartmentalization of medication closer to the target tissue, using the same microinjector as the FDA-approved Xipere.[10]

The OASIS Phase I/IIa extension trial evaluated escalating doses of CLS-AX following intravitreal aflibercept in previously treated wet AMD patients with active disease. Patients were evaluated monthly and could be retreated with aflibercept for 10 or greater letter loss with exudation, CST increase of 75 μm or new hemorrhage. The patients demonstrated stable visual acuity (BCVA from baseline) as well as CST values, while demonstrating a 77 to 85 percent reduction in treatment burden in cohorts 3 and 4 for up to six months. Sixty-seven percent of

While newly approved drugs have been excellent additions to our armamentariums, numerous companies and investigators continue to search for even more durable treatments ...

Table 1. TKIs in Development

Treatment	Company
AIV007	AiViva BioPharma
Axpaxli	Ocular Therapeutix
AXT107	AsclepiX Therapeutics[1]
CLS-AX	Clearside Biomedical
D4517.2	Ashvattha Therapeutics
EYP-1901	EyePoint Pharmaceuticals
PAN-90806	PanOptica

patients required no supplemental therapy out to six months, and CLS-AX displayed an excellent safety profile at all doses and timepoints.

Recruitment has subsequently been completed for the Phase IIb Odyssey trial evaluating 60 previously treated wet AMD patients with reading center confirmation of active disease. Both arms will receive three monthly aflibercept loading injections. Arm 1 will continue with aflibercept every eight weeks, while arm 2 receives CLS-AX at baseline and at least every 24 weeks. Patients are evaluated monthly at disease activity assessment (DAA) visits and can receive supplemental therapy if certain vision and anatomic criteria are met. These results, expected in the coming months, will help to inform a future Phase III development program.

• ***D4517.2 (Ashvattha Therapeutics)***. D4517.2 inhibits VEGF receptor tyrosine kinases selectively in activated microglia and macrophages and hypertrophic retinal pigment epithelial (RPE) cells. Preclinical studies have demonstrated that the agent crosses the blood-retinal barrier after systemic administration. Both oral and subcutaneous routes of administration are being explored.[11] A single oral dose has shown reduction in CNV lesion size in mouse models, comparable to that provided by subcutaneous administration.[12] The ongoing Phase II TEJAS study is evaluating the safety, efficacy and durability of multiple doses of subcutaneous D4517.2 compared to afibercept injections in previously treated wet AMD and DME patients.[13]

• ***EYP-1901 (EyePoint).*** EYP-1901 pairs vorolanib, a selected and patented TKI, with Eyepoint's Durasert E technology. The Durasert E implant consists of drug embedded within a bioerodible matrix, providing an initial burst of drug followed by zero order kinetics and continuous, stable drug release for up to nine months via in-office intravitreal administration. In addition to pan-VEGF receptor inhibition, vorolanib also blocks PDGF, potentially providing antifibrotic benefits. Of note, it doesn't inhibit TIE2 at clinically relevant doses. Vorolanib has also demonstrated neuroprotection in a validated retinal detachment animal model.

On the heels of impressive durability results from the Phase I DAVIO trial, the DAVIO 2 trial is a multicenter, randomized, double-masked non-inferiority trial evaluating two doses of EYP-1901 against an aflibercept control in 160 previously treated wet AMD patients.[14] Patients had received a mean of 10 injections in the year prior to screening. All three arms received three aflibercept loading doses. The control arm then was treated with aflibercept every eight weeks.[15] Both the low- and high-dose EYP-1901 arms received the implant concomitantly with the third aflibercept loading dose, and could then receive supplemental anti-VEGF if certain vision and anatomic criteria were met, or at the investigators' discretion.[16]

The primary endpoint was met with non-inferior change in BCVA compared with aflibercept monotherapy. There were no EYP-1901-related serious adverse events, and ocular AEs were mild and as expected for intravitreal injections. There were no cases of implant migration into the anterior chamber or occlusive retinal vasculitis. All secondary endpoints were met, including a greater than 80 percent reduction in treatment burden, both relative to the six months prior to study onset, as well as aflibercept control. Sixty-five percent of the 3-mg implant patients and 64 percent of the 2-mg patients were supplement-free six

months after a single injection, while maintaining stable anatomy with OCT change at week 32 relative to aflibercept of less than 10 µm.

The PAVIA trial evaluating the vorolanib implant in moderate to severe non-proliferative diabetic retinopathy patients is ongoing with topline results expected soon.[17] The VERONA trial is a single-masked, Phase II trial in previously treated DME patients. Lastly, a global Phase III trial in wet AMD is expected to commence shortly.

• ***PAN-90806 (PanOptica)***. PAN-90806 is a topical TKI eye drop studied in a Phase I and II, dose-escalating, quadruple-masked, randomized clinical trial evaluating once-daily use for 12 weeks in 51 treatment-naïve nAMD patients.[18] Patient best-corrected acuity and CST remained stable, while also demonstrating a substantial 79-percent reduction in injection burden. Fifty-one percent of patients required no rescue injections. PanOptica has entered into a license agreement with Zhaoke Ophthalmology Pharmaceutical to fine tune the formulation for PAN-90806.[19]

Bottom Line

Highly encouraging results from numerous tyrosine kinase inhibitor clinical development programs are providing increasing levels of confidence that this new class of molecules may advance the treatment landscape for wet age-related macular degeneration and diabetic macular edema. Although patient outcomes have improved tremendously in the anti-VEGF era, challenges remain in terms of the need for frequent ongoing therapy in populations of elderly patients and diabetics, both of whom may struggle to maintain adherence to the prescribed treatment regimen.[20]

The promising candidates above may alleviate these obstacles, allowing improved long-term outcomes and quality of life for our patients.

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Advances in AI screening for diabetic retinopathy and DME

Artificial intelligence has the potential to make screening for these diseases easier in various clinical settings.

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Take-home points

- AI-driven DR screening can be cost-effective and scalable, and can increase accessibility, especially in underserved areas.
- Remaining challenges are the need for diverse datasets, regulatory approvals and ethics/privacy concerns.
- Head-to-head comparisons of the AI models will help define which systems work better in different settings.

Though diabetic retinopathy screening is a crucial aspect of maintaining patients' vision, it's fraught with challenges. The current obstacles to more effective DR screening include limited access to specialized health care and a shortage of ophthalmologists or trained screeners. The high cost of screening technology and lack of awareness about the importance of early detection also contribute to low screening rates. Additionally, the variability in disease progression and the need for regular, often lifelong, monitoring complicate consistent follow-up.

Implementing and maintaining effective screening programs also faces logistical and financial barriers. These challenges collectively hinder early diagnosis and timely treatment, critical for preventing vision loss in diabetic patients. Here, we'll describe how artificial intelligence may help ease some of this screening burden.

Principles of AI in DR and DME Screening/Monitoring

Recent innovations in artificial intelligence are revolutionizing screening and monitoring of DR and DME. The principles behind AI in this context involve several components that enable effective and efficient detection of DR and DME:

- ***Data collection and preprocessing.*** AI systems rely on large datasets of retinal images for training. These images are often obtained from diverse populations to ensure the model can generalize well across different demographic groups. Preprocessing steps include normalization, resizing and enhancement of images to improve the quality and consistency of the input data.[1]
- ***Machine learning algorithms.*** At the core of AI for DR screening are machine learning algorithms, particularly convolutional neural networks. CNNs are designed to automatically and adaptively learn spatial hierarchies of features from input images.[2] In the context of DR, these features may include minute details such as microaneurysms, hemorrhages, exudates and neovascularization. For DME, these include macular thickness and structural changes from optical coherence tomography imaging.
- ***Training the model.*** The training

Bios

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process involves feeding the neural network a curated dataset of labeled retinal images, where the presence and severity of DR have been annotated by expert ophthalmologists.[3] The model learns to recognize patterns and correlations between the retinal features and the labels through iterative optimization techniques *(Figure 1)*. During training, the model's parameters are adjusted to minimize the error in its predictions.

• ***Validation and testing.*** After training, the model's performance is validated using a separate set of images not seen during training. This step helps in tuning the model parameters and avoiding overfitting. The final evaluation involves testing the model on a completely independent dataset to assess its accuracy, sensitivity, specificity and overall robustness in detecting DR.[4]

• ***Deployment and integration.*** Once validated, the AI model can be deployed in clinical settings. It can be integrated into existing health-care workflows and screening programs. Typically, retinal images are captured using fundus cameras and then analyzed by the AI system, which can provide rapid, automated diagnoses.[5] The system highlights images with signs of DR, prioritizing cases that need urgent attention from ophthalmologists. However, it's important to emphasize that regulatory requirements for AI applications remain and a clinical trial at the level required by the FDA will be needed for fully autonomous use in the United States.

