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GENE THERAPY FOR WET AMD

What you need to know about the current agents in clinical trials. **P. 22**

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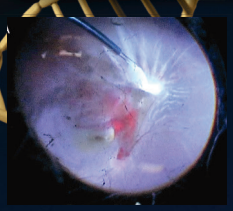
Online Video



- *Surgical Pearl Video: Repairing TRD in Eales' disease* – **Page 6**

INDICATION

IZERVAY™ (avacincaptad pegol intravitreal solution) is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD)

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

IZERVAY 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 IZERVAY, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering IZERVAY 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.

Neovascular AMD

- In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

Increase in Intraocular Pressure

- Transient increases in intraocular pressure (IOP) may occur after any intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed appropriately.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5%) reported in patients receiving IZERVAY were conjunctival hemorrhage, increased IOP, blurred vision, and neovascular age-related macular degeneration.

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

astellas

IZERVAY™ (avacincaptad pegol intravitreal solution)
Rx only

Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 609-474-6755.

1 INDICATIONS AND USAGE
IZERVAY is indicated for the treatment of geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
IZERVAY must be administered by a qualified physician.

2.2 Recommended Dosage
The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days) for up to 12 months.

2.4 Injection Procedure
Only 0.1 mL (2 mg) should be administered to deliver a single dose. Any excess volume should be disposed.

Prior to the intravitreal injection, patients should be monitored for elevated intraocular pressure (IOP) using tonometry. If necessary, ocular hypotensive medication can be given to lower the IOP.

The intravitreal injection procedure must be carried out under controlled aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum topical microbicide should be given prior to the injection.

Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.1 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each vial and syringe should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial and syringe should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle, and injection needle should be changed before IZERVAY is administered to the other eye. Repeat the same procedure steps as above.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

3 DOSAGE FORMS AND STRENGTHS
Intravitreal solution: 20 mg/mL clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
IZERVAY is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
IZERVAY is contraindicated in patients with active intraocular inflammation.

5 WARNINGS AND PRECAUTIONS
5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

5.2 Neovascular AMD
In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

5.3 Increase in Intraocular Pressure
Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

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

- Ocular and periocular infections
- Active intraocular inflammation
- Endophthalmitis and retinal detachments
- Neovascular AMD
- Increase in intraocular pressure

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 safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham.

Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY pooled across GATHER1 and GATHER2, are listed below in Table 1.

Table 1: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye

Adverse Drug Reactions	IZERVAY N=292	Sham N=332
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Choroidal neovascularization	7%	4%
Blurred Vision*	8%	5%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

* Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently.

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits.

Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.1 times and 3.2 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 2 mg once monthly, respectively.

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

Animal Data
An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rats received daily intravenous (IV) injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.1 times the MRHD, based on Area Under the Curve (AUC).

An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.2 times the human exposure at the MRHD, based on AUC.

8.2 Lactation
There is no information regarding the presence of avacincaptad pegol in human milk, the effects of the drug on the breastfed infant or on milk production.

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

8.4 Pediatric Use
Safety and effectiveness of IZERVAY in pediatric patients have not been established.

8.5 Geriatric Use
Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

17 PATIENT COUNSELING INFORMATION
Advise patients that following IZERVAY administration, patients are at risk of developing neovascular AMD, endophthalmitis, elevated intraocular pressure and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops a change in vision, instruct the patient to seek immediate care from an ophthalmologist.

Patients may experience temporary visual disturbances and blurring after an intravitreal injection with IZERVAY and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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Study Analyzes Spending on Anti-VEGF Injections

The factors influencing differences in adoption of anti-VEGF injections are still poorly characterized, and trends in national anti-VEGF use and associated costs have only been documented until 2015 in the population insured by Medicare.

A recent study characterized trends in use of and expenditure for the intravitreal injection of anti-VEGF agents aflibercept, ranibizumab and bevacizumab among the population enrolled from 2014 to 2019.[1] In this period, 17,588,995 intravitreal injection claims were filed by 4,218 U.S. ophthalmologists. Medicare costs for anti-VEGF injections increased from $2.51 billion in 2014 to $4.02 billion in 2019.

Increased state-level ophthalmologist availability and incremental increases in average reimbursement amounts were found to be significantly associated with a 6.8-fold variation in 2019 overall anti-VEGF injection rates across states. The researchers found a 7.3-fold difference in aflibercept use, a 231.9-fold difference in ranibizumab injection rate and a 37.9-fold difference in bevacizumab injection rates across all 50 United States and the District of Columbia.

"While the determinants of regional variation are multifactorial, we found access to injecting ophthalmologists to be one factor significantly associated with this variation," the authors wrote in their paper. "States with a higher density of injecting physicians were associated with a higher anti-VEGF injection rate, as well as higher aflibercept and bevacizumab agent-specific injection rates."

Study co-author Sarishka Desai, a medical student at the University of Connecticut, also comments on an interesting interaction between reimbursement and injection rate.

"In our study, increased reimbursement was also found to be minimally associated with overall anti-VEGF injection rate; a $1 increase in reimbursement rate was associated with 3.3 additional injections per 100,000 beneficiaries," she says.

She notes that this effect was inconsistent across individual anti-VEGF agents. "We found a $1 increase in reimbursement rate to be negatively associated with bevacizumab injection rate," she says. "We believe this may be due to increased use of aflibercept and/or ranibizumab–it's important to remember the market for anti-VEGF injections is a zero-sum game. We hypothesize practitioners in states with higher reimbursements have higher practice expenses and patients with greater access to care, which may increase aflibercept injection rates and decrease bevacizumab injection rates as a result. However, in our study we cannot draw any causal associations, and further research is needed."

Population-adjusted aflibercept injection rate increased 138 percent from 2014 to 2019, while ranibizumab injection rate marginally increased and bevacizumab injection rate slightly decreased. "Though aflibercept was initially approved for wet AMD, expanding indications (e.g., proliferative diabetic retinopathy, diabetic macular edema) in the management of ophthalmic disease may partially explain the nationwide increase in injection rate," the authors noted.

"Additionally," they say, "the ability to extend patients for a longer period between injections may also explain an increase in aflibercept injection rates."

"Future studies are warranted to better elucidate whether the observed gaps in state-level injection rates result from physician-specific characteristics, regional characteristics or payments provided by the pharmaceutical industry (e.g., consultation, education, travel, food and beverage)," they added. "This will help reveal the most appropriate policies which may help decrease observed disparities in injection rates unaccounted for by the distribution of eye disease burden."

1. Desai S, Sekimetsu S, Rossin EJ, Zebardast N. Trends in anti-vascular endothelial growth factor original Medicare part B claims in the United States, 2014-2019. Ophthalmic Epidemiol. February 5, 2024. [Epub ahead of print].

Pachydrusen in AMD Eyes Raises Risk of MNV

A new study explored associations between the risk of progression to advanced AMD and the type of drusen present, if any. Of particular interest was a recently identified type called pachydrusen, which have well-defined margins with an irregular outer contour and which occur in isolation or in groups of a few at the posterior pole, the researchers explained in their paper for *Scientific Reports*.[1]

Many aspects of pachydrusen, including the long-term prognosis and risk factors for progression to advanced AMD remain unclear,

(Continued on page 10)

How to repair Eales' disease TRD

Tips for surgical repair of a tractional retinal detachment with full-thickness macular hole secondary to a rare form of retinal vasculitis.

By Mark D. Bamberger, MD, and Kenneth T. Eng, MD

Mark D. Bamberger, MD

Kenneth T. Eng, MD

Eales' disease is a rare idiopathic retinal vasculitis that's characterized by a peripheral retinal periphlebitis leading to capillary nonperfusion, retinal vein occlusions and ischemia predisposing the patient to neovascular complications such as vitreous hemorrhage.[1,2]

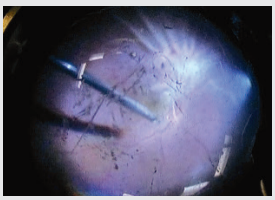
Eales' disease is suspected in the appropriate demographic group with an otherwise negative review of systems and work-up for other conditions that include:

- syphilis;
- active tuberculosis;
- sarcoidosis;
- systemic lupus erythematosus;
- anti-phospholipid antibody syndrome;
- antineutrophil cytoplasmic antibody-related diseases; and
- rheumatic diseases.

A possible association with latent TB has been described.[3]

View the Video

Dr. Bamberger and Dr. Eng surgically repair a tractional retinal detachment with a full thickness macular hole in a patient with Eales' disease. Scan the QR code or go to https://bit.ly/VideoPearl-39.



Treatment for Eales' disease is based on managing the complications and reducing the risk of disease progression. In cases of nonclearing vitreous hemorrhage (41 percent), retinal detachment (11 percent) or macular hole (<1 percent), pars plana vitrectomy may be required.[4] If the ocular media are sufficiently clear, ablation of ischemic retina with panretinal laser

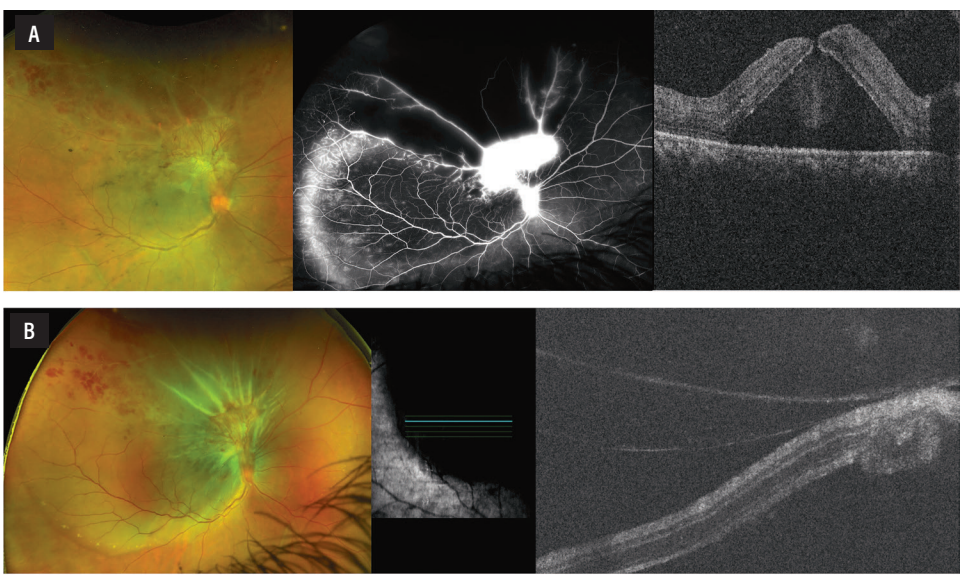


Figure 1. A) Color widefield fundus and optical coherence tomography images of the right eye document the tractional retinal detachment, vasculitis and peripheral nonperfusion and full-thickness macular hole with subretinal fluid due to foveal traction on presentation and visual acuity of 20/200. B) At one month following presentation, color widefield fundus images and OCT images of the right eye demonstrated rapidly worsening TRD with a decline in visual acuity to count fingers.

BIOS

Dr. Bamberger is a retina specialist in Toronto.

Dr. Eng is a vitreoretinal surgeon and chief of ophthalmology at Sunnybrook Health Sciences Centre, University of Toronto.

Dr. Felfeli is an ophthalmology resident at the University of Toronto.

DISCLOSURES: The authors and Dr. Felfeli have no relevant relationships to disclose.

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photocoagulation can be considered, as long as the vasculitis has been sufficiently controlled with immunosuppressive therapy. Although controversial, the use of intravitreal anti-VEGF therapy may lead to a higher risk of retinal detachment.[4]

Our case

A 40-year-old phakic male originally from India presented with a subacute decrease in Snellen visual acuity in his right eye to 20/200. His ocular history included a retinal detachment repair in the fellow eye with vitrectomy, laser panretinal photocoagulation and scleral buckling 15 years earlier in India. He had no history of diabetes or sickle cell disease, and the review of systems was negative.

On examination, the patient's right eye had a shallow tractional retinal detachment involving the macula and extending to the near periphery with phlebitis and a large plaque of neovascularization along the proximal superior arcade emanating from the disc. Macular optical coherence tomography showed a small full-thickness macular hole and fluorescein angiography revealed peripheral vascular sheathing and non-perfusion superiorly (*Figure 1A, page 6*).

The patient underwent screening for tuberculosis using a TB QuantiFERON Gold assay and tested positive. All other investigations from the extensive uveitis work-up, including screening laboratory and imaging investigations for syphilis and sarcoidosis, were negative.

He was immediately referred to the infectious disease service and an anti-latent TB therapeutic regimen was initiated. With the presumed diagnosis of Eales' disease, the patient was started on 80 mg daily of oral prednisone followed by a six-month taper and appropriate oral calcium and vitamin D supplementation (*Table)*.[1] Within one month, the retinal detachment progressed significantly with a corresponding decline in visual acuity to counting fingers, and the patient decided to proceed with pars plana vitrectomy *(Figure 1B, page 6)*.

Our surgical approach

In our surgical video, after a limited core vitrectomy, we gently elevated the posterior hyaloid from the optic disc using 23G internal limiting membrane forceps to create a plane of dissection. We avoided excessive traction while moving from posterior to anterior to mitigate the risk of iatrogenic break formation. Once lifted, we divided the hyaloid along the 3-to-9-o'clock meridian to isolate the superior and inferior hemispheres. We then evaluated the neovascular plaque superiorly with the forceps and lifted the remaining hyaloid gently with the cutter using aspiration (*Figure 2*).

We then turned our attention to the macular hole and applied a flat contact lens. In this case, given the ILM had to be peeled

After a limited core vitrectomy, we gently elevated the posterior hyaloid from the optic disc using 23G internal limiting membrane forceps to create a plane of dissection.

Table. Oral prednisone dose and duration for the patient.

Dose	Taper (decrease in daily dose / week)	Duration
80 mg	10 mg / week	4 weeks
40 mg	5 mg / week	4 weeks
20 mg	2.5 mg / week	4 weeks
10 mg	1 mg / 2 weeks	10 weeks
5 mg	1 mg / week (if quiescent)	5 weeks

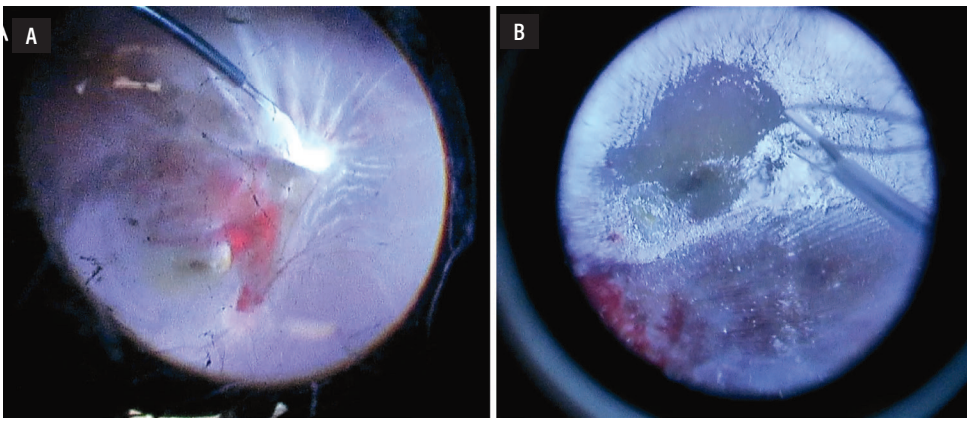

Figure 2. Intraoperative images depicting the key surgical steps. A) After a limited core vitrectomy, the posterior hyaloid was elevated using internal limiting membrane forceps to create a plane of dissection, and the hyaloid was divided along the 3-to-9-o'clock meridian. B) The ILM peeling was done under a flat contact lens from nasal to temporal to initiate the flap.

over the detached retina, we elected to avoid the use of dyes such as indocyanine green, which can migrate into the subretinal space and potentially increase the risk of toxicity.

Using a 1:1 dilution of triamcinolone, we obtained a light dusting of the ILM by aspirating with low vacuum to leave only a fine layer of white crystals. We could then visualize the ILM adequately without obscuring the deeper layers.

We initiated the flap from the nasal to the temporal, taking advantage of the countertraction the optic disc provided. Our priority was to completely remove the ILM around the macular hole, followed by enlarging the ILM rhexis as much as safely possible.

The final steps included a peripheral scleral depressed examination, fluid-air exchange with careful drainage from the macular hole, sectoral retinal photocoagulation and C_3F_8 gas fill. Postoperatively, the patient was asked to position face-down

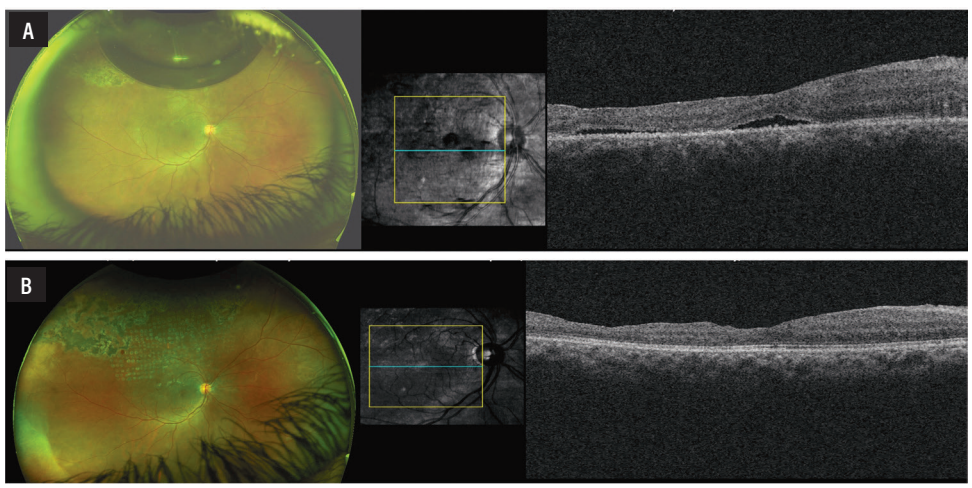

Figure 3. Postoperative color widefield fundus images and optical coherence tomography images of the right eye. A) At month one, flattening of the retina and closure of the macular hole with trace residual subretinal fluid were evident, with a visual acuity of 20/100. B) At month six, there was sectoral pan-retinal photocoagulation laser fill-in posteriorly with distinct ellipsoid zone and external limiting membrane centrally and a closed macular hole on OCT. Visual acuity was 20/50 at the last follow-up.

We initiated the flap from the nasal to the temporal, taking advantage of the countertraction provided by the optic disc. Our priority was to completely remove the ILM around the macular hole, followed by enlarging the ILM rhexis.

while awake and sleep on either side for two weeks. One year later, final best-corrected visual acuity was 20/50 (*Figure 3, page 9*).

Patient outcome

In our case, although the macular hole was small, we still peeled the ILM to ensure all residual traction was relieved and to decrease the risk of epiretinal membrane formation.[7] After C_3F_8 gas tamponade and two weeks of postoperative face-down positioning, the macular hole was closed and the patient's final visual acuity reached a level of 20/50, comparing favorably to other Eales' cases reported in the literature.

A recent meta-analysis reported a 95-percent pooled surgical success estimate of PPV for Eales' disease, with a 17 percent reoperation rate due to recurrent vitreous hemorrhage or retinal detachment.[4] Final visual outcomes were >20/400 in 87 percent of patients and >20/40 in 32 percent.[4]

As a study in India reported, although patients with a vitreous hemorrhage may be more likely to also have a PVD, uncomplicated surgery isn't guaranteed, even if more complex problems such as retinal detachment aren't present preoperatively.[5] Complete delamination of the posterior hyaloid and identification of vitreoschisis is critical in all these cases to avoid leaving residual tangential traction.[6] The India study found a lower rate of failure when adding an encircling scleral buckle—a consideration for adding additional support in select cases with residual peripheral traction or diffuse peripheral breaks.[5]

Bottom line

A full-thickness macular hole is rare in Eales' disease, and to our knowledge this is the first detailed description of a surgical repair for one. Our case highlights the importance of a comprehensive diagnostic work-up and a tailored treatment and surgical approach for achieving a favorable outcome in this patient.

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RETINA UPDATE

Pachydrusen in AMD
(Continued from page 5)

due to a lack of a longitudinal study. Researchers in South Korea investigated the occurrence of advanced AMD and risk factors for progression to advanced AMD in eyes with pachydrusen. They found that age and macular pigmentary changes were risk factors for the progression to wet AMD in eyes with pachydrusen. However, the number of macular pachydrusen and the presence of macular neovascularization in the fellow eye didn't show a statistically significant relationship with MNV development.

This retrospective longitudinal study included 248 eyes of 156 patients with pachydrusen without advanced age-related macular degeneration at baseline. The mean age at baseline was 65.4 years, and the mean follow-up duration was 6.4 years.

The mean total number of pachydrusen and macular pachydrusen were 4.1 and 2.27 per eye, respectively. Pachydrusen was accompanied by other types of drusen in 4.8 percent of eyes at baseline. During follow-up, MNVs occurred in 2.8 percent (seven eyes), which included polypoidal choroidal vasculopathy in six eyes; however, no geographic atrophy occurred.

The cumulative incidence curves differed significantly based on the presence of macular pigmentary changes. In eyes with pachydrusen, the 10-year cumulative incidence of macular neovascularization was significantly higher when macular pigmentary changes were present than when they were absent (17.39 percent vs. 0.57 percent). In the analysis of MNV development according to the age at baseline, those aged older than 67 years showed a higher frequency of MNV development than did those aged 67 years or younger, although they had a short period of follow-up.

"If pachydrusen eyes have a risk profile for progression to advanced age-related macular degeneration that is different from that of AMD eyes with drusen other than pachydrusen, the current advanced AMD risk prediction methods may not work in eyes with pachydrusen," the researchers wrote in their paper.

"We believe that the current age-related macular degeneration classification should be updated to distinguish drusen types if pachydrusen has a different risk profile from that of other drusen," they concluded. "Further studies with larger sample sizes should be performed to confirm the results of this study."

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EDITORIAL

By Jason Hsu, MD

A heavy burden

When I started my residency many years ago, I would have laughed if someone told me my future clinic would be filled with patients getting intravitreal injections. More than that, I would have been astounded to hear that these treatments could generally show a rapid biologic response and enthusiastic gratitude from many for improving their quality of life.

Fast forward to the present where our clinics are bursting at the seams as the indications for intravitreal injections as well as therapeutic options are ever growing. Couple that with the aging U.S. population and the epidemic of diabetes—a recipe for disaster. Each day, it's commonplace that patients ask me, "Is there a cure coming out soon?"

Another frequent one that I sometimes find humorous and other times perceive as a not-so-subtle jab is, "Are you really the only doctor here today?" I believe that our patient volume, stress to stay on time, and inadequate opportunity to cultivate meaningful physician-patient relationships may be contributing to burnout.

On the flip side, I imagine what it's like for our patients. Many older patients must rely on others to bring them in. They often express concern about overburdening their children. Those who are still working must take time off, translating into lost productivity. Several told me that they have to map out their lives around the clinic visits or prioritize their health-care based on what they can afford or what other issues require more urgent attention.

My group previously published studies looking at the rates of loss to follow-up and found about 20-to-25 percent of patients did not return for a year or more after an anti-VEGF injection.[1,2] Rahul Khurana, MD, subsequently used the American Academy of Ophthalmology IRIS registry and found nearly a 12-percent rate of loss to follow-up.[3] These patients are often at highest risk for vision loss without treatment. I feel like we are failing them despite our best intentions. It's a heavy burden to bear.

Fortunately, hope is in sight. Newer agents, including faricimab (Vabysmo, Genentech/Roche) and high-dose aflibercept (Eylea HD, Regeneron Pharmaceuticals) are demonstrating greater durability, allowing less frequent injections and fewer visits. More drugs and drug-delivery platforms are in the works or becoming available soon.

Tremendous progress is being made in gene therapy to create an internal bio-factory, potentially allowing a single treatment to hijack the patient's cells to produce the effective drugs that we have been delivering via injections. While it's already been an exciting journey in our field over the last couple decades, I expect that the best is yet to come. Put on those shades, folks. The future is going to be ever so bright.