Clinical Trials of AI

Several clinical trials have demonstrated the efficacy and reliability of artificial intelligence in screening and monitoring DR and DME. Processing of data for DR and DME requires different approaches. DR is identified by photographic imaging while DME relies on macular thickness measurements and structural changes from OCT imaging. The following trials highlight AI's role for enhancing diagnostic accuracy, predicting disease progression and optimizing treatment strategies for screening and monitoring DR and DME:

• ***Google Health's AI system for diabetic retinopathy and DME.*** A significant study by Google Health and published in *JAMA Ophthalmology,* developed and validated an AI system to detect DR

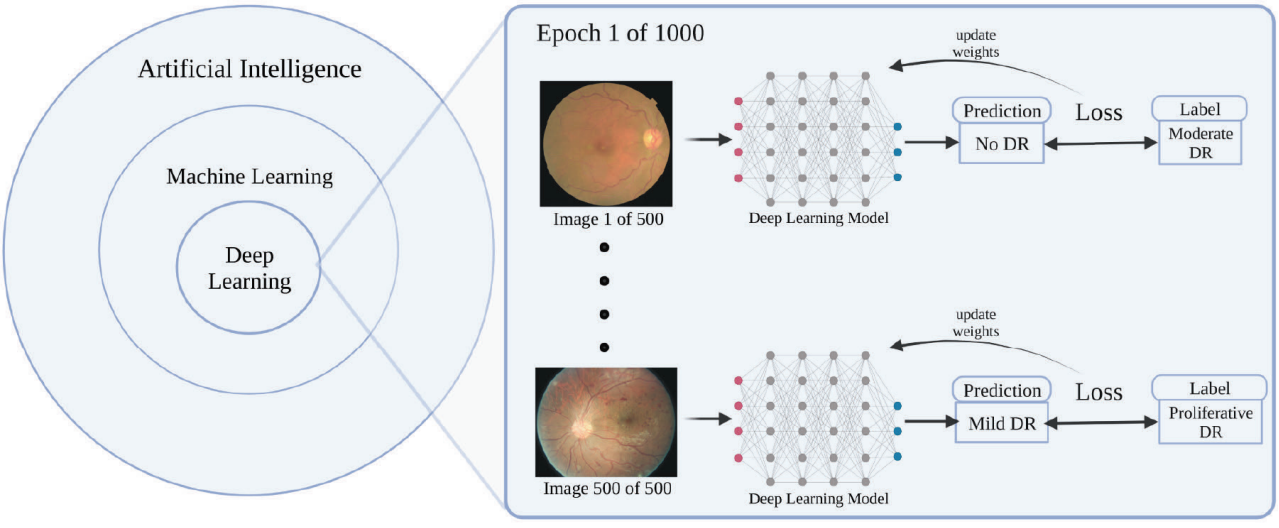


Figure 1. An example of a deep learning model being trained to classify diabetic retinopathy severity using a dataset of 500 images. ***(Image taken from: Rajesh, AE, Davidson, OQ, Lee, C S, Lee AY. Artificial intelligence and diabetic retinopathy: AI framework, prospective studies, head-to-head validation, and cost-effectiveness. Diabetes Care 2023;46:10:1728–1739.)***

and DME from retinal images and OCT scans. The AI system used in this study demonstrated high sensitivity and specificity in detecting DME. It concluded that the model's performance was comparable to that of expert ophthalmologists.[3] This study highlighted the potential for AI to assist in screening programs, particularly in regions with limited access to specialized care.

• ***IDx-DR system for autonomous detection of diabetic retinopathy.*** The IDx-DR system, an AI-based diagnostic tool, underwent a pivotal clinical trial to evaluate its accuracy in detecting diabetic retinopathy, including macular edema, from retinal images. This clinical trial involved 900 patients across 10 primary care sites in the United States. The IDx-DR achieved sensitivity and specificity rates of 87.2 percent and 90.7 percent, respectively, for detecting more than mild diabetic retinopathy.[3] This led to the IDx-DR system becoming the first FDA-approved AI device for autonomous diabetic retinopathy screening.

• ***Retinal Deep Learning system for OCT analysis.*** A study published in *The Lancet Digital Health* evaluated the performance of the Retinal Deep Learning (RDL) system, an AI-powered tool designed to analyze OCT scans for detecting DME and other retinal diseases. The RDL system was trained on a large dataset of OCT images and validated on an independent test set. This AI model demonstrated high accuracy in detecting DME, with sensitivity and specificity exceeding 90 percent.[6] The results showed the potential for AI to improve early detection and monitoring of DME, aiding in timely treatment interventions.

• ***VoxelCloud AI platform for treatment response evaluation.*** VoxelCloud developed an AI platform to monitor treatment response in DME patients using OCT imaging. A clinical trial was conducted to assess the platform's ability to track changes in macular thickness and fluid accumulation. The trial involved multiple clinical centers and included a diverse patient population. The results demonstrated accurate quantified changes in retinal morphology, which correlated well with clinical outcomes. The study highlighted the platform's utility in evaluating treatment efficacy and adjusting management plans based on AI-driven insights.[7]

• ***Optovue's AngioAnalytics for predictive analytics.*** Optovue's AngioAnalytics, an AI-powered OCT system, was evaluated in a clinical trial to determine its effectiveness in predicting disease progression in DME patients. This trial demonstrated that the AI system could identify biomarkers associated with DME progression.[8] Predictive analytics provided by AngioAnalytics may enable personalized monitoring schedules, improving

(Continued on page 35)

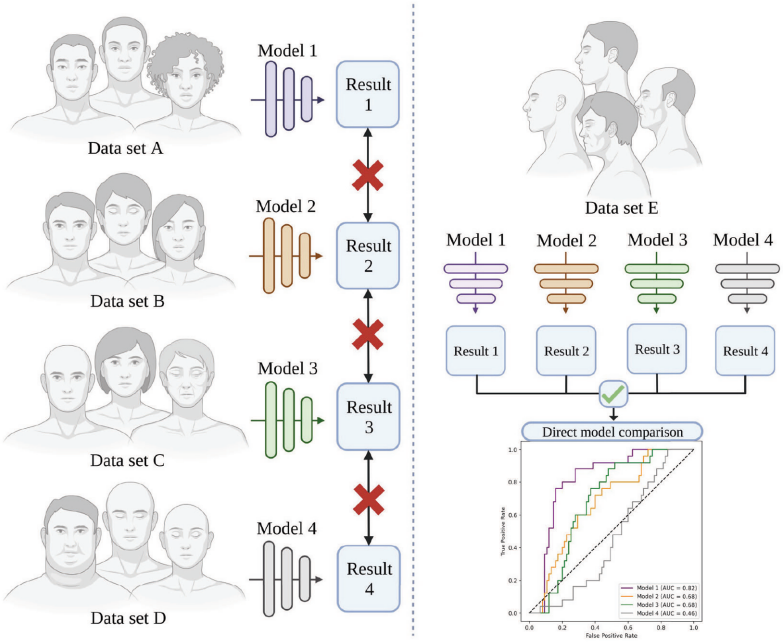
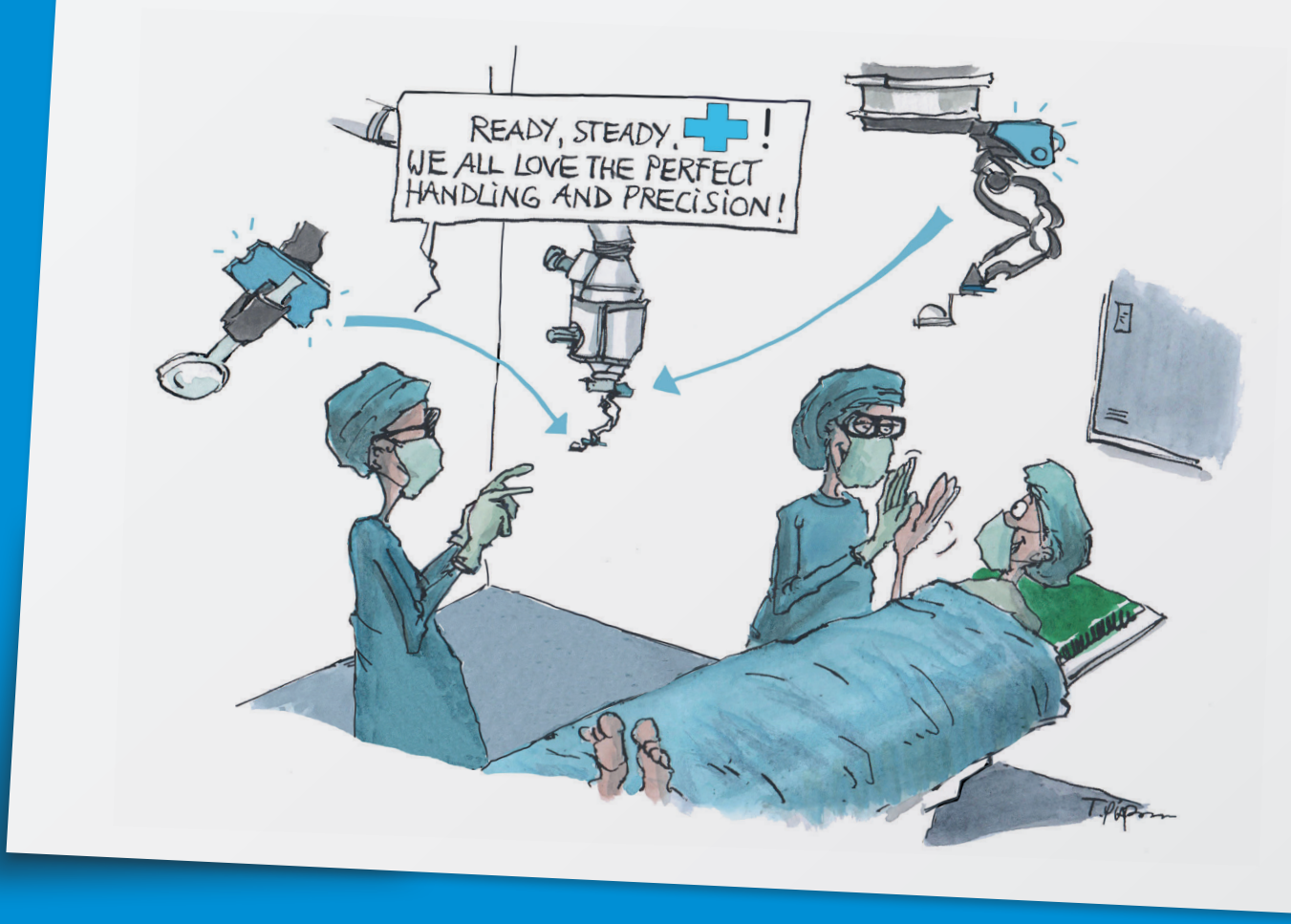


Figure 2. Evaluation of different learning models using different datasets (left) make them incomparable. On the other hand, assessment of the same models using one dataset (right) allow their performance to be directly compared. ***(Image taken from: Rajesh AE, Davidson OQ, Lee CS, Lee AY. Artificial intelligence and Diabetic retinopathy: AI framework, prospective studies, head-to-head validation, and cost-effectiveness. Diabetes Care 2023;46:10:1728–1739.)***



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Choosing the right patient for today's GA treatments

A closer look at the nuances of selecting a patient, an agent and dosing frequency to achieve the best outcomes.