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RETINA SPECIALIST

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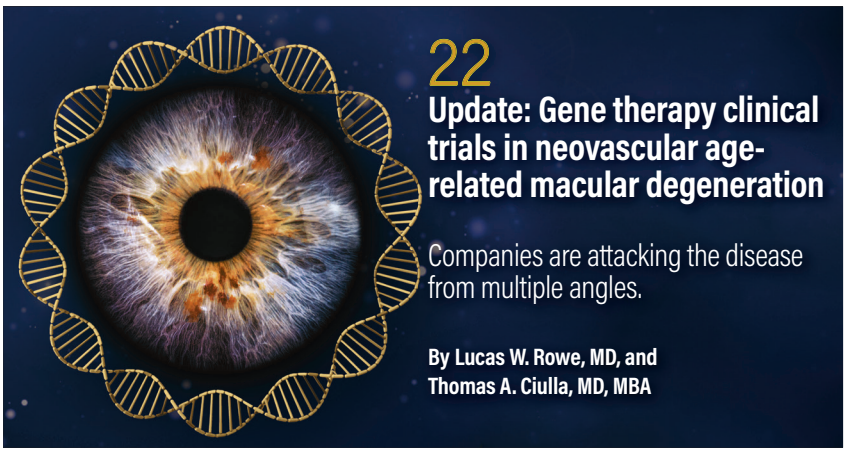
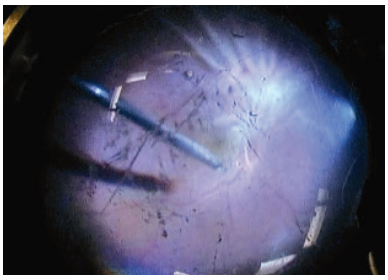
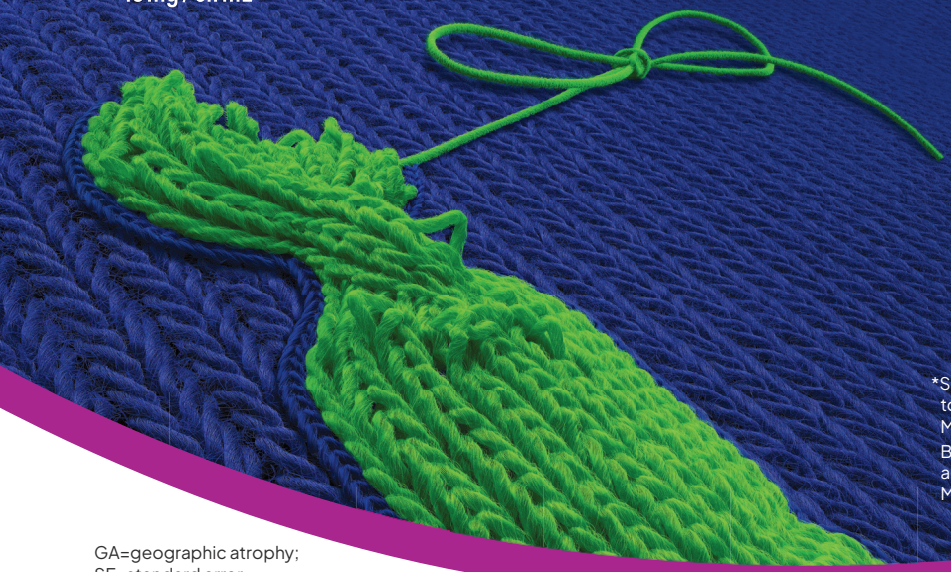
FEATURES



DEPARTMENTS



SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL



GA unravels so much
SAVE RETINAL TISSUE BY SLOWING PROGRESSION[1-3]

SYFOVRE achieved continuous reductions in mean lesion growth rate* vs sham pooled from baseline to Month 24[1,4]

Monthly	Every Other Month (EOM)
OAKS trial (mm^2): (3.11 vs 3.98) **22%**	OAKS trial (mm^2): (3.26 vs 3.98) **18%**
DERBY trial (mm^2): (3.28 vs 4.00) **18%**	DERBY trial (mm^2): (3.31 vs 4.00) **17%**

SE in trials (monthly, EOM, sham pooled): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17.

*Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1]

Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]

GA=geographic atrophy;
SE=standard error.

Explore the long-term data

The CMS-assigned permanent J-code for SYFOVRE is J2781—effective 10/1/23[1]

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.
- **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.

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

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 24-month, 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 EOM, sham monthly, or sham EOM for 24 months. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[1,4]

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023. **2.** Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2020;138(10):1026–1034. **3.** Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. *JAMA Ophthalmol*. 2014;132(3):338–345. **4.** Data on file. Apellis Pharmaceuticals, Inc.

Apellis

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

Department Editor ***Christopher R. Fortenbach, MD, PhD***

Three strikes of inflammation

A case of Susac syndrome.

By Hannah Hashimi, MD, Nathan Agi, MD, and Thellea K. Leveque, MD, MPH

Hannah Hashimi, MD

Nathan Agi, MD

Thellea K. Leveque, MD, MPH

Presentation

A 33-year-old male was referred to our tertiary care hospital for ophthalmic evaluation of transient vision loss in both eyes. The patient was in his usual state of good health but developed a sore throat, fever, chills and full body aches prior to presentation. He tested positive for SARS-CoV-2 (COVID-19) and was treated with azithromycin, hydroxychloroquine and ivermectin. Four days later, he experienced episodic periods of dizziness, arm numbness, headaches, tinnitus and bilateral vision loss.

Examination Findings

During the initial presentation to an outside emergency room, he underwent an immediate stroke protocol work-up, including MRI of the brain, which demonstrated multifocal small infarcts. Laboratory testing was unremarkable, but ultrasound of the lower extremities revealed a unilateral deep vein thrombosis, for which he was started on a heparin drip. Unfortunately, his encephalopathy progressed with worsening confusion and seizures, so he underwent repeat MRI which showed a concomitant increase in the number of infarcts, localizing around the corpus callosum. CT angiogram, however, didn't show occlusion or vascular anomalies.

In the setting of his episodic vision loss, the patient was transferred to our center for ophthalmic evaluation. At that time, the patient's best corrected Snellen visual acuity had improved to 20/20 bilaterally with normal eye pressures and no afferent pupillary defect. He didn't have any signs of anterior or intermediate uveitis, but dilated fundus exam revealed bilateral sectoral arterial box-caring and Gass plaques (GPs) in the temporal and superior quadrants *(Figure 1)*.

Work-up

To further evaluate the retinal changes, we obtained widefield fluorescein angiography with transit of the right eye *(Figure 2)*. There was a normal arm-to-eye time of 11 seconds, but later frames demonstrated multiple branch retinal artery occlusions and peripheral non-perfusion in the temporal retina bilaterally. There was also perivascular leakage in the superonasal mid-periphery of the right eye. Given his retinal findings and tinnitus, the patient also underwent audiology testing, which confirmed moderately-severe sensorineural hearing loss.

Diagnosis and Management

The patient was diagnosed with Susac Syndrome given the complete triad of encephalitis, branch retinal artery occlusions and sensorineural hearing loss.

The mainstay of treatment is immunosuppression to mitigate the auto-immune mediated inflammatory response. Our patient was started on five days of high-dose IV methylprednisolone 1,000 mg/day for CNS vasculitis. The neurology team initiated intravenous immunoglobulin therapy for three days before transitioning to Rituximab 1,000 mg every six months with a slow taper off high-dose oral steroids.

Given the extent of peripheral retinal ischemia, he was seen in the Retina

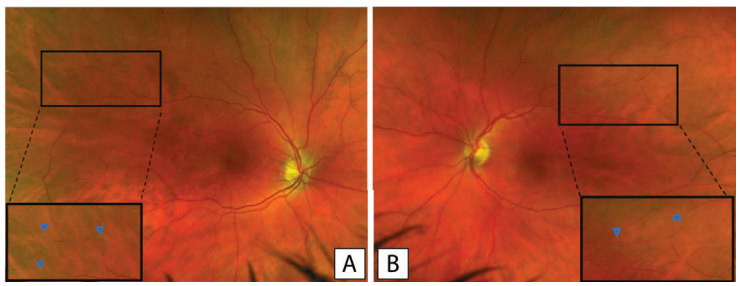


Figure 1. Pseudocolor fundus photography of the right (A) and left (B) eyes respectively with a magnified view showing bilateral artery attenuation and arrows pointing to the Gass plaques.

BIOS

Dr. Leveque is a clinical professor of ophthalmology at the University of Washington in Seattle where **Dr. Hashimi** is an ophthalmology resident and **Dr. Agi** is a retina fellow.

DISCLOSURES: The authors have no relevant disclosures.

UW Medicine EYE INSTITUTE

Department for pan retinal photocoagulation of the areas of non-perfusion as prophylaxis against neovascularization. He has subsequently followed in the Uveitis Department for monitoring for re-activation as he tapered off oral steroids.

Discussion

Susac Syndrome (SuS) is an idiopathic systemic vasculitis presumed to be due to an immune-mediated inflammation of the vascular endothelium presenting clinically as a triad of central nervous system dysfunction, branch retinal artery occlusion and sensorineural hearing loss. It most commonly occurs in the second to fourth decades of life. While typically a single episode, recurrences have been reported in up to 42 percent of cases.[1]

While our patient presented with all three symptoms in rapid succession, SuS can be difficult to diagnose, as the triad is usually incomplete at disease onset. Diagnostic criteria are divided into definite and probable SuS based on constellations of clinical symptoms and diagnostic signs.[2] Brain MRI findings include multifocal hyperintense round small lesions, typically involving the corpus collosum. In the eye, in addition to multiple branch retinal artery occlusions, other exam findings may aid with diagnosis including Gass plaques. Initially described by Don Gass,[3] GPs are small yellow or yellow-white plaques located along the lumen of vessels, and frequently occur away from arteriolar bifurcations, which can help differentiate them from Hollenhorst plaques. While GPs are not unique to Susac Syndrome, they are a common feature and should be differentiated from other types of plaques.

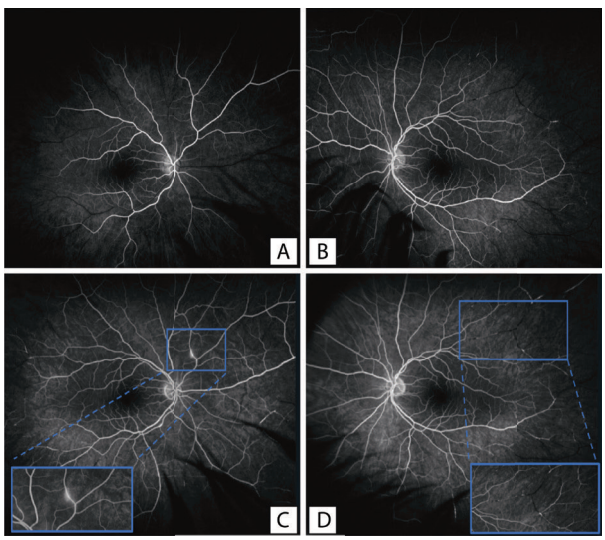


Figure 2. Optos fluorescein angiography demonstrating multiple peripheral retinal artery occlusions with associated peripheral non-perfusion. Frames A and B demonstrate early phase filling of the right and left eye, respectively. Frame C demonstrates a magnified view of the arterial wall hyperfluorescence, which can be observed in the peripheral vasculature, most significantly in the superonasal quadrant. Panel D demonstrates late filling of the left eye with a magnified view of multiple retinal artery occlusions in the vascular periphery.

Fluorescein angiography can also be a helpful modality for diagnosis and treatment. Typical findings were reported in 2007,[4] including GPs and arterial wall hyperfluorescence (AWH), which can also be seen in the case presented here *(Figure 2)*. In addition, the FA can be useful to evaluate areas of non-perfusion and neovascularization, which may guide preventative treatment with PRP.

Interestingly, our patient developed SuS shortly following a COVID-19 infection, which is known to be associated with systemic vasculitis[5] and retinal microvascular occlusions.[6] The unique clinical and diagnostic findings in our patient confirmed a named SuS diagnosis. To date, a few cases of SuS occurring following COVID-19 infection have been reported in the literature,[7,8] although the high prevalence of COVID-19 infection in the general population and the rarity of SuS precludes us from drawing definitive conclusions about causation.

This case serves as a reminder that seemingly routine diagnoses such as artery occlusions require a high level of suspicion with a carefully obtained history and review of systems, which may help guide the workup and aid in revealing an underlying diagnosis. RS

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- Remote Patient Management
- Vision Alert Management

References: 1. Ho AC, Kleinman DM, Lum FC, et al. Baseline Visual Acuity at Wet AMD Diagnosis Predicts Long-Term Vision Outcomes: An Analysis of the IRIS Registry. *Ophthalmic Surg Lasers Imaging Retina.* 2020;51:633-639. **2.** Real-World Performance of a Self-Operated Home Monitoring System for Early Detection of Neovascular AMD (ForeseeHome device), presented by Allen Ho, American Society of Retina Specialist Meeting 2020.

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SM-125.3

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What's different (and not) about injecting GA drugs

Tips for injecting pegcetacoplan and avacincaptad pegol for geographic atrophy.

Andrew J. Clark, MD, PhD

Nathan Steinle, MD

By Andrew J. Clark, MD, PhD, and Nathan Steinle, MD

Take-home points

- Pegcetacoplan and avacincaptad pegol have precautions that retina specialists should discuss with their patients prior to injection.
- Pegcetacoplan has increased viscosity and volume compared to many commonly used intravitreal injections.
- Avacincaptad pegol has the same large injection volume as pegcetacoplan (0.1 mL), although its viscosity is similar to the most-used intravitreal injections.
- Both agents require close monitoring for postinjection intraocular pressure elevation.

The treatment paradigm for geographic atrophy associated with advanced age-related macular degeneration has changed rapidly in the past year thanks to the approval of two new intravitreal injections, pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izveray, Iveric Bio/Astellas). These new medications inhibit the complement cascade implicated in development of retinal pigment epithelium cell death leading to GA.[1–3]

Several other medications are also being developed in the therapeutic pipeline, and we may someday have gene therapy products, suprachoroidal drugs and other novel biologics as part of our armamentarium against this devastating disease.[4,5] As these new treatment options enter into our clinical practice, we'll face new challenges for safe and effective care delivery. Here, we describe our technique for performing safe intravitreal injection of pegcetacoplan and avacincaptad pegol.

Indications for injection

Pegcetacoplan should be given every 25 to 60 days. In clinical trials, pegcetacoplan was shown to reduce the rate of GA lesion growth 16 to 22 percent in the first 12 months of treatment, depending on whether patients receive monthly or bimonthly injections,[6] with an enhanced reduction effect of 25 to 35 percent in lesion growth rate in years two and three.[7,8]

Avacincaptad pegol has the same indication. It's approved for monthly dosing up to one year and, in clinical trials, demonstrated an 18-to-35-percent reduction in the GA lesion growth rate over the first 12 months of treatment.[9,10]

Before the injection

As with any intervention, careful discussion regarding the risks and benefits with patients is paramount before initiating therapy. Both pegcetacoplan and avacincaptad pegol have known risks that patients should be told about before the injection. Besides risks inherent to any

Bios

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Dr. Steinle is a retina specialist with California Retina Consultants in the Central Coast region of California.

DISCLOSURES:
Dr. Clark has no relevant disclosures.

Dr. Steinle disclosed relationships with Appelis Pharmaceuticals, Genentech/Roche, Novartis and Regeneron Pharmaceuticals.

intravitreal injection, namely endophthalmitis and damage to other structures of the eye, including retinal detachment, both medications have several notable additional risks. They include conversion to wet macular degeneration, nonartertic ischemic optic neuropathy, and a greater likelihood of transient elevated intraocular pressure.[6–10]

Complement inhibition has also been associated with rare instances of retinal vasculitis following the first administration of the medication.[11,12] Data are still being gathered to better define this risk profile, but unofficial reported estimates place the incidence of retinal vasculitis at around 0.01 percent for pegcetacoplan. Apellis has recommended switching from a previously supplied 19G filter needle to an 18G filter needle when preparing the injection.

Preparing the injection

On the day of the injection, the eye should be inspected to ensure it's free of both infection and active inflammation. Both medications should be stored at temperatures between 2 and 8C until they're used and allowed to reach room temperature prior to the injection, which eliminates the increased viscosity associated with colder storage temperatures. Vials should not be frozen or shaken, and vials should only be used for a single injection for a single eye in a single patient. The medications should appear as a colorless to light yellow liquid. If the vial contains any particulate, turbidity or discoloration, it should be discarded.

Pegcetacoplan is a 0.1 mL injection of a 150 mg/mL solution, providing 15 mg of drug into the vitreous cavity. The medication is distributed in a vial, with an accompanying injection kit that contains an 18G filter needle and a 29G thin-walled Luer-lock needle (*Figure 1*). The injection also requires a sterile 1-cc Luer-lock syringe and alcohol swab. A sterile 27G needle with Luer-lock can also be used in lieu of the thin-walled 29G needle.[13]

Avacincaptad pegol is 0.1-mL injection of a 20-mg/mL solution for a total of 2 mg of drug per injection. The medication vial is packaged with a 19G filter needle and sterile 1-cc Luer-lock syringe. The injection can be performed with a 30G needle (*Figure 2, page 20*).[14]

Similarities between the two injections

The following procedures we describe apply to both treatments. They include:

1) Remove the cover from the vial cap and clean the septum with an alcohol swab.

2) Transfer the medication from the vial to the syringe using the supplied filter needle. Sitting the vial upright for one minute prior to withdrawing the medication can help the liquid accumulate at the base of the vial and make the transfer easier. Tilting the vial slightly to pool the liquid in one corner will also limit introducing air bubbles during withdrawal.

3) Exchange the filter needle for the

Figure 1. Pegcetacoplan (Syfovre) comes with an accompanying injection kit that contains an 18G filter needle and a 29G thin-walled Luer-lock needle. ***(Courtesy: Apellis Pharmaceuticals)***

injection needle (29G thin-walled needle for pegcetacoplan, 30G for avacincaptad pegol) and discard excess medication until 0.1 mL remains in the syringe. This step is critical to expel any air bubbles within the solution.

For pegcetacoplan, don't shake or tap the syringe. This will cause more bubbles to form within the solution. Rather, perform a smooth and controlled withdrawal and advancement (charging) of the plunger until no bubbles are visible within the syringe.

For avacincaptad pegol, lightly tapping the side of the syringe will bring the bubbles to the top, where they can be expelled.

Cleaning the ocular surface

As with all intravitreal injections, the ocular surface should be cleaned meticulously with an antiseptic agent. One suggestion is to press a sterile, betadine-soaked cotton tip against the globe at the intended injection site until an indentation is visible on the globe surface. By holding this position for 10 to 30 seconds, we hope to soften the globe to better accommodate the 0.1-mL injection volume. With this decompression technique, we have seen few significant IOP elevations immediately after the injection.

Figure 2. Avacincaptad pegol (Izervay) comes with an injection kit that includes a glass vial, a sterile 5-μm filter needle (19G x 1.5 inch) and an empty sterile 1-mL Luer lock syringe with a 0.1-mL dose mark. The glass vial, filter needle and empty syringe are for single use only. (*Courtesy Iveric Bio/Astellas*)

Injection technique for pegcetacoplan

One of the unique aspects of pegcetacoplan is its increased viscosity relative to other common intravitreal injections. The medication's thick consistency will cause it to move more slowly through the filter needle and may require increased back pressure on the syringe to remove the fluid from the vial. This increased viscosity also plays a role when performing the injection. Apply continued pressure to the syringe plunger when performing the injection to express the medication. The thin-walled, larger 29G needle is provided to aid with fluid flow and the Luer locks provide an extra layer of security during the injection.

Stabilizing hand-holding of the syringe also aids in achieving a safe injection. We typically use a bimanual technique. Hold the syringe in the dominant hand while, with the nondominant hand, lightly holding around the distal end of the syringe to stabilize the injection. Once the needle is within the vitreous, use the thumb of the nondominant hand to slowly and firmly depress the plunger. We recommend injecting over about five seconds.

While withdrawing the needle, a sterile cotton-tip applicator can tamponade the wound to minimize medication reflux. Because the injection push takes longer than other intravitreal injections, a lid speculum can minimize the chance of eyelash contamination of the injection needle.

Once the injection is completed, inspect the optic nerve to confirm it's perfused and that vision is at least counting fingers. If the nerve is pale and vision declines to no light perception, consider an anterior chamber paracentesis to reduce the elevated IOP. If the vision declines but the nerve remains perfused with venous pulsations, the patient should remain in the clinic and rechecked in five to 10 minutes as the vision and perfusion will often improve on their own. Failure for the vision to improve after

brief observation should prompt an anterior chamber paracentesis.

Injection technique for avacincaptad pegol

Avacincaptad pegol has a viscosity similar to that of anti-VEGF agents. Thus, it doesn't have the same considerations in regard to medication preparation and injection pressure as pegcetacoplan, but it still comes with an accompanying injection kit (*Figure 2*). A 30G needle is recommended for the injection. Smaller-bore needles may limit fluid flow. Avacincaptad pegol is also a 0.1-mL injection, so it's important to monitor the patient for an immediate postinjection IOP spike and to intervene.

Bottom line

With minor adjustments to the typical intravitreal injection techniques, vitreoretinal specialists can safely and reproducibly deliver pegcetacoplan and avacincaptad pegol. RS

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Update: Gene therapy clinical trials in neovascular age-related macular degeneration

Companies are attacking the disease from multiple angles.

Lucas W. Rowe, MD

Thomas A. Ciulla, MD, MBA, FASRS

By Lucas W. Rowe, MD, and Thomas A. Ciulla, MD, MBA

Take-home points

- Gene therapy holds the potential to alleviate the significant treatment burden in neovascular age-related macular degeneration by delivering sustained and enduring therapeutic effects through the production of endogenous anti-vascular endothelial growth factor within the chorioretina.
- Many challenges face the ongoing development of these therapies, yet significant progress has been realized regarding their routes of administration, safety profiles and efficacy outcomes..
- Viral vector gene therapy appears to be a particularly promising avenue in advancing the treatment landscape for nAMD.
- Ongoing Phase II and Phase III clinical trials for ABBV-RGX-314 (subretinal, suprachoroidal), ixoberogene soroparvovec (intravitreal) and 4D-150 (intravitreal) are highly anticipated with encouraging preliminary results.

BIOS

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Dr. Ciulla is a retina specialist and board member of Midwest Eye Institute of Indianapolis, Indiana, volunteer clinical professor of ophthalmology at Indiana University School of Medicine, chief medical officer at Viridian Therapeutics, and chief medical advisor and the chair of the Scientific Advisory Board at Clearside BioMedical, where he previously served as chief medical officer and chief development officer.

DISCLOSURES: Dr. Rowe reports no relevant disclosures.

Dr. Ciulla reports employment by, and holds equity in, Viridian Therapeutics. He holds equity in Clearside BioMedical and Nanoscope Therapeutics. In addition to Clearside and Nanoscope, he has served as a consultant for Ocuphire Pharma.

Intravitreal anti-vascular endothelial growth factor injections have become the standard of care for treating neovascular age-related macular degeneration.[1] Monthly or bimonthly anti-VEGF injections demonstrate favorable long-term best-corrected visual acuity preservation in real-world studies compared to less frequent dosing,[2-5] but at the expense of significant time and cost burden due to the disease's chronic nature and limited medication half-life. Gene therapy biofactories offer a potential solution to address the need for long-acting and more durable therapies in nAMD. In this article, we'll review the latest gene-therapy efforts in this area.

Gene therapy backgrounder

Retina has been at the forefront of gene therapy in medicine, particularly since the FDA clearance of voretigene neparvovec-rzyl (Luxturna, Spark Therapeutics/Genentech) for confirmed biallelic *RPE65*-mediated inherited retinal disease in December 2017. Luxturna represented the first FDA-approved gene therapy for inherited disease. When a therapeutic gene is delivered and integrates into patient cells, it has the capacity to continually generate a desired protein, such as endogenous anti-VEGF, and thus offers the prospect of alleviating the treatment burden of frequent intravitreal injections for nAMD through sustained and enduring therapeutic effects.