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By Masumi Asahi, DO, Baruch D. Kuppermann, MD, PhD, and Kapil Mishra, MD

Take-home points

- Intravitreal complement inhibitors pegcetacoplan and avacincaptad pegol have demonstrated a dose-dependent reduction of the rate of geographic atrophy lesion with every-other-month and monthly dosing, and exhibit further improvement with extended duration of therapy, suggesting more benefit from earlier intervention.
- Agent selection and dosing frequency should involve a risk-benefit analysis that considers the location, extent and rate of progression of GA lesions among other factors, such as patient age, treatment burden and fellow eye status.
- Some clinicians have suggested initiating a treatment trial in the worse-seeing eye first to possibly avoid rare events of intraocular inflammation in the better-seeing eye.
- The increased incidence of neovascularization associated with intravitreal complement inhibitors can be managed with concurrent anti-VEGF therapy.

Unlike neovascular age-related macular degeneration, no treatment options for geographic atrophy existed until recently. Intravitreal complement inhibitors have demonstrated efficacy in slowing the progression of GA, with two agents in this class approved by the United States Food and Drug Administration—pegcetacoplan (Syfovre, Apellis) and avacincaptad pegol (ACP, Izervay, Iveric Bio/Astellas).

These agents have opened the doors for a new age of management in the GA space. Now, with a large patient class eligible for treatment, retina specialists face previously unanswered questions on patient selection for GA treatment and the risk-benefit profiles of these new agents. Here, we review trial data for these agents and present management pearls for patients with GA.

C3 inhibition

The OAKS and DERBY Phase III trials for pegcetacoplan, a complement factor C3 inhibitor, demonstrated an 18- and 22-percent reduction in GA lesion growth rate over 24 months compared to sham with every-other-month (EOM) and monthly dosing, respectively. The trials included patients with GA lesions with or without subfoveal involvement and excluded patients with choroidal neovascularization in the study eye (fellow-eye CNV wasn't exclusionary).

The GALE extension study continued to demonstrate increasing treatment effects over a 36-month period, with a 24- and 35-percent reduction in lesion growth rate for EOM and monthly dosing, respectively. This is compared to the projected rate of GA lesion growth in the sham arm, which has been assumed to be linear.

These study findings have also suggested that longer treatment duration is associated with continued divergence in the rates of GA progression between the treatment and sham groups. A post-hoc analysis demonstrated functional benefits with preservation of the mean threshold sensitivity in the

perilesional zone and reduction in scotomatous points.[1,2] However, the findings showed no statistical differences in vision between treated and sham groups overall.

C5 inhibition

The GATHER1 and GATHER2 pivotal trials for ACP, a complement factor C5 inhibitor, included patients with extrafoveal GA lesions within 1,500 µm of the center point, and excluded patients with CNV in either eye. GATHER1 explored monthly dosing at different doses of ACP and demonstrated a 35-percent reduction in GA lesion growth at 12 months. GATHER2, which focused on the 2-mg dose and then re-randomized participants to monthly or EOM dosing after 12 months of monthly dosing, reported a 17.7-percent reduction in GA lesion growth at 12 months.

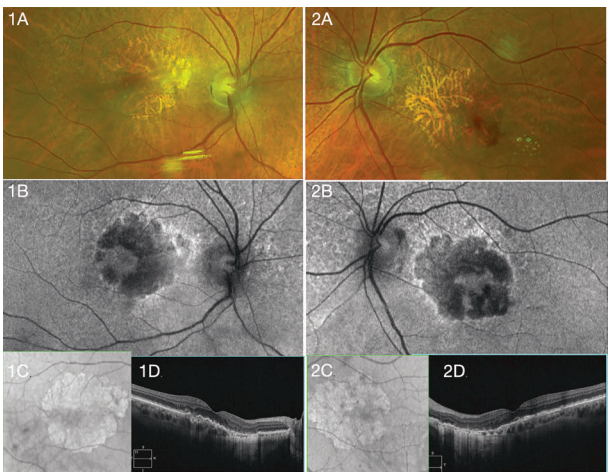
Notably, EOM dosing produced a GA growth rate reduction that was similar to monthly dosing: a 14- vs. a 19-percent reduction for monthly vs. EOM dosing. A post-hoc analysis of pooled data from both trials over the first 12 months of treatment found a 56-percent decrease in the risk of persistent vision loss in ACP-treated patients vs. sham, with persistent vision loss defined as a 15-letter decrease in best-corrected visual acuity for any two consecutive visits.[3]

The 24-month data didn't reach significance. However, similar to the pivotal trials for pegcetacoplan, the efficacy analysis of the ACP pivotal trials showed no statistical difference in vision between treated and sham groups in the overall study population.

Efficacy of complement inhibition

Due to the variance in design between the two trials, it's difficult to compare the efficacy of the two available agents with trial data alone. A subpopulation analysis aimed to evaluate potential differences in their efficacy.[4] The analysis applied the more restrictive enrollment criteria from GATHER2 to the OAKS/DERBY population with propensity score matching of baseline characteristics to select and compare similar patients with nonsubfoveal GA and no CNV in the fellow eye.

The monthly dosing arm had a 30-percent greater reduction in the GA lesion growth rate favoring pegcetacoplan at 12 months. A nonsignificant but numerically greater trend favored EOM pegcetacoplan to monthly ACP. Generalizability is limited by the study design, statistical methodology and small sample size (roughly 50 in each arm). Currently, barring any head-to-head trials, it's difficult to make any definitive statements about the relative efficacy of the two complement inhibiting agents.



A 72-year-old Caucasian woman with geographic atrophy in both eyes received treatment for neovascular age-related macular degeneration in the left eye. Vision is 20/20 OD and 20/25 OS. She's considering complement inhibition. Right (1A-D) and left (2A-D) eye show appearance of GA with fundus photos (A), fundus autofluorescence (B), near-infrared *en face* imag (C) and optical coherence tomography (D).

Potential safety concerns

The overall safety profiles of intravitreal C3 and C5 complement inhibition has shown additional risks compared to other intravitreal medications. Three safety concerns have been identified in particular:

- ***nAMD.*** For pegcetacoplan, the rate of nAMD at 24

Bios

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Dr. Kuppermann disclosed financial relationships with Allergan/AbbVie, Apellis Pharmaceuticals, Genentech/Roche, Ionis, Iveric Bio, Novartis, Regeneron Pharmaceuticals, RegenXBio, Allegro Ophthalmics, Amgen, Aviceda Therapeutics, Clearside Biosciences, Coherus, EyeBio, Eyedaptic, EyePoint Pharmaceuticals, InflammX Therapeutics, jCyte, Mobius, Molecular Partners, Ocular Therapeutix, Priviterra, ReVana Therapeutics, Ripple Therapeutics, Santen, Stealth Therapeutics, Theravance Biopharma and Visgenix.

Dr. Mishra is a consultant for Bausch + Lomb and RegenxBio.

months in the OAKS and DERBY trials was 11.9 percent for monthly, 6.7 percent for EOM and 3.1 percent for sham. For ACP, the respective nAMD rates at 24 months in GATHER2 were 7.4, 5 and 5 percent.

- ***Ischemic optic neuropathy.*** ION was seen with pegcetacoplan at rates of 1.7, 0.2 and 0 percent for the respective arms at two years, and one case reported for ACP, which exited the study.
- ***Intraocular inflammation***. IOI rates were 4, 2 and <1 percent, respectively, for pegcetacoplan, and one case reported for ACP at two years. The clinical trials for both agents had no reports of retinal vasculitis or vascular occlusive events.[1-3] Real-world cases of retinal vasculitis and intraocular inflammation have been reported at higher rates and severities than in the clinical trials. Of the 14 eyes of 13 patient cases in the postmarketing reports of retinal vasculitis after intravitreal pegcetacoplan, 57 percent of eyes had a 3-line decrease and 43 percent had a 6-line decrease in vision from baseline to final follow up. Two eyes were enucleated.

Interestingly, all cases of retinal vasculitisand intraocular inflammation with pegcetacoplan occurred after the first injection in the first eye in both the trials and in real-world reports.