The standard for ocular gene therapy administration is subretinal injection; however, suprachoroidal and intravitreal gene delivery are being investigated as alternative routes of administration to avoid the potential complications of pars plana vitrectomy-associated procedures, such as macular hole and/or potential photoreceptor disruption associated with bleb creation, retinotomy with hemorrhage and/or fibrosis, retinal tear and detachment and cataract *(Figure 1)*.[6] Suprachoroidal delivery also offers a targeted, compartmentalized delivery of gene therapy to the chorioretina while mini-

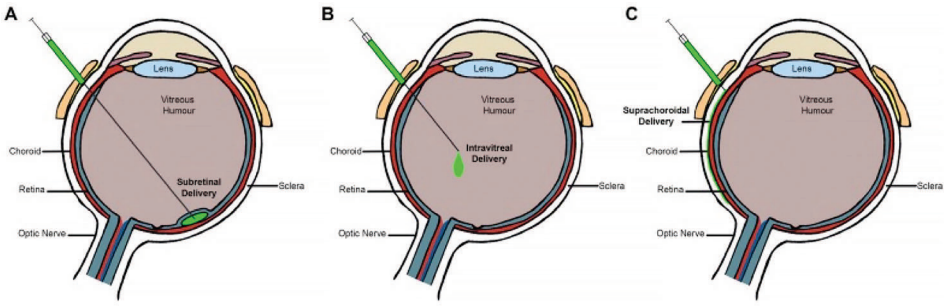

Figure 1. Routes of ocular gene therapy administration: subretinal delivery (A); intravitreal delivery (B); suprachoroidal delivery (C). From Guimaraes TAC, Georgiou M, Bainbridge JWB, Michaelides M. Br J Ophthalmol. 2021;105(2):151-157.[11] *Licensed for reuse under the Creative Commons Attribution (CC BY) license.*

mizing exposure to the vitreous and anterior segment which may elicit an immune and inflammatory response.[7-10]

ABBV-RGX-314

ABBV-RGX-314 is a novel gene therapy intervention being developed by RegenxBio and AbbVie that delivers a transgene encoding a ranibizumab-like anti-VEGF monoclonal antibody fragment to the retina through an adeno-associated virus (AAV) 8 vector *(Figure 2, page 24)*. The administration of the therapy entails a single subretinal or suprachoroidal injection, strategically designed to produce enduring cellular expression of anti-VEGF therapy within the retinal tissues.

A Phase I/IIa, open-label, multiple-cohort, dose-escalation study (NCT03066258) reported positive safety and efficacy results with the subretinal delivery of ABBV-RGX-314 in nAMD. ABBV-RGX-314 was well-tolerated at all five doses and demonstrated stability of best-corrected visual acuity and central retinal thickness at six months.[12]

There are currently two ongoing Phase IIb/III trials: ATMOSPHERE (NCT04704921) and ASCENT (NCT05407636), investigating subretinal ABBV-RGX-314 in nAMD.[13,14] The ATMOSPHERE (Phase IIb/III) and ASCENT (Phase III) trials are randomized, partially masked, controlled studies evaluating two dose levels of ABBV-RGX-314 against monthly intravitreal ranibizumab and bimonthly intravitreal aflibercept, respectively. The primary outcome of the trials is the mean change in BCVA from baseline to 54 weeks. RegenxBio has plans for the trials to support a global regulatory submission in late 2025 and first half of 2026.[15]

Simultaneously, RegenxBio is evaluating the suprachoroidal delivery of ABBV-RGX-314 in individuals with nAMD. AAVIATE (NCT04514653) is a multicenter, open-label, randomized, active-controlled, dose-escalation, Phase II trial investigating the efficacy, safety and tolerability of suprachoroidal delivery of ABBV-RGX-314 using the Clearside Suprachoroidal Space (SCS) Microinjector in comparison to monthly intravitreal ranibizumab *(Figure 3, page 24)*.

Three dose levels of ABBV-RGX-314 are included in the trial at $2.5x10^{11}$ (Cohort 1), $5x10^{11}$ (Cohorts 2 and 3), and $1x10^{12}$ (Cohorts 4 to 6) genomic copies per eye. The primary efficacy endpoint is the mean change in BCVA at week 40 from baseline, with secondary endpoints including mean change in central retinal thickness and number of anti-VEGF injections following administration.

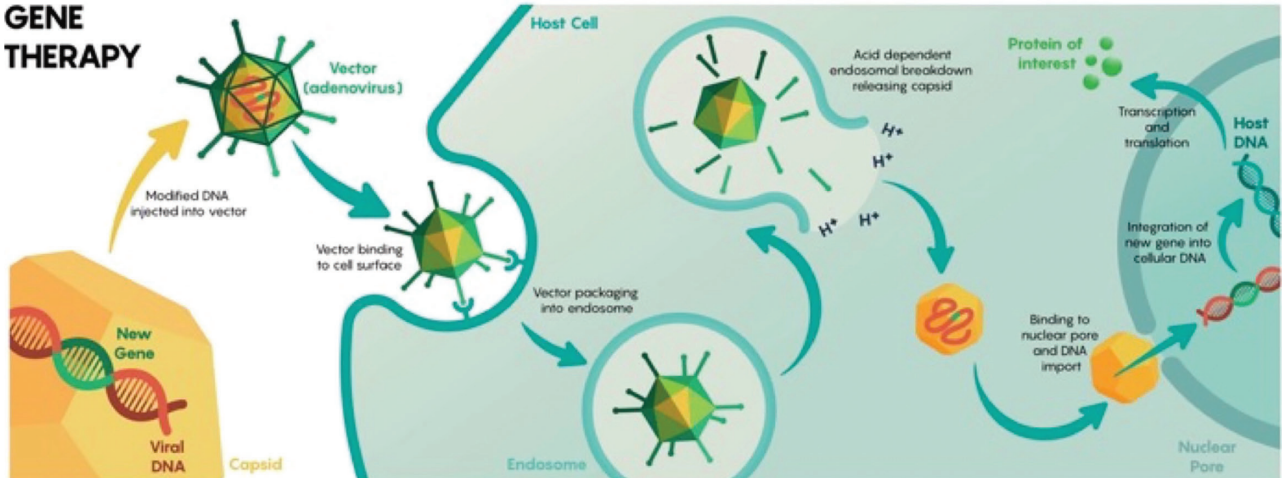

Figure 2. Overview of adenovirus-mediated delivery of recombinant genetic material to host cells for endogenous expression of a desired protein. ***(From: https://commons.wikimedia.org/wiki/File:Viral_mediated_delivery_of_genes_to_neurons_1.jpg.[16] Licensed for reuse under the Creative Commons Attribution-Share Alike 4.0 International license.)***

Encouragingly, RegenxBio recently announced interim data that more than 50 patients in Cohorts 4 through 6 achieved an 80-percent reduction in annualized injection rate and a 50 percent injection-free rate through six months following a single suprachoroidal injection of ABBV-RGX-314.[17]

Furthermore, the therapy was well-tolerated across more than 100 patients from the three dose levels with no drug-related serious adverse events. Mild intraocular inflammation was reported at similar incidence rates in the first and second dose levels, while mild to moderate intraocular inflammation was reported at the third dose level in Cohorts 4 and 5; all of which resolved with topical corticosteroids. Of note, however, patients at the third dose level who received a short course of prophylactic topical steroids (Cohort 6) displayed no cases of intraocular inflammation.[17] These early results support ABBV-RGX-314's potential as a one-time, in-office treatment that may offer long-term durability and safety in nAMD.

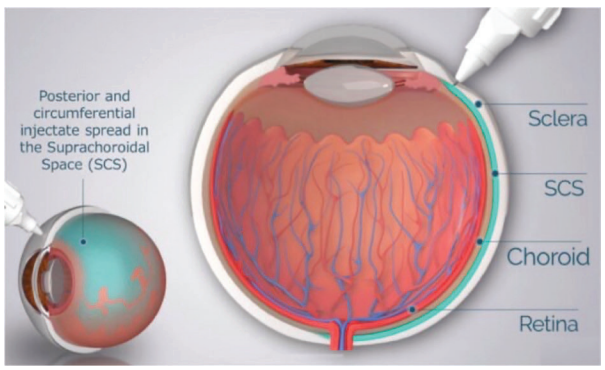

Figure 3. Schematic of microneedle injection into the suprachoroidal space (SCS). From Wan C-R, Muya L, Kansara V, Ciulla TA. Pharmaceutics. 2021;13:288.[7] ***(Licensed for reuse under the Creative Commons Attribution (CC BY) license.)***

Ixo-vec

Ixoberogene soroparvovec (ixo-vec, formerly ADVM-022) (Adverum Biotechnologies) is a single-use intravitreal gene therapy that employs the AAV2.7m8 capsid for efficient retinal transduction and expression of the proven anti-VEGF protein, aflibercept *(Figure 4)*.[18,19]

OPTIC (NCT03748784) was a two-year, open-label, prospective, multicenter Phase I study investigating the safety and tolerability of ixo-vec in non-naive nAMD.[20] Patients were assigned to four cohorts differing by dose ($2x10^{11}$ or $6x10^{11}$ vector genomes per eye [vg/eye]) and prophylactic steroids (oral prednisone vs. topical difluprednate).

The majority of ocular treatment-emergent adverse events (TEAEs) were dose-dependent and mild (84 percent) to moderate (16 percent) in severity, with anterior chamber cell and vitreous cell the most commonly reported.[21] Five serious TEAEs were reported, with two deemed probably related to ixo-vec, including an asymmetric

progression of dry AMD and a case of recurrent uveitis.

Notably, the high-dose group and low-dose group had 98 percent and 80 percent reduction in annualized anti-VEGF injection burden, respectively, and 80 percent and 53 percent injection-free rate, respectively.[21] Furthermore, both dose groups displayed maintenance of BCVA and CRT measurements throughout the study. The superior safety and similar efficacy of the $2x10^{11}$ vg/eye dose relative to the $6x10^{11}$ vg/eye dose in the OPTIC trial supported continued evaluation of the latter dose in nAMD.

LUNA (NCT05536973) is an ongoing Phase II trial investigating the safety and efficacy of ixo-vec at the $2x10^{11}$ vg/eye dose and a lower dose of $6x10^{10}$ vg/eye, in combination with enhanced corticosteroid prophylaxis.

Adverum recently announced positive preliminary results from the LUNA study, with both doses demonstrating maintenance of visual and anatomic outcomes. At 26 weeks, the $2x10^{11}$ and $6x10^{10}$ vg/eye doses achieved annualized reduction in anti-VEGF injection rates of 94 percent and 90 percent, respectively, and injection-free rates of 85 and 68 percent, respectively.[23] Both doses displayed a maintenance of functional and anatomical outcomes from baseline to 26 weeks, in addition to apparent improved inflammatory profiles with corticosteroid prophylaxis compared to those from the OPTIC study.

These early results support the potential of a single in-office intravitreal injection of ixo-vec as a possible paradigm shift in nAMD treatment away from frequent anti-VEGF injections to durable and effective cellular-based biofactories.

4D-150

4D-150 (4D Molecular Therapeutics) is a single-use, low-dose intravitreal gene therapy using an evolved vector, R100, and a transgene cassette that expresses both aflibercept and a VEGF-C inhibitory RNAi to inhibit a total of four antiangiogenic factors: VEGF A; B; C; and placental growth factor (PlGF).[24]

PRISM (NCT05197270) is a prospective, multicenter, Phase I/II dose-escalation and randomized, controlled, masked expansion trial investigating the safety and tolerability of 4D-150 in nAMD.[25] Phase I PRISM results revealed that all three dose cohorts of 3×10^{10}, 1×10^{10}, and 6×10^{9} vg/eye were safe and well-tolerated in the dose exploration phase of the study.[26] Furthermore, in the 3×10^{10} vg/eye cohort, patients experienced a 96.7-percent overall reduction in the mean annualized anti-VEGF injection rate and four of five eyes were supplemental aflibercept-free.