Interestingly, in the trials and in real-world reports, all cases of retinal vasculitis and IOI occurred after the first injection in the first eye. These events haven't been reported with ACP to date, with the exception of one unusual case of a patient with Stargardt disease who was injected initially with pegcetacoplan in one eye followed four days later by ACP in the fellow eye, with vasculitis occurring subsequently in both eyes.[5]

In light of these findings, the retina community has expressed varying degrees of enthusiasm for complement inhibition therapy, which has influenced management strategies for using these agents.

Patient selection

Treatment scenarios we may need to consider for GA patients who may qualify for the new complement inhibitors include bilateral GA with preserved vision, presence of concomitant nAMD in one or both eyes, and the monocular patient who has already lost central vision in one eye from GA or advanced nAMD. We must also consider symptoms, visual acuity, age, fellow-eye status, ocular comorbidities and the risk-benefit profile. Patients at the highest risk for progression are ideal candidates for therapy.

Optical coherence tomography biomarkers, such as hyperreflective foci and drusen volume, have been established as strong predictors of GA development.[6] The appearance of incomplete retinal pigment epithelium and outer retinal atrophy (iRORA) is a precursor lesion and portends a high risk of developing GA.[7] The near-infrared *en face* imaging can provide information regarding total area of GA lesion, unifocal or multifocal lesions, and their proximity to the fovea.

Fundus autofluorescence can provide similar information and can help identify specific lesion characteristics through distinct patterns of hyperautofluorescence along lesion borders. Multifocal lesions tend to progress more rapidly, and extrafoveal lesions have been shown to progress more rapidly than foveal lesions.[8]

After GA is identified and diagnosed, central visual function can begin to decline within 2.5 years, with GA developing bilaterally in 65 percent of cases.[9–11] Knowing this can help us to identify the patients who may benefit most from treatment.

Counseling patients

Given that these agents didn't demonstrate a VA benefit in the overall pivotal trial populations, counseling patients before initiating treatment is of utmost importance. Patients who have lost vision in one eye from GA may be more motivated to raise the topic of complement inhibition.

Those with early GA and good vision or a newer diagnosis may need more education to truly understand the commitment to treatment they will be undertaking. Because initiating treatment frequently isn't urgent, some patients may benefit from photographs taken during serial visits demonstrating GA

progression before they start treatment.

Furthermore, no evidence exists of the implications of discontinuing treatment or having intermittent dosing. Before a patient starts treatment, consider the rate of lesion progression, size, whether it's unifocal or multifocal, and location in relation to the fovea. Follow-up can be shortened to assess more closely the rate of lesion change before deciding on treatment.

The monocular patient who has lost central vision in one eye to either nAMD or GA and is looking to preserve vision in their better eye may be motivated to seek treatment. Given that the inflammatory events occurred with the first injection in all reported cases thus far, one strategy might be to consider treating the worse-seeing eye first.

If no signs of inflammation emerge, treatment might be considered in the better-seeing eye. However, no formal recommendations have been made on how to initiate treatment. Rather, it may be case-specific depending on the patient's informed decision-making.

Selecting an agent

Factors most likely to drive agent selection are the treatment interval, available agents, and the discussion between physician and patient. Regarding dosing, the label for pegcetacoplan allows for every 25 to 60 days, whereas ACP's label states every 28 days +/- seven days. Less frequent dosing brings a decreased incidence of IOI and nAMD, but that may come at the cost of possibly less favorable reduction in GA lesion growth. Monthly treatment is typically considered in patients at higher risk for vision loss from more rapid GA progression or patients who elect for monthly dosing over EOM.

In the face of concurrent nAMD changes, the provider's discretion, as well as healthcare system requirements and the patient's treatment burden, will likely determine treatment with anti-VEGF agents, either during the same-day visit or at another visit.

In the trials, anti-VEGF injection was administered 30 minutes before complement inhibition injection, and only when intraocular pressure was <21 mmHg.[12] We've found that many clinicians elect to treat with anti-VEGF and complement inhibition at separate visits. Some manage IOP elevations with topical glaucoma medications or anterior chamber paracentesis.

Bottom line

Factors that guide starting treatment with complement inhibitors for GA include the location, extent and rate of progression of GA lesions, as well as patient age, treatment burden and fellow eye status. The risk-benefit profile of reducing the GA lesion growth rate, nAMD incidence and shared decision-making will inform agent selection and dosing frequency. A trial in the worst eye first may minimize the risk of IOI and vasculitis in the better seeing eye. RS

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The monocular patient who has lost central vision in one eye to either nAMD or GA and is looking to preserve vision in their better eye may be motivated to seek treatment.

Highlights of ARVO 2024

A look at the interesting presentations on the latest retina research from this year's meeting.


Bita Momenaei, MD


Jason Hsu, MD

By Bita Momenaei, MD, and Jason Hsu, MD

Take-home points

- Vitrectomy for post-injection endophthalmitis may be unnecessary.
- Mediterranean diet has no effect on GA progression.
- Topical aflibercept shows penetration in mouse eyes.
- Laser treatment for wet AMD demonstrates potential.
- Optogenetic therapy for RD shows visual acuity benefit at a year follow-up.
- New AREDS scale for late AMD includes noncentral GA and incorporates reticular pseudodrusen.
- Suprachoroidal delivery of an AAV vector encoding a complement protein shows potential as a treatment.

In the spring, just over 11,600 physicians, scientists and members of industry descended on the Emerald City of Seattle to discuss the latest findings in all facets of ophthalmology at the annual meeting of the Association for Research in Vision and Ophthalmology. A good bit of this research was centered on the retina and vitreous.

Here, we'll take a look at interesting research that ranges from management of post-injection endophthalmitis to novel insights on age-related macular degeneration and geographic atrophy. To catch up on the latest data, read on.

Vitrectomy for post-injection endophthalmitis shows no benefit vs. antibiotics alone

Endophthalmitis has been well-documented as a rare but potentially vision-threatening complication of anti-VEGF injections. Evidence on the best treatment for post-injection endophthalmitis—whether intravitreal antibiotics alone or intravitreal antibiotics along with pars plana vitrectomy—is limited.

A multi-institutional group of investigators in New England performed a retrospective cohort analysis of 1,044 postinjection endophthalmitis patients from 2016 to 2020 entered into the American Academy of Ophthalmology's IRIS (Intelligent Research in Sight) Registry, with 935 patients in the injection-only group and 109 who had PPV plus antibiotic injections within two days of diagnosis. The study excluded patients who had cataract surgery during the study period, received intravitreal steroids within 30 days of their endophthalmitis diagnosis, or had intermediate/posterior uveitis or cystoid macular edema.

The researchers matched 218 patients—109 from each group—with similar visual acuity at baseline and at the time of endophthalmitis diagnosis. The median logMAR VAs among all matched patients were 0.32 at baseline, 0.88 at diagnosis, and 0.57 post-treatment, Sophia Ghauri, a postgraduate researcher in the lab of Magdalena Krzystolik, MD, at Massachusetts

Bios

Dr. Momenaei is a research fellow at the retina service at Wills Eye Hospital in Philadelphia.

Dr. Hsu is *Retina Specialist*'s chief medical editor and an associate professor at the Sidney Kimmel Medical College at Thomas Jefferson University. He is an attending surgeon on the retina service at Wills Eye.

Disclosures:
Dr. Momenaei has no pertinent financial interests.
Dr. Hsu is a consultant to Astellas/Iveric Bio, Gyroscope Therapeutics and receives grant support from Genentech/Roche, Astellas/Iveric Bio, Stealth Biotherapeutics and Regeneron.

Eye and Ear Infirmary in Boston, reported. Dr. Krzystolik is senior study author.

Post-treatment VA was significantly associated with VA before endophthalmitis (p<0.001) and VA at the time of endophthalmitis diagnosis (p<0.001). No statistically significant differences in the visual outcomes were found between the two matched treatment groups.

Ms. Ghauri is an owner of Codified Health. Dr. Krzystolik has no relevant disclosures.

Ghauri S, Ross C, Ullanat V, et al. ARVO Abstract No. 3826. Early vitrectomy for postinjection endophthalmitis: An IRIS Registry analysis. Invest Ophthalmol Vis Sci. 2024;65:3826.

Mediterranean diet seems to have no impact on GA progression

Researchers at the National Eye Institute analyzed color fundus photographs from annual study visits of participants with noncentral GA in the Age-Related Eye Disease Study to see if dietary intake had any influence on GA progression toward the central fovea. They detected a signal that intake of a number of nutrients, including lutein/zeaxanthin, seems to slow GA progression toward the central macula, but the Mediterranean diet not so much.

The study population consisted of 413 eyes of 347 patients with noncentral GA (88 prevalent, 325 incidental). They analyzed intake of nine different nutrients along with Mediterranean diet index (aMedi), using food frequency questionnaires. Elvira Agron, MS, a statistician at NEI, reported that the following nutrients were associated with slower GA progression toward the foveal center, based on eyes of participants with the highest intake compared to those with the lowest intake:

- Zinc, 34.8 (95% CI 29.6,40.1) vs. 45.5 (95% CI 39.9,51.1, p=0.006).
- β-carotene, 29.8 (95% CI 24.2,35.3) vs. 46.6 (95% CI 41.3,51.9, p<0.0001).
- Lutein/zeaxanthin, 32.9 (95% CI 26.2,39.6) vs. 47.5 (95% CI 42.4,52.7, p=0.001).
- Eicosapentaenoic acid (EPA), 35.5 (95% CI 29.2,41.8) vs. 43.7 (95% CI 38.8, 48.6, p=0.05).