Interim Phase II PRISM results met all endpoints through 24 weeks in nAMD patients with severe disease activity and high treatment burden.[27] 4D-150 at a dose of 3×10^{10} vg/eye showed equivalent and stable

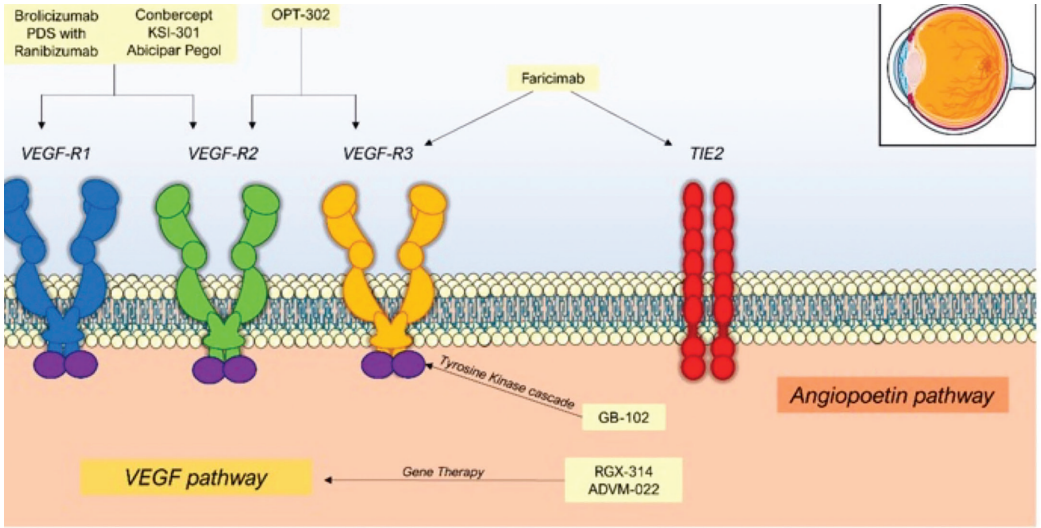

Figure 4. Mechanisms of action of therapies for nAMD, including novel gene therapies in development. ***(From: Patel P, Sheth V. J. Clin. Med. 2021, 10, 2436.[22] Licensed for reuse under the Creative Commons Attribution (CC BY) license.)***

BCVA outcomes and improved retinal anatomical control with reduced central subfield thickness variability compared to the bimonthly aflibercept arm, in addition to an 89 percent overall reduction in annualized anti-VEGF injection rate and a 63 percent injection-free rate.

Notably, a favorable safety profile was achieved with no significant or recurrent intraocular inflammation with a 20-week prophylactic topical corticosteroid taper. Following the positive initial results from PRISM, the FDA and European Medicines Agency granted the RMAT and Priority Medicines (PRIME) designations, respectively, to 4D-150 with the goal of increasing collaboration on regulatory approval planning and expediting drug development.[24]

Bottom line

Gene therapy holds the potential to alleviate the treatment burden in nAMD by delivering sustained and enduring therapeutic effects through the production of endogenous anti-VEGF within the retina. Many challenges face the ongoing development of these therapies, yet significant progress has been realized regarding their routes of administration, safety profiles and efficacy outcomes.

The prospect of reduced treatment frequency offers benefits for patients, including substantial enhancements in quality of life, vision preservation and a reduction in the socio-economic impact associated with vision impairment. Viral-vector gene therapy appears to be a particularly promising avenue and the aforementioned therapies support the great potential in advancing the treatment landscape for nAMD.

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How anti-VEGF biosimilars are changing retina care

Biosimilars are reducing costs and increasing access, but in retina they also face unique challenges compared with other medical specialties.

Rajat Agrawal, MD, MS

By Rajat Agrawal, MD, MS

Take-home points

- Biosimilars are highly similar to the reference product and, once approved, can be used in place of the latter in clinical practice.
- In the United States, two biosimilars to ranibizumab, Byooviz and Cimerli, are currently approved.
- More biosimilars to ranibizumab are awaiting approval, while biosimilars to aflibercept are likely to be approved later this year.
- Although at the outset retina specialists were slow to adopt biosimilars, they have slowly and steadily increased their use of biosimilars, with more payers adding biosimilars to their formularies.

BIO

Dr. Agrawal is a retina specialist and currently the ophthalmology lead and vice president for clinical development at Rezolute. Previously, he was senior vice president, clinical development, with Coherus Biosciences. Before Coherus, he was senior director, global research and development, at Santen. Previously, he was a clinical retina faculty member at Doheny Eye Institute, University of Southern California, and Los Angeles County Hospital. He is also the founder and chief executive officer of Retina Global, an international nonprofit that provides specialized retinal care in the United States and other countries.

DISCLOSURE: Dr. Agrawal led ophthalmology biosimilar programs and was involved in the approval of Cimerli as senior vice president of clinical development with Coherus Biosciences, a position he left in 2021.

Biosimilars have been shown to reduce costs across a broad range of therapeutic areas, savings that have increased as clinicians become more familiar with biosimilars and prescribe them in a growing number of patients—a dynamic that's coming to retina now that biosimilars to the two leading anti-VEGF treatments are widely available or will be soon. Most studies also calculated that these cost savings could result in tens of thousands of additional patients being treated with biologics, which could increase substantially as the benefits of biosimilars become more widely understood.[1]

What are biosimilars?

A biosimilar is a biologic medication that is highly similar in its physical, chemical and biological properties to and has no clinically meaningful differences from an existing U.S. Food and Drug Administration-approved biologic, referred to as the reference product. Compared to a reference product, biosimilars are made with the same types of living sources, are given to the patients in the same way, and have the same strength, dosage, treatment benefits and potential side effects.[2]

Biosimilars undergo an extensive review and approval process to determine that they have no clinically meaningful differences from the reference product.[3] This approval process assures that biosimilars have the same treatment benefits and risks. Considering they're quite similar to the reference product, the Biologics Price Competition and Innovation (BPCI) Act of 2009 that defined biosimilars, proposed an abbreviated pathway for approval.[4] With less time and fewer resources required for development, a biosimilar that the FDA deems safe and effective is likely to be cheaper than its reference product, thus providing patients with more treatment options, increasing access to lifesaving medications and potentially lowering health-care costs.[2]

Biosimilars and interchangeability

An interchangeable biological product is a biosimilar that meets additional requirements and may be substituted for the reference product at the pharmacy, depending on state pharmacy laws.[2,5]

It's important to remember that not all biosimilars are interchangeable. Companies must submit an application with adequate information to support such a determination for their product to be approved as an interchangeable biosimilar. [2,5]

Recently, the FDA recommended that all labeling for biosimilars include a biosimilarity statement, which would likely avoid any confusion about interchangeable biosimilars vs. those that don't carry that designation. Previously, the agency recommended that labeling include a statement of biosimilarity or interchangeability in the highlights section that describes the product's relationship to its reference product. The FDA wants to make sure that a designation of *interchangeability* doesn't indicate a higher level of biosimilarity in biosimilars designated as interchangeable.[6]

Lucentis biosimilars in the United States

The FDA has approved 45 biosimilars in total,[4] only two of which are approved for ophthalmic use, and both as biosimilars to ranibizumab.

The first was Byooviz (ranibizumab-nuna or SB11), which was approved in September 2021. This drug, which was developed by Samsung Bioepis and marketed in the United States by Biogen, launched with a 0.05-mg single-use vial and hence is only approved for three of the five indications for which Lucentis is approved: neovascular age-related macular degeneration; macular edema following retinal vein occlusion; and myopic choroidal neovascularization. Although it was the first ranibizumab biosimilar approved in the United States, it was the second to receive an interchangeability designation.

The FDA approved Cimerli (ranibizumab-eqrn or FYB-201) in August 2022. Developed by Bioeq AG and initially marketed in the United States by Coherus Biosciences, Sandoz has since acquired the franchise. Cimerli was approved in both 0.3- and 0.5-mg doses for all five indications for which Lucentis is approved, including diabetic macular edema and diabetic retinopathy. Cimerli is also the first to receive the interchangeability designation from the FDA.

Clinical trials for Lucentis biosimilars

Each of these Lucentis biosimilars had to go through a Phase III study to demonstrate safety and similar efficacy to Lucentis.

Byooviz underwent a randomized, double-masked, multicenter Phase III study that evaluated efficacy, safety, pharmacokinetics and immunogenicity. The study had a primary endpoint of change from baseline in best-corrected visual acuity at eight weeks and central subfield thickness at four weeks. The secondary endpoints included pharmacokinetics, safety, long-term efficacy and immunogenicity. [7,8] The study recruited 705 nAMD patients who were randomized to receive either SB11 or ranibizumab in monthly injections (0.5 mg), with 634 patients continuing to receive treatment for the entire study length of 48 weeks.

The study met the primary endpoint, as the adjusted treatment difference between SB11 and ranibizumab in BCVA was -0.8 letters (90% confidence interval [CI] -1.8 to 0.2) and the CST change from baseline was -8 µm (95% CI -19 to 3).

The randomized clinical equivalence trial demonstrated equivalence in efficacy for both primary end points between SB11 and ranibizumab, with SB11 similar in safety and immunogenicity profiles to ranibizumab.[7]

The COLUMBUS-AMD trial evaluated the clinical equivalence of Cimerli to the reference product ranibizumab in patients with treatment-naive, subfoveal choroidal neovascularization caused by nAMD. The primary end point was change from baseline in BCVA, as measured

To date, the only anti-VEGF biosimilars approved in the United States are Cimerli (Sandoz) and Byooviz (Biogen), both referencing Lucentis (ranibizumab, Genentech/Roche).

by Early Treatment Diabetic Retinopathy Study letters at eight weeks before the third monthly intravitreal injection.

A two-sided equivalence test assessed the biosimilarity of FYB201 to ranibizumab, with an equivalence margin in BCVA of three ETDRS letters. This study involved 477 patients, with 238 randomized to FYB-201 and the rest to ranibizumab. Both treatment arms demonstrated an improvement in BCVA throughout the study period, with a mean improvement of +5.1 (FYB201) and +5.6 (reference ranibizumab) ETDRS letters at eight weeks. By week 48, the mean change from baseline was +7.8 ± 11.7 (median 8.0) for FYB201 and +8.0 ± 11.3 (median 8.0) ETDRS letters for ranibizumab. The ANCOVA least squares mean difference for change from baseline in BCVA between FYB201 and reference ranibizumab at week 48 was a negligible -0.1 ETDRS letters (90% CI -1.8 to 1.7, p>0.5).

The study also reported comparable adverse events between treatment groups, with no evidence of increased side effects, elevated intraocular pressure, or signs of ocular toxicity. Based on the study results, FYB201 was found to be biosimilar to ranibizumab in terms of clinical efficacy and ocular and systemic safety in the treatment of patients with nAMD.[9]

Additionally, a meta-analysis of four clinical trials comparing ranibizumab to four biosimilars in 1,544 eyes found no significant differences between the reference product and biosimilars for visual and anatomical outcomes, or treatment-emergent adverse events.[10]

A meta-analysis of 1,544 eyes found no significant differences between reference ranibizumab and four biosimilars for visual and anatomical outcomes, or treatment-emergent adverse events.

Other Lucentis biosimilars

As of this writing, there is one Lucentis biosimilar awaiting approval in the United States: Xlucane, or XSB-001, also known as Ximluci in Europe (Xbrane Biopharma/Stada Arzneimittel). The European Union granted approval in 2022 and the United Kingdom did so last year. The FDA last year accepted the supplemental Biologics License Application (BLA) for Xlucane and set a Biosimilar User Fee Amendment goal date for April 21, 2024.

A comprehensive comparative analytical assessment demonstrated equivalency with Lucentis in terms of change in BCVA from baseline, with a least squares mean of 4.57 (95% CI 3.54 to 5.61) vs. 6.37 for Lucentis (95% CI 5.31 to 7.42).[11] Likewise, change from baseline in central foveal thickness was also equivalent: -117.44 (95% CI, -125.33 to -109.56) for Xlucane vs. -115.14 (95% CI -123.14 to -107.14) for Lucentis.