The results suggest these nutrients may contribute to the natural phenomenon of relative foveal sparing in GA, which higher dietary intake may augment. Patients with noncentral GA may benefit from dietary advice that targets these specific nutrients, above and beyond general advice on the adoption of a healthy diet, Ms. Agron stated.

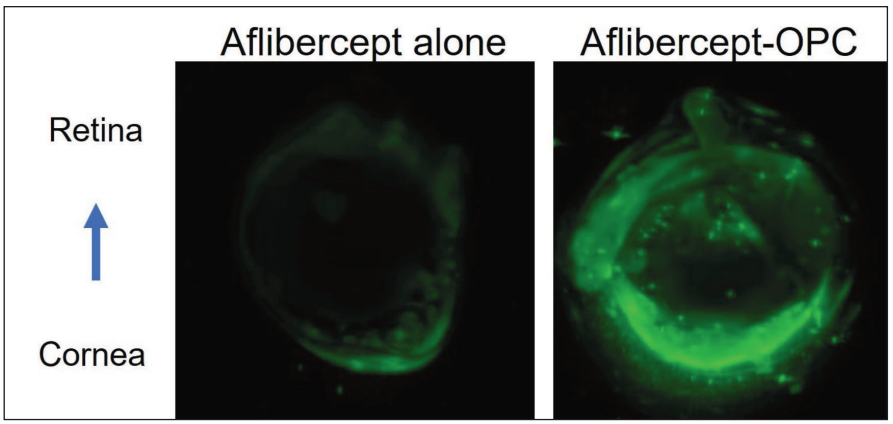
Ms. Agron and co-authors have no relevant disclosures.

Agron E, Keenan TDL, Vitale S, Chew EY. ARVO abstract No. 4363. Associations between dietary nutrient intake and geographic atrophy progression towards the central macula. Invest Ophthalmol Vis Sci. 2024;65:4363.

Aflibercept in a drop shows signal in mouse eyes

In preclinical studies, an eye drop has been shown to deliver potentially therapeutic levels of aflibercept in mouse eyes with laser-induced choroidal neovascularization. Venice Chiueh, PhD, director of research development at Wincal Biopharm, the San Francisco-based company investigating the drug-delivery platform, reported on ocular penetrating carrier (OPC) eye drops.

Mice received eye drops for seven days



Researchers instilled an experimental aflibercept drop in mouse eyes to analyze the drug uptake. Shown here is a mouse eye section after aflibercept alone or aflibercept-OPC eyedrop. IR800-aflibercept in green. ***(Chiueh V, Lee L, Tau S, et al. ARVO 2024. Abstract No. 2159.)***

immediately after CNV was induced, or five to seven days post-laser when lesions were analyzed point-to-point over time. The investigators used fundus fluorescein angiography to measure vascular leakage, optical coherence tomography to evaluate lesion volume, and isolectin-B4 staining and imaging to evaluate CNV area. They compared the change in CNV leakage, volume and area of aflibercept-OPC treatment to buffer control, and also compared efficacy of the eye drop to intravitreal injection of aflibercept.

Several OPCs demonstrated what the investigators described as relatively high intraocular penetration of aflibercept in mouse and pig eyes. In mice with laser-induced CNV, the aflibercept drop showed a decrease in leakage, lesion volume and area with efficacy similar to intravitreal injection: a 24.9-percent reduction of leakiness with intravitreal injection and 20.1-percent reduction with OPC compared to control. The company is also investigating topical formulations of brolucizumab, ranibizumab, bevacizumab and faricimab.

Dr. Chiueh and co-authors are employees of Wincal Biopharm.

Chiueh V, Lee L, Tau S, Luu M, Yoo J-S, Lee TW. ARVO Abstract No. 2159. Development of eyedrops for anti-VEGF therapeutic antibodies as a substitute for IVT injection for posterior ocular disease indications. Invest Ophthalmol Vis Sci. 2024;65:2159.

For endophthalmitis following an anti-VEGF injection, researchers have found that antibiotics alone are probably the most useful vs. adding an adjunct vitrectomy.

A potential new laser treatment for neovascular age-related macular degeneration

Investigators in Japan reported on their experience using a common cancer treatment, photoimmunotherapy (PIT), to treat age-related macular degeneration. PIT attaches photosensitive antibodies to cells that express specific antigens. Exposure to near-infrared (NIR) light activates the antibodies, inducing targeted cell death while preserving healthy tissue.

The study involved mice with laser-induced CNV. Six days following laser irradiation, they were given Alexa 488-conjugated anti-VEGFR2 antibody systemically, with localization of the antibody confirmed 24 hours after administration.

The next step occurred six days after CNV induction, the antibody-IR700 complex, in which the anti-VEGFR2 antibody was conjugated to the photosensitive IR700 substance, was administered systemically. NIR-PIT was performed by irradiating the retina with NIR light 24 hours after the antibody was administered. Three days after the NIR-PIT, isolectin IB4 staining on the retinal front was done to measure CNV volume.

After 24 hours following administration, the researchers confirmed the presence of the antibody-Alexa 488 complex within the area of CNV. The finding suggests the antibody-photosensitizer complex was localized at the core of the CNV, Hideto Osada, MD, of Keio University in Tokyo, reported at ARVO.

Dr. Osada disclosed a financial relationship with Tsubota Laboratory, as did co-authors.

Osada H, Chen SSW, Guzman N, et al. ARVO abstract 2160. New laser treatment for neovascular AMD targeting VEGFR2 with near-infrared photoimmunotherapy. Invest Ophthalmol Vis Sci. 2024;65:2160.

Optogenetic therapy for retinitis pigmentosa yields BCVA improvement at one year

The Phase IIb/III RESTORE trial is evaluating MCO-010 (sonpiretigene isteparvovec, Nanoscope Therapeutics) gene therapy in patients with advanced retinitis pigmentosa. Allen Ho, MD, director of retina research at Wills Eye Hospital in Philadelphia, reported on 52-week longitudinal data that showed that patients treated with MCO-010 demonstrated improvement in BCVA compared to patients in the sham group.

MCO-010 is a gene mutation-agnostic optogenetic therapy, a multi-characteristic opsin transgene delivered by adeno-associated virus (AAV) 2 through an intravitreal injection. It transduces bipolar cells to express a photosensitive opsin protein that's designed to restore photosensitivity in people with permanent photoreceptor loss.

Study participants had advanced RP with baseline VA <1.9 logMAR (Snellen equivalent: 20/2000) in the study eye and ≤1.6 logMAR (Snellen equivalent: 20/800) in the fellow eye. Participants were grouped into three treatment arms: a low-dose arm that received a single dose of 0.911 gc/eye (n=9); a high-dose arm that received a single dose of 1.211 gc/eye (n=9); or sham (n=9). VA was evaluated systematically until week 52 using Freiburg VA.

Both treatment arms demonstrated greater improvement compared to sham in BCVA at weeks 16, 24, 36 and 52. In the low-dose arms, mean improvement of BCVA at the respective intervals were 0.171, 0.207, 0.438 and 0.337 logMAR (p=0.2242, 0.1424, 0.0021 and 0.0164) compared to sham. In the high-dose arm, mean improvement of BCVA was 0.077, 0.220, 0.228 and 0.301 logMAR (p=0.6016, 0.1277, 0.1091 and 0.0355) compared to sham.

Dr. Ho also reported that MCO-010 was also well-tolerated with no serious adverse events observed through week 52.

Dr. Ho disclosed he is a consultant and contractor for Nanoscope Therapeutics.

Ho A. Longitudinal BCVA analysis of low- or high-dose MCO-010 mutation agnostic optogenetic therapy for retinitis pigmentosa: 12-month results from a Phase 2b/3 randomized, sham-controlled, patient- and assessor-masked clinical trial (RESTORE). Invest Ophthalmol Vis Sci. 2024;65:2137.

An updated AREDS scale for late age-related macular degeneration

The AREDS Simplified Severity Scale (SSS) for five-year risk of progression to late AMD has undergone the following three updates, Tiarnan D.L. Keenan, MD, PhD, of the National Eye Institute, reported: the definition of late AMD to include noncentral GA; incorporating reticular pseudodrusen (RPD); and performing an external validation of AREDS2.

The AREDS AMD SSS underwent two significant updates. For individuals without RPD, the new 0–4 scale for five-year progression rates is similar to the original scale: around 0.5, 4, 12, around 25 and 50 percent. For those with RPD, the new scale for five-year progression is approximately double for most level: 3; 8; around 30; around 60 and around 70 percent.

Dr. Keenan reported that the new scale fits modern definitions of late AMD, has increased prognostic accuracy and appears generalizable between study applications, but remains simple enough for broad risk categorization.

The AREDS researchers arrived at the new scale by evaluating five-year progression rates to late AMD among AREDS (n=2,719) and AREDS2 (n=1,658) study participants with no late AMD at baseline. They calculated five-year progression rates to late AMD according to levels 0–4 on the SSS after two

NEI research has found that the Mediterranean diet may not have an effect on the progression of geographic atrophy.

updates: noncentral GA was now considered part of the outcome rather than a risk feature; and the scale was divided by RPD status at baseline.

In AREDS, following the first scale update, the five-year rates of progression to late AMD for levels 0–4, respectively were 0.3, 4.5, 12.9, 32.3 and 55.6 percent. Following both updates, the proportion progressing to late AMD at five years was 8.4 percent without RPD and 40.6 percent with RPD.

As the final SSS, the five-year progression rates for levels 0–4, respectively, were 0.3, 4.3, 11.6, 26.7 and 50 percent without RPD, and 2.8, 8, 29, 58.7 and 72.2 percent with RPD. In external validation on AREDS2, for levels 2–4, the progression rates were similar, at 15.3, 30.4 and 45.7 percent (without RPD) and 27.3, 47.9 and 73 percent (with RPD), respectively

The study authors have no relevant disclosures.

Keenan TDL, Agron E, Domalpally A, Cukras CA, Chew EY. The Updated AREDS simplified severity scale for age-related macular degeneration, incorporating reticular pseudodrusen. Invest Ophthalmol Vis Sci. 2024;65:2790.

Early test of suprachoroidal delivery of an AAV vector to inhibit complement pathway

A number of studies are evaluating the efficacy of a range of ocular drugs administered into the suprachoroidal space, but researchers from RegenXbio have reported on the first experience using the suprachoroidal space to deliver gene therapy.

Brendan Lilley, PhD, principal scientist at RegenXbio, reported that the researchers developed multiple formats of complement C5 inhibitors designed for AAV vectors. They evaluated the binding kinetics, affinity and bioactivity toward C5 from human, cynomolgus macaque nonhuman primate (NHP) and mouse.

The researchers transduced Human iPSC-derived retinal pigment epithelium cells with AAV vectors expressing C5 inhibitors and they measured the inhibition of membrane attack complex (MAC) using immunohistochemistry. They examined expression *in vivo* in mice after subretinal injections.

They also tested a format optimized for ocular biodistribution for expression and tolerability in NHP following with a subretinal injection with a one-month duration or suprachoroidal administration for three months. They used *in vivo* imaging and processed a subset of eyes for histopathology to evaluate tolerability. In subretinally injected eyes, they examined the bioactivity of *in vivo* expressed inhibitor in NHP vitreous humor.

Dr. Lilley reported that C5 inhibitors showed a high affinity for human and NHP ligands, and potentially suppressed complement activation. Transduction of human induced pluripotent stem cell-derived RPE cells with vectorized C5 inhibitors reduced MAC formation on the cell surface.

The lead C5 inhibitor demonstrated improved expression and distribution to outer ocular layers following subretinal delivery in mice. In NHPs, the one-month study following subretinal delivery and the three-month study of suprachoroidal delivery both showed the lead AAV vector was well-tolerated and yielded high expression of bioactive C5 inhibitor in ocular fluids and tissues (including the RPE/choroid) with minimal levels of C5 inhibitor in serum.

The study showed that suprachoroidal delivery of an AAV vector encoding a complement inhibitor optimized for ocular expression resulted in localized and durable expression of bioactive protein, Dr. Lilley stated. This represents a potential minimally invasive approach to treat dry AMD to reduce treatment burden and deliver therapeutic molecules directly to the site of AMD pathogenesis. RS

Dr. Lilley and all co-authors are employees of RegenXbio.

Lilley B, Lee WH, Giles A, et a. Delivery to the suprachoroidal space of an AAV vector encoding a complement pathway inhibitor as a possible treatment for dry age-related macular degeneration. Invest Ophthalmol Vis Sci. 2024;65:1941.

Faricimab: How to navigate real-world challenges

Physicians must adopt a flexible and patient-centered approach in clinic.

Parnian Arjmand, MD, MSc, FRCSC

Parnian Arjmand, MD, MSc, FRCSC

In the ever-shifting landscape of medical retina, the introduction of faricimab represents a significant stride forward. Approved by the FDA and Health Canada in January and May 2022, respectively, this new therapy has garnered attention due to its longer durability in comparison to its predecessors within the anti-VEGF class, while maintaining a similar safety profile.

As we delve into the initial real-world experiences with faricimab, valuable practical insights and challenges have emerged, shedding light on nuances with its administration in the clinic, as well as the promising potential it holds for patients dealing with diabetic macular edema and neovascular age-related macular degeneration.

Faricimab (6 mg/0.05 mL) (Vabysmo, Genentech/Hoffman La Roche) is a humanized monoclonal antibody with bispecificity to VEGF-A and Ang-2. The VEGF-A pathway inhibition impedes endothelial cell proliferation and neovascularization, while Ang-2 blockade reinforces anti-VEGF signaling cascades and increases vascular stability.[1,2] It's currently approved for treatment of patients with nAMD and DME with the option for treatment from one to four months apart in the first year following an initial once monthly loading dose for four months.

The real world vs. clinical trials

Like prior classes of anti-VEGF drugs, the product monograph instructions for Faricimab may differ from practical considerations outside of clinical trials.

- Although patients can be extended up to 16 weeks between doses, the product monograph instructs visual acuity and anatomic evaluations at weeks "20 and 24 to inform dosing at intervals of eight, 12 or 16 weeks through week 60."[2,3] While these instructions may well apply to treatment-naïve patients, in the real world, many "switch" patients agree to start on faricimab on the premise that they would have fewer visits to the clinic. Acuity and OCT imaging at extra monthly intervals after the loading dose isn't practical in the real world.
- Most early adopters of faricimab may choose to switch two classes of patients who aren't the primary focus of clinical trials. The first group includes patients who need anti-VEGF therapy every four to six weeks. The second group are suboptimal responders with persistent intraretinal or subretinal fluid despite monthly treatments. TENAYA, LUCERNE, YOSEMITE and RHINE all primarily recruited treatment-native patients; however, only 25 percent of those in YOSEMITE and RHINE comprised switch patients.[2,3] As such, loading and dosing data for this class of patients isn't yet well-guided by evidence.
- There are several differences in the administration of the drug in clinical trials versus in the real world. The drug monograph for faricimab indicates that the procedure must be carried out under aseptic conditions with the use of surgical hand disinfection, sterile gloves, drape and a sterile speculum.[1] Meanwhile, the most recent ASRS PAT survey indicates that most specialists in the United States and Canada use a clean but not aseptic technique for intravitreal injections in the clinic. As well, many have moved away from the use of speculums, which may cause additional discomfort, corneal abrasions and sensitivity post-procedure. Most specialists now use cotton-tip applicators or fingers to keep the lid margin away from the injection site.
- While many of our patients in the real world require bilateral, same-day, anti-VEGF treatment, bilateral use hasn't been studied in the trials.

BIOS

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Dr. Mandelcorn is an associate professor of ophthalmology at the University of Toronto.

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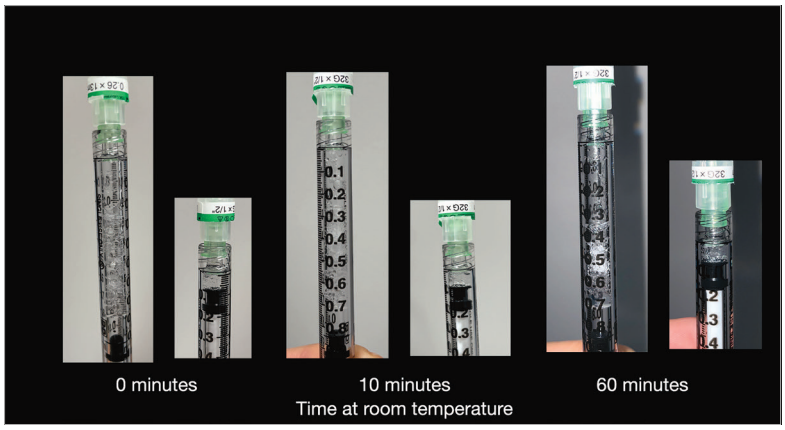

Figure 1. Three vials of faricimab drawn up in a Luer-lock 1 mL syringe before and after priming to 0.05 mL. Faricimab drawn up from the vial taken immediately out of the fridge (left), kept at room temperature for 10 minutes (middle) and 60 minutes (right). No discernable difference was noted in the number of bubbles, the number of times the syringe had to be tapped, ease of priming the syringe or the speed of injection.

Thoughts on drug handling

As busy retina specialists, we may not always have time to carefully examine the product monographs for medications we administer in the clinic. Faricimab shouldn't be injected while it's cold. Instead, it should be warmed to room temperature (~25 degrees C/77 F) and is deemed stable at room temperature for up to 24 hours.[1]

In our practice, anti-VEGF medications (ranibizumab/Aflibercept) are often taken out at the beginning of the day and kept on ice until used. As we currently have fewer patients on routine faricimab injections on any injection day, this drug often gets taken out of the fridge a few minutes before its use. To warm up the drug, one could keep the vial in a scrub/white coat pocket for a few minutes prior to use. However, it should also be kept still on a flat surface prior to drawing up the medication to minimize bubbles.

It's been anecdotally speculated that, at room temperature, the drug will be more easily drawn up with fewer trapped air bubbles. We put this hypothesis to the test, comparing three vials of faricimab. All variables were the same except for the duration of time the drug was left at room temperature. Vial 1 was taken out of the refrigerator and immediately drawn up into a TB syringe. Vial 2 was kept at room temperature for 10 minutes prior to being drawn, and vial 3 was kept at room temperature for an hour prior to being drawn. The same physician performed the procedure all on three vials. There was no visible difference in the volume of trapped air bubbles, the number of times the syringe had to be tapped to let out the trapped air bubbles, ease of priming the syringe or the speed of injection. *(See Figure 1)*

Faricimab's introduction into the treatment arena for DME and nAMD represents a significant advancement and comes with unique challenges in the real-world clinical setting. The application of this therapy may diverge from clinical trial protocols in several key aspects, such as patient selection, dosing intervals and administration techniques. These variations necessitate a flexible and patient-centered approach in clinical practice. Additionally, practical considerations, such as the proper warming and handling of the medication, are crucial for effective administration. Our experience underscores the importance of adapting and refining clinical practice to bridge the gap between the controlled trial setting and the dynamic nature of everyday clinical care.