Eylea biosimilars

No Eylea biosimilar has been approved in the United States, although one, Yesafili (Biocon Biologics), received market authorization from the European Commission and UK's Medicines and Healthcare Products Regulatory Agency. [12]

Regeneron Pharmaceuticals received pediatric exclusivity for Eylea in October 2022, which extended the U.S. market exclusivity of Eylea through to May 2024.[13] Several companies, including Biocon Biologics, Amgen and Formycon, have filed BLAs with the FDA for Eylea biosimilars. Provided there are no legal challenges to the marketing of biosimilars, we should expect the first Eylea biosimilar to hit the market by late 2024. With Eylea generating more than $9 billion in global sales, expect to see a number of lawsuits and countersuits in the days ahead.

Use and market penetration

It's apparent that the quality of physician–patient communication can have a large impact on the success of a biosimilar switch, and particularly on a phenomenon known as the "nocebo effect." This is the opposite of the placebo effect, defined as "a negative effect of a pharmacological or non-pharmacological medical treatment that is induced by patients' expectations, and that is unrelated to the physiological action of the treatment."[14]

The nocebo effect may come into play when patients are switched from a reference biological to a biosimilar and may be triggered by perceptions of biosimilars as "cheap

copies" of branded medicines. It can have a number of potential consequences—increased symptom burden, psychological distress, the number of adverse events patients experience, non-adherence, reduced quality of life, wasted medication, increased healthcare costs, more complicated treatment regimens and no apparent cost savings. Physicians can mitigate the effects of the nocebo effect by having a better understanding of biosimilars, including how they're approved, and passing this increased confidence onto their patients.[1,15]

Because the two Lucentis biosimilars were the first biosimilars to be marketed to ophthalmologists in the United States, uptake by retina specialists was initially slow. It took time to educate retina specialists about biosimilars and what they mean in terms of treatment options for patients. At the same time, some retina specialists were also concerned about intraocular inflammation-related adverse events that were observed in some patients who were treated with other approved nonbiosimilar drugs.[16] But consistent and clear messaging on the advantages of biosimilars, along with efficacy and safety data from postmarketing pharmacovigilance has played a significant role in the uptick in acceptance by the retina community.[17]

Unique challenges in ophthalmology

Biosimilar penetration in ophthalmology has encountered some unique challenges, the biggest of which is off-label Avastin (bevacizumab, Genentech/Roche) for treating retinal diseases. Although Avastin isn't FDA-approved for use in retinal diseases, multiple studies, including those led by the National Eye Institute and the DRCR Retina Network, have demonstrated equivalency between use of Avastin and the approved anti-VEGF injections. Avastin must be compounded before it's administered into the eye, and even with some cases of floaters, retina specialists have continued to prescribe it, usually as a first line of treatment before getting approval from payers for the more expensive Lucentis or Eylea.

Another factor that may be playing a role in acceptance of Lucentis biosimilars by retinal specialists is the recent approval of anti-VEGF injections such as Vabysmo (faricimab, Genentech/Roche) and Eylea HD (aflibercept, Regeneron), which have demonstrated longer durability and thus a decrease in injection frequency.

Lastly, some retina specialists have been averse to take up the Lucentis biosimilars due to financial reasons; they perceive that payers are benefiting more from the use of these biosimilars than the physicians or patients do. Biosimilar companies will need to provide retina specialists with information on how the use of biosimilars is going to benefit their practices.

The economics of biosimilars

Achieving the full cost-saving benefits of biosimilars requires patients currently receiving the reference product to switch.[1] This would be ideal, although more work needs to be done in this regard.

When Byooviz was launched in June 2022, it was listed at a price of $1,130 per 0.05-mg single-use vial, approximately 40 percent lower than the list price of Lucentis. Cimerli launched with a list price of $1,360 for the 0.5-mg dose single-use vial and $816 for the 0.3-mg dose vial.[18] This downward pressure on pricing in relation to the reference drug has definitely pushed payers to consider the biosimilars in place of the reference product.

A few companies that manage prescription drugs have chosen to remove the reference product, Lucentis, and have decided to add the two Lucentis biosimilars instead to their formulary.[19] More such instances will come to light as the biosimilars continue to push their way into the mainstream.

Bottom line

The sponsoring companies are monitoring the two approved Lucentis biosimilars in post-marketing pharmacovigilance. Since their introduction, no reports of any major issues related to their use have emerged. This suggests that these biosimilars in ophthal-

Some retina specialists have been averse to take up Lucentis biosimilars due to financial reasons; they perceive that payers are benefiting more from the use of these biosimilars than the physicians or patients do.

mology are equally safe, while achieving similar visual acuity outcomes as the reference product.

The current approved Lucentis biosimilars, Byooviz and Cimerli, have helped change access to medications for retina specialists and reduce costs for patients and payers, or both. It's imperative that we continue to have enough resources in our armamentarium to benefit patients, in terms of efficacy, access to care and reduced costs. As in other fields in medicine, biosimilars in ophthalmology will continue to play a substantial role in helping reduce barriers to access while reducing the cost of health care in general.

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Pearls for the Port Delivery System with Ranibizumab refill-exchange procedure

This modality may help decrease the treatment burden.

By Noorulain Khalid,MBBS, and Dilsher S. Dhoot, MD


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Take-home points

- The Port Delivery System with ranibizumab requires two refill-exchanges per year and can significantly reduce treatment burden for patients with neovascular age-related macular degeneration, especially those who require frequent intravitreal anti-VEGF injections.
- The refill-exchange procedure is performed in the office setting under strict aseptic conditions while using good task lighting and magnification.
- The EVP strategy (Environment, Visualization and Perpendicularity) maximizes the ability to complete refills in one attempt.
- Proper refill-exchange technique reduces the risk of complications.
- We additionally describe key pitfalls to be avoided in order to minimize the risk of complications.

Vascular endothelial growth factor has been implicated in the pathogenesis of a range of conditions, including neovascular age-related macular degeneration and diabetic macular edema.[1] As we all know, the use of anti-VEGF therapy has dramatically revolutionized the treatment of these conditions, leading to both visual and anatomic benefits.[2]

First approved in 2006, ranibizumab is an anti-VEGF monoclonal antibody fragment indicated for the treatment of neovascular age-related macular degeneration among other VEGF-driven eye conditions.[3] Anti-VEGF agents like ranibizumab have traditionally been delivered via frequent intravitreal injections as often as every four weeks. This approach results in a significant burden to patients and their caregivers. Moreover, each injection carries risk, the most feared being endophthalmitis, which risks potential sight-threatening consequences.

A recognized unmet need in the treatment of NVAMD is durability. More durable treatments have the potential to reduce cumulative long-term risk as well as burden for patients. The biologic agents currently used typically have short intraocular half-lives, thus the development of a long-acting ocular drug delivery platforms is ideal for increasing treatment intervals.[4]

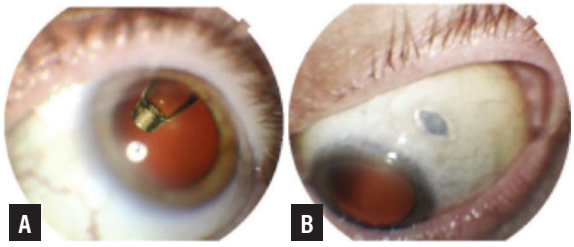

Figure 1. Port Delivery System with Ranibizumab. A) Supero-temporal gaze with implant visible through dilated pupil. B) Inferonasal gaze allowing visualization of PDS septum.[5]
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BIOS

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Consultant: Apellis Pharmaceuticals, Alimera, Allergan, Bayer, Biocryst, Coherus, EyePoint, Genentech, Iveric Bio, Ocular Therapeutix, Outlook Therapeutics, Oxular, Regeneron, RegenXBio, Roche, Novartis

Stockholder: Outlook Therapeutics and Vortex Surgical.

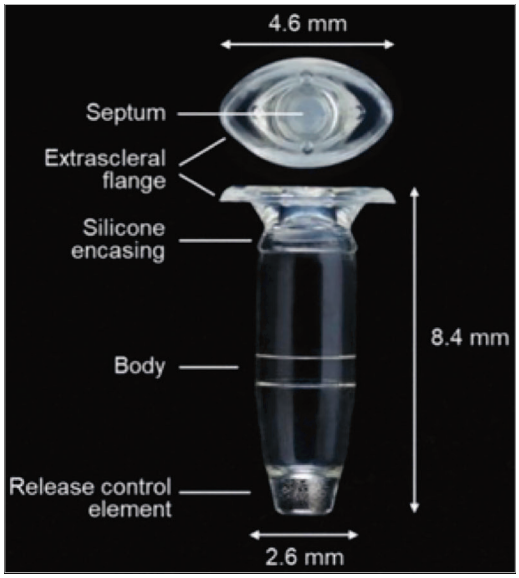


Figure 2. Components of the Port Delivery System with Ranibizumab.[9]

Here, we'll discuss one of the options to help ease this treatment burden, the Port Delivery System with Ranibizumab, and share pearls for its use in anticipation of its potential re-introduction into the U.S. market.

The Port Delivery System

The PDS was first approved by the United States Food and Drug Administration in October of 2021 for NVAMD in adults who have previously responded to at least two anti-VEGF injections.[3] The PDS allows for continuous delivery of ranibizumab and requires two refills a year thereby reducing the burden associated with frequent injections.

The PDS is surgically implanted at the pars plana and allows for sustained delivery of a customized drug formulation of ranibizumab *(Figure 1)*. The ocular implant is refilled using a proprietary refill needle via an in-office refill-exchange procedure.

The Phase III Archway trial evaluated the safety and efficacy of PDS with Ranibizumab with 24-week refill exchanges versus monthly intravitreal anti-VEGF injections for treatment of neovascular AMD in patients responsive to anti-VEGF therapy.[5] The study demonstrated noninferiority and equivalence of the PDS in achieving vision outcomes in comparison with intravitreal ranibizumab injections.[6,7]

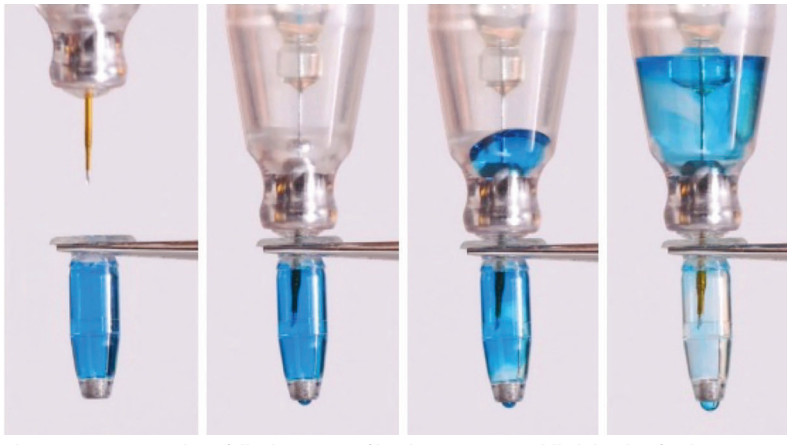


Figure 3. Demonstration of displacement of implant contents while injecting fresh new solution.[9]

Voluntary recall/potential relaunch

In October 2022, Genentech/Roche initiated a voluntary recall of the PDS ocular implant and insertion tool assembly after identifying that the implant didn't meet pre-specified standards. Refill-exchange procedures could continue in patients who had already received an implant, however.[8] A thorough root-cause investigation was conducted. Updates to the PDS implant and the refill needle have been implemented to optimize performance and mitigate the risk of septum dislodgment which has resulted in the resumption of PDS clinical studies and an anticipated relaunch in the commercial setting.

Refill-exchange

Understanding the nuances of the PDS implantation and surgical technique is vital to the successful performance of the device. The nuances of the in-office refill-exchange procedure are also equally important to understand for optimal device performance. The refill-exchange is within the wheelhouse of the practicing retina specialist, though the procedure differs from a typical intravitreal injection. The individual elements of the PDS and their dimensions are illustrated in Figure 2. The implant body can hold 20 µL of drug.

The solution within the implant body is exchanged via the refill-exchange procedure wherein existing ranibizumab is replaced with fresh drug. An injection of 0.1 mL of drug can replace >95 percent of implant contents, as demonstrated in Figure 3.[9]

Preparing for the procedure

The refill-exchange procedure is performed under strict aseptic conditions, typically in an office-based setting.

Dilated slit-lamp examination (and/or indirect ophthalmoscopy) should be carried out prior to the procedure to inspect the implant in the vitreous cavity, through the pupil. This helps to identify if septum dislodgement has occurred, in which case no further refill-exchange procedures should be performed as normal device functioning can't be assured.[10]

A slit lamp exam should additionally be conducted to identify the clock-hour location of the implant and any landmarks which may aid in septum targeting. Careful examination of the conjunctiva should be performed to exclude conjunctival retraction or erosion, implant exposure or other complications.

Following this, we recommend the Environment, Visualization, Perpendicularity (EVP) strategy which has been developed through clinical experience for a successful refill-exchange procedure.[11] EVP is explained further below.

Setting up for a successful refill-exchange procedure: EVP

The following is key to understanding the EVP concept:

- ***Environment.*** Creating an optimal environment helps to ensure a smooth procedure. The key steps for this can be remembered by the acronym SEPTM (Sterility, Eyelid Speculum, Positioning, Task lighting and Magnification).

Sterility is paramount for avoiding infectious complications; the procedure should be conducted within a sterile field, with a surgical mask and sterile gloves worn throughout *(Figure 4)*. Needles and syringes should be transferred into the field as required. A broad-spectrum microbicide such as povidone-iodine should be applied to the periocular skin, eyelid and ocular surface. An optional sterile drape may be used, and a topical antimicrobial applied to the fornix.[10]

The patient is optimally positioned supine at a 20 to 30 degree angle with the chin up. Use of an eyelid speculum facilitates easy access for the physician and frees up

Figure 4. The procedure is performed in a sterile in-office environment.[9]

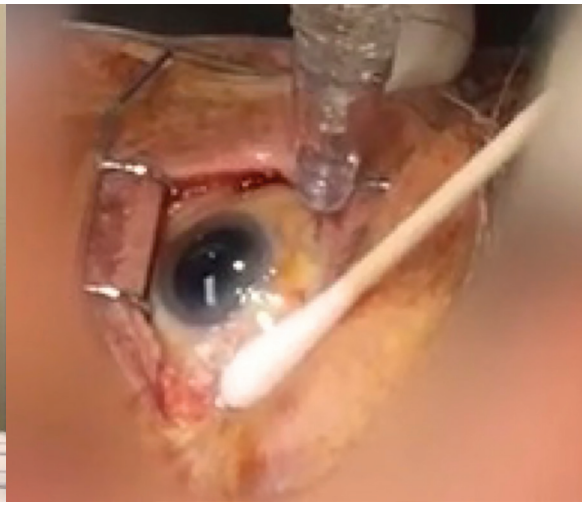


Figure 5. Stabilizing the globe during the refill-exchange procedure with a cotton-tipped applicator.[10]

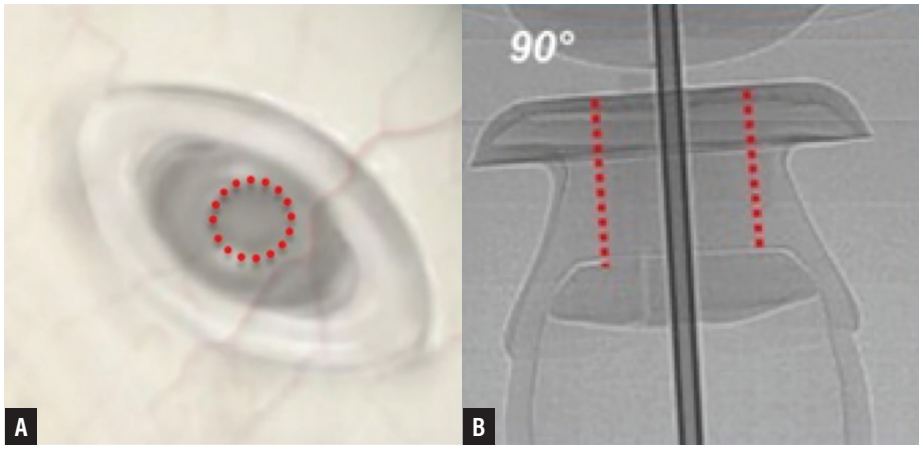


Figure 6. (A) Targeting the center of the septum. (B) Perpendicular approach to entry.[9]

their hands for precise needle positioning.

The physician should consider standing on the contralateral side to the implanted eye. This allows the physician to target the center of the implant septum while maintaining a perpendicular direction of entry of the refill needle. It additionally allows good visualization of the septum entrance point.

Lastly, optimal task lighting and magnification assist in providing a comfortable working environment for the physician.

• ***Visualization.*** The implant flange is best visualized by asking the patient to maintain an inferonasal gaze, as demonstrated in Figure 1B.

Use of a cotton-tipped applicator can be helpful to stabilize the globe, keeping the eye in the correct position for the flange to be appropriately visualized throughout the procedure. This is illustrated in Figure 5.

If visualization of the septum is proving difficult, the extrascleral flange outline may be helpful in guiding towards the expected location; the septum should be found at the intersection of the long and short axes.[10]

If septum visualization is challenging despite the above measures, transillumination through a dilated pupil may be helpful.

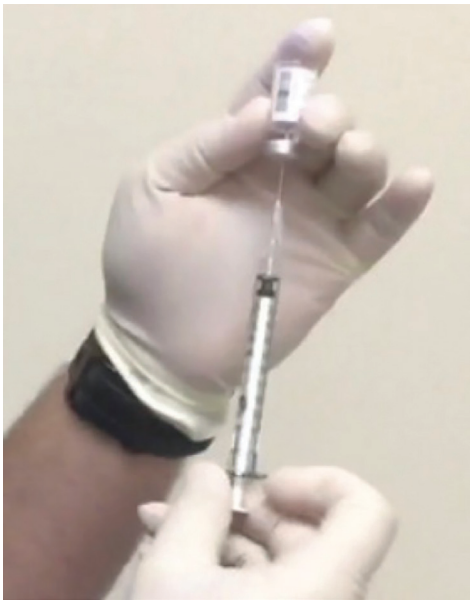


Figure 8. Non-sterile vial being held with sterile gloved hand.[10]

• ***Perpendicularity.*** The prepared syringe and refill needle should be advanced through the overlying conjunctiva and Tenon's capsule into the septum. The septum is self-sealing, enabling access to the implant body while preventing drug egression.

The refill needle should be inserted at a 90-degree angle to the implant flange, through the Tenon's capsule into the center of the septum *(Figure 6)*.

This orientation should then be maintained throughout the procedure as this ensures successful exchange and prevents implant movement *(Figure 7)*.[10]

Perpendicularity should additionally be maintained when removing the needle, which avoids damage to the septum or conjunctiva.

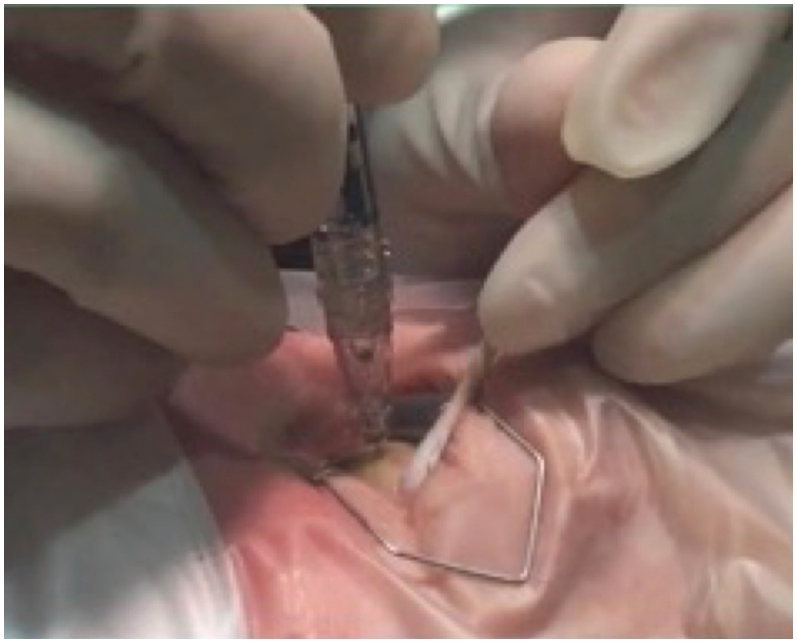


Figure 7. Maintain a perpendicular orientation throughout the procedure.[9]

Pitfalls

Some key pitfalls should be avoided when carrying out the refill-exchange procedure.

Ideally, when preparing the syringe and

drawing up the ranibizumab solution, an assistant should handle the non-sterile vial. Figure 8 shows a physician holding the vial with a sterile, gloved hand, which contaminates the hand, increasing infection risk.

Twisting should not be used as a mechanism to gain access to the implant septum through the conjunctiva and Tenon's capsule. Additionally, avoid a twisting action when attempting to reorient the angle of the needle, after entry has been gained. Twisting causes unnecessary frictional damage to both the implant septum and overlying conjunctival tissue, and may lead to septum dislodgement.

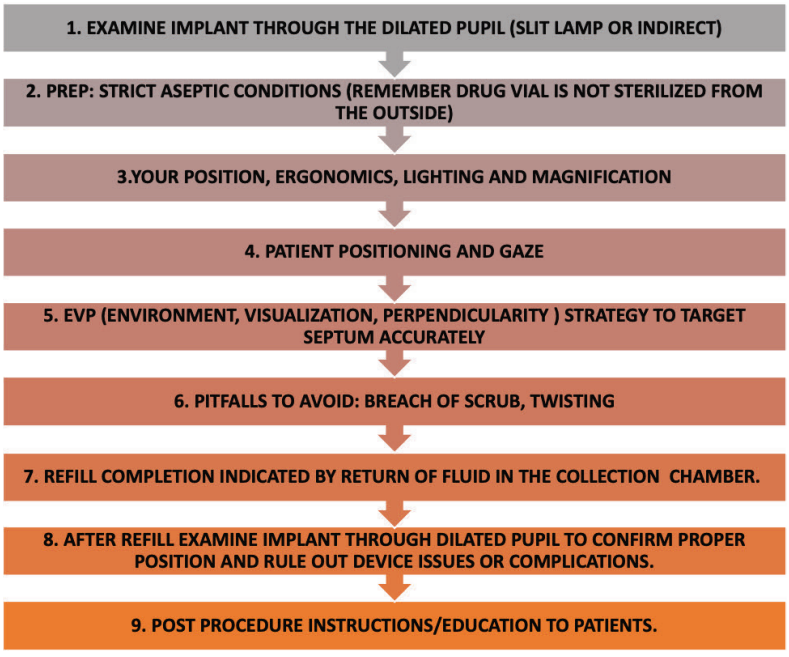
Post-procedure assessment and instructions

Following the procedure, the flange of the implant should be inspected to ensure correct positioning under the conjunctiva. There should be no subluxation or displacement. The positioning of the device inside the vitreous cavity should also be inspected via dilated indirect ophthalmoscopy/slit lamp examination, at which point complications such as vitreous hemorrhage, retinal tears, retinal detachment or lens trauma should also be ruled out.

Patients should be instructed to refrain from touching or rubbing the eye, be made aware of signs and symptoms that may require immediate medical attention and to take post-procedure drops as prescribed.

The Port Delivery System with Ranibizumab results in meaningful durability gains for patients with as little as two in-office injections per year. Following a successful PDS implantation procedure, the keys to success hinge on successful and smooth in-office refill procedures.

By keeping these key pearls and pitfalls in mind, the practicing retina specialist will be positioned for success.



A summary of key considerations while performing the refill exchange procedure.

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Clinical primer on Eylea HD: Review of the current data

Here's what we know about the new high-dose aflibercept based on the pivotal trials.

John S.Y. Park MD, FRCSC

David R. Chow MD, FRCSC

By John S.Y. Park, MD, FRCSC, and David R. Chow, MD, FRCSC

Take-home points

- Eylea HD is 8 mg aflibercept (0.07 mL of 114.3 mg/mL solution)—a four-times higher molar dose than its original counterpart (2-mg aflibercept, Eylea). It was approved by the FDA in August 2023 for treatment of DME and nAMD.
- PHOTON (for DME) and PULSAR (for nAMD), two multicenter, randomized, double-masked trials, demonstrated comparable visual and anatomical improvements between the 8-mg and 2-mg aflibercept doses, which were sustained during the two-year trial periods despite fewer injections