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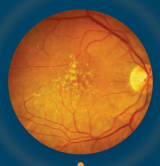

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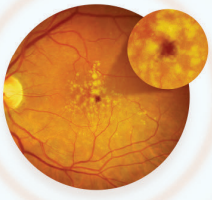

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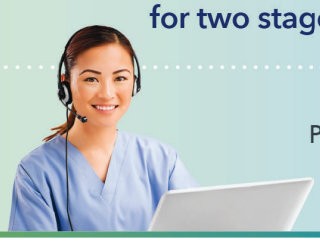

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FDA Indications for Use
ForeseeHome is intended for use in the detection and characterization of central and paracentral metamorphopsia (visual distortion) in patients with AMD.
SCANLY Home OCT is indicated for visualization of intraretinal and subretinal hypo-reflective spaces in a 10 by 10-degrees area centered on the point of fixation of eyes diagnosed with NV-AMD.
Visit the website for complete indications for use and important safety information.

SM-281.1

The need for supplemental ranibizumab in PDS Archway trial patients

Recently, researchers evaluated the safety and efficacy of supplemental ranibizumab injections in eyes with the port delivery system with ranibizumab.

The post hoc analyses of data from the Phase III, randomized, multicenter, open-label active-comparator Archway trial included adults with nAMD diagnosed within nine months of screening previously responsive to anti-VEGF therapy.

A total of 418 patients were randomized to the PDS with ranibizumab 100 mg/mL with fixed refill-exchanges every 24 weeks (Q24W) or monthly intravitreal ranibizumab 0.5 mg for 96 weeks.

Here are some of the findings:

• Of the 246 eyes treated with the PDS Q24W and assessed for supplemental treatment criteria, the vast majority (94.6 to 98.4 percent) didn't receive supplemental treatment during each retreatment interval, with 87.4 percent not receiving supplemental treatment at any point during the trial.

• Of the 31 eyes receiving supplemental treatment, 58.1 percent received one injection and 32.3 percent received two.

• At baseline, eyes receiving supplemental treatment were significantly more likely to have thicker retinas (mean CST 370.5 vs. 304.4 µm; p=0.0001), subretinal fluid (54.8 vs. 21.2 percent; p<0.0001) and larger pigment epithelial detachment height (215.7 vs. 175.9 µm; p=0.003). These features have previously been associated with difficult-to-treat nAMD.

• While BCVA and CST generally remained constant throughout the trial in eyes without supplemental treatment, the small number of eyes receiving supplemental treatment on average lost one line of vision from baseline to week 96, and CST continued to increase over time.

• Absolute BCVA at week 96 was similar to baseline, irrespective of supplemental treatment status (71.1 and 73.7 letters, respectively).

• BCVA and CST generally improved within 28 days of supplemental treatment.

Researchers found that, although the Port Delivery System with ranibizumab every 24 weeks effectively maintained vision and retinal stability in most eyes with neovascular age-related macular degeneration, a small proportion of patients with features of difficult-to-treat neovascular age-related macular degeneration may benefit from supplemental intravitreal anti-vascular endothelial growth factor injections, and initial close monitoring is recommended.

Nielsen JS, Chang A, Holekamp NM, et al. Supplemental intravitreal ranibizumab injections in eyes treated with the PDS with ranibizumab in the Archway trial. Ophthalmol Retina 2024; Jun 22. [Epub ahead of print].

A look at home OCT-guided management of wet AMD

Investigators evaluated the impact of home OCT-guided patient management.

An interventional trial was conducted to compare frequency of treatment and visual acuity for neovascular AMD patients before and during use of home OCT over six months. Patient adherence to regular scanning was measured by the number of scans performed per week. Analysis of fluid recurrence episodes and classification of typical fluid volume trajectories was performed.

Here are some of the findings:

• 27 eyes (21 with nAMD diagnosis and one that converted during the study) of 15 patients were monitored for six months, scanning at 6.2 times/week/eye and yielding 4,435 scans, of which 91.2 percent were eligible for AI-based fluid volume quantification.

• Total number of monitoring weeks prior to the study was 1,555 and during the study was 509.

• The mean number of weeks per injection before OCT management was 8±4.7 and

during OCT management was 15.3 ±8.5 (p=0.004).

• The mean VA change before home OCT-based management was 3.5 ±12 letters, and during home OCT-based management was 0.0 ±9.5 letters (p=0.45), showing no significant impact on VA.

Investigators wrote that remote patient monitoring enabled personalized management of wet AMD and significant reduction in treatment burden.

Holekamp NM, de Beus A, Clark WL, et al. Prospective trial of Home OCT guided management of treatment experienced nAMD patients. Retina 2024 May 22. [Epub ahead of print].

Pegcetacoplan Treatment Studied

Despite its advantages for detailed imaging of geographic atrophy, researchers wrote that spectral-domain optical coherence tomography might benefit from automated quantitative OCT analyses in GA diagnosis, monitoring and reporting of its landmark clinical trials.

They analyzed the association between pegcetacoplan and consensus GA SD-OCT endpoints, as part of a post hoc analysis of 11,614 SD-OCT volumes from 936 of 1,258 participants in two parallel Phase III GA studies: OAKS and DERBY. This analysis was conducted from September to December 2023.

Study participants received pegcetacoplan, 15 mg per 0.1 mL intravitreal injection, monthly or every other month, or sham injection monthly or every other month.

The primary endpoint was the least squares mean change from baseline in area of RPE and outer retinal atrophy in each of the three treatment arms (pegcetacoplan monthly, pegcetacoplan every other month, and pooled sham [sham monthly and sham every other month]) at 24 months.

Among 936 participants, the mean age was 78.5 ±7.22 years; 570 participants (60.9 percent) were female. Here are some of the findings:

• pegcetacoplan monthly: -0.86 mm²; CI, -1.15 to -0.57; p<0.001;

• pegcetacoplan every other month: -0.69 mm²; CI, -0.98 to -0.39; p<0.001).

This association was more pronounced with more frequent dosing (pegcetacoplan monthly vs. every other month at month 24: -0.17 mm²; p=0.17). Stronger associations were observed in the parafoveal and perifoveal regions.

Fu DJ, Bagga P, Naik G, et al. Pegcetacoplan treatment and consensus features of geographic atrophy over 24 months. JAMA Ophthalmol 2024; May 9. [Epub ahead of print].

(Continued from page 20)

patient management. The study underscored the role of AI in forecasting disease trajectory and optimizing follow-up protocols.

Benefits and Challenges

AI-driven DR screening offers numerous benefits, including increased accessibility, especially in underserved areas with limited health-care resources. It provides a cost-effective and scalable solution for regular and widespread screening. Additionally, AI can reduce the burden on health-care professionals by automating routine analysis, allowing them to focus on complex cases.[9]

However, several challenges remain. Ensuring the AI models are trained on diverse datasets is crucial to avoid biases and ensure accuracy across different populations. Regulatory approvals and acceptance from medical professionals are essential for widespread adoption. Privacy and ethical considerations regarding the use of patient data must be addressed. Another crucial step is the head-to-head evaluation and comparison of the various models produced. Given that different models use information from different demographic groups, the performance of these may be affected depending on the given data sets *(Figure 2)*.

In conclusion, these clinical trials and studies illustrate the transformative impact of AI-powered OCT in monitoring diabetic macular edema. AI systems enhance diagnostic accuracy, facilitate early detection, provide predictive insights and improve treatment response evaluation. As a result, they hold significant promise for improving clinical outcomes and patient care in diabetic retinopathy management.

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TikTok on the Clock …

A crash course in becoming a retinal education TikTok star.

By Jayanth Sridhar, MD

"…but the party don't stop." No, TikTok isn't referring to the 2009 pop hit by Ke$ha, but rather to one of the most popular social media platforms in the world. Created by the Chinese company ByteDance, TikTok was released to an international audience in late 2017 and captured the attention of users worldwide for its short-form video format. As of today, there are over one billion users of TikTok monthly worldwide and nearly a quarter of all internet users are using TikTok.

TikTok's impact is so profound that it has spread into ophthalmology. If we dig into the literature, there have been a few ophthalmology studies examining its impact. Tiffany Cheng and her co-workers[1] from the Albert Einstein College of Medicine in New York described 386 oculoplastic-related videos on the platform with over 218 million views. Ironically, they discovered that not only were patients the most likely group to post these videos, but also that oculoplastic surgeon-created videos were the least likely to be shared. As you would expect, physician content was statistically more likely to be understandable.

Quotable

"The conceit of this article is to educate retinal specialists to become TikTok stars that can help us educate our patients and the public in a fun way."

University of Miami research student, Tiffany Eatz, and her team[2] looked at both TikTok and Instagram posts related to strabismus and found that the former were statistically more likely to achieve likes and new followers. They also noted that negative posts regarding the strabismus surgery experience were more likely to be liked than positive posts. Finally, from the Baylor College of Medicine in Houston, Ritu Sampige and her team[3] examined TikTok posts with 37 ophthalmology-related hashtags over about a one-month period. They discovered that the vast majority of posts were created by non-physicians, and these posts were more likely to include misinformation. More alarming, misinformation posts received more likes and shares!

All of this helps us arrive at the conceit of this article: To educate regular retinal specialists to become TikTok stars that can help us educate our patients and the public in a fun way. Compiling tips from TikTok stars and the TikTok developers themselves, here are the top seven tips for creating a viral TikTok video:

1. Use a 9:16 aspect for a full screen experience.
2. Include some combination of voiceover, music and sound effects.
3. The shorter the better; aim for under 30 seconds.
4. Use at least 720p video resolution, but your mobile phone is enough!
5. Make sure your lighting is bright.
6. Use the hashtag "Popular Trends" to see what is getting views on TikTok and try to match.
7. Recruit well-known TikTok creators to collaborate.

What's missing from the list? Content choice! In the end, your choice of content will be less important than how you deliver your message. You could talk about geographic atrophy, intravitreal injections, diabetic retinopathy, retinal detachment surgery…the list goes on and on. So go out there, retinal specialists, and make some videos!

BIO

Dr. Sridhar is an associate professor of clinical ophthalmology at Bascom Palmer Eye Institute, Miami.

DISCLOSURE: Dr. Sridhar is a consultant to Alcon, DORC, Genentech/Roche and Regeneron Pharmaceuticals.

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3. Sampige R, Rodgers EG, Huang A, et al. Education and misinformation: Exploring ophthalmology content on TikTok. Ophthalmology and Therapy. 2024;13:1:97-112.

SYFOVRE® (pegcetacoplan injection), for intravitreal use
BRIEF SUMMARY OF PRESCRIBING INFORMATION
Please see SYFOVRE full Prescribing Information for details.

INDICATIONS AND USAGE

SYFOVRE is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

CONTRAINDICATIONS

Ocular or Periocular Infections

SYFOVRE is contraindicated in patients with ocular or periocular infections.

Active Intraocular Inflammation

SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE in order to minimize the risk of endophthalmitis. 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 SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.

Neovascular AMD

In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

Intraocular Inflammation

In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves patients may resume treatment with SYFOVRE.

Increased Intraocular Pressure

Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

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 practice.

A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.

The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

Table 1: Adverse Reactions in Study Eye Reported in ≥2% of Patients Treated with SYFOVRE Through Month 24 in Studies OAKS and DERBY

Adverse Reactions	PM (N = 419) %	PEOM (N = 420) %	Sham Pooled (N = 417) %
Ocular discomfort*	13	10	11
Neovascular age-related macular degeneration*	12	7	3
Vitreous floaters	10	7	1
Conjunctival hemorrhage	8	8	4
Vitreous detachment	4	6	3
Retinal hemorrhage	4	5	3
Punctate keratitis*	5	3	<1
Posterior capsule opacification	4	4	3
Intraocular inflammation*	4	2	<1
Intraocular pressure increased	2	3	<1

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:

Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye

Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization

Punctate keratitis included: punctate keratitis, keratitis

Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

Endophthalmitis, retinal detachment, hyphema and retinal tears were reported in less than 1% of patients. Optic ischemic neuropathy was reported in 1.7% of patients treated monthly, 0.2% of patients treated every other month and 0.0% of patients assigned to sham. Deaths were reported in 6.7% of patients treated monthly, 3.6% of patients treated every other month and 3.8% of patients assigned to sham. The rates and causes of death were consistent with the elderly study population.

Postmarketing Experience

The following adverse reactions have been identified during postapproval use of SYFOVRE. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure. Eye disorders: retinal vasculitis with or without retinal vascular occlusion.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.

Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.

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.

Lactation

Risk Summary

It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when SYFOVRE is administered to a nursing woman.

Females and Males of Reproductive Potential

Contraception

Females: It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.

Pediatric Use

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

Geriatric Use

In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥ 65 years of age and approximately 72% (607/839) 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 recommended based on age.

PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing endophthalmitis, retinal detachments, retinal vasculitis with or without retinal vascular occlusion and neovascular AMD. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist. Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured for:
Apellis Pharmaceuticals, Inc.
100 Fifth Avenue
Waltham, MA 02451

SYF-PI-30NOV2023-2.0

12/23 US-PEGGA-2200163 v4.0

INDICATION

SYFOVRE® (pegcetacoplan injection) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- SYFOVRE is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation

WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. 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 SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

Save More Retinal Tissue

Slowed GA progression over 2 years with increasing effects over time[3]

More Time Between Treatments

Demonstrated efficacy with as few as 6 doses per year[3]*

After 2 years, SYFOVRE slowed GA progression (mm^2) by 18% (-0.73 difference [-1.14 to -0.31]) to 22% (-0.87 difference [-1.27 to -0.47]) monthly and by 17% (-0.70 difference [-1.11 to -0.28]) to 18% (-0.72 difference [-1.10 to -0.33]) every other month compared to sham pooled. The greatest differences were observed in the last 6 months.[3]

*The recommended dose for SYFOVRE is 15 mg (0.1 mL of 150 mg/mL solution) administered by intravitreal injection to each affected eye once every 25 to 60 days.[3]

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IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- **Intraocular Inflammation**
  - In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves, patients may resume treatment with SYFOVRE.
- **Increased Intraocular Pressure**
  - Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

- Most common adverse reactions (incidence ≥5%) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, conjunctival hemorrhage.

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 2-year, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration) with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE every other month, sham monthly, or sham every other month, for 2 years. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[3,4]

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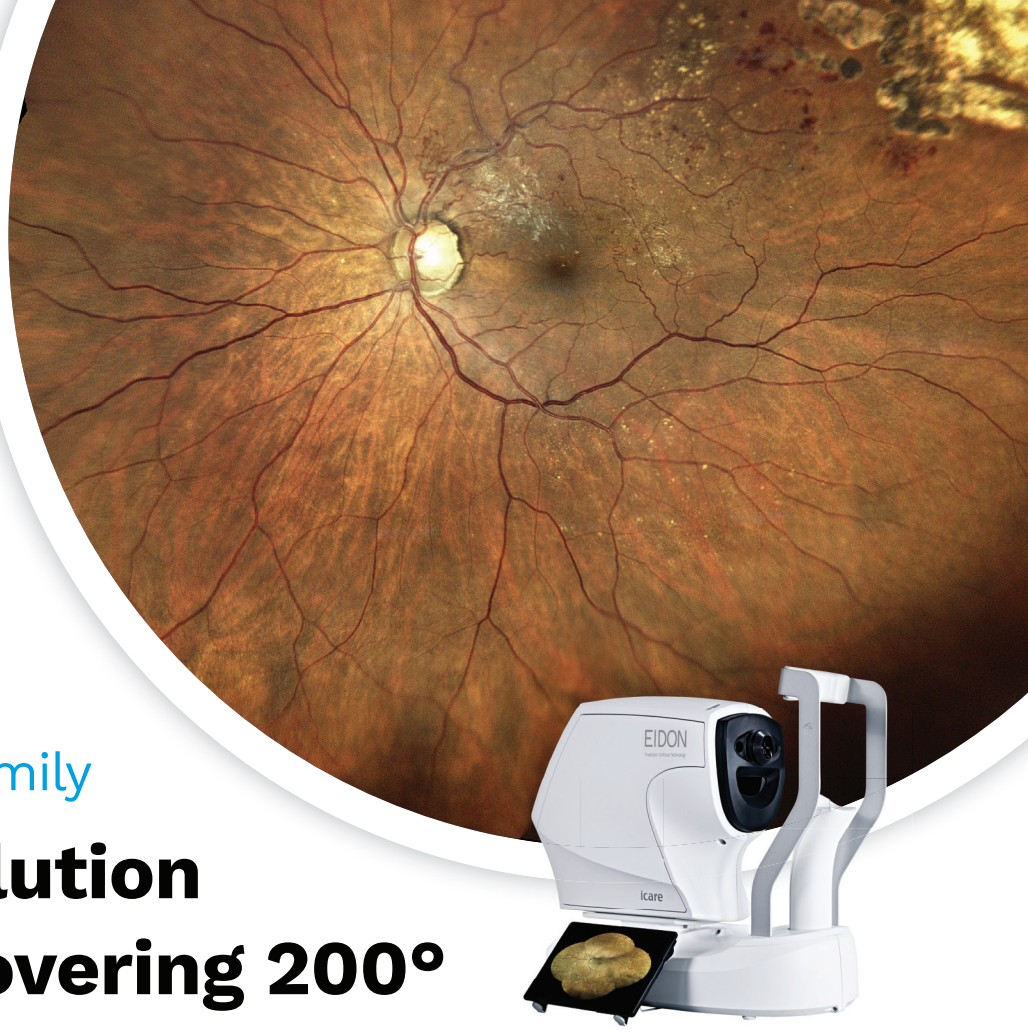
Please see Brief Summary of Prescribing Information for SYFOVRE on the adjacent page.

EOM=every other month; GA=geographic atrophy.

Apellis

20+ YEARS OF INNOVATION



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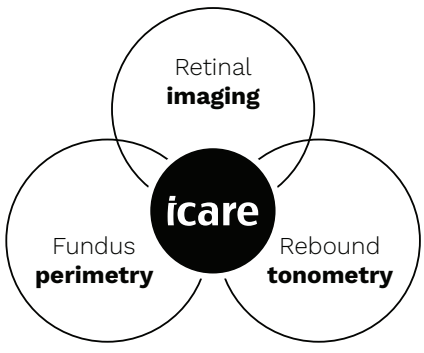
High-resolution imaging covering 200°

- Using white LED light provides TrueColor detail rich retinal images from the macula to the periphery
- Confocal Technology allows scanning through media opacities and pupils as small as 2.5 mm resulting in high resolution images
- Fully automated easy-to-use family of products with advanced features and multiple imaging modalities



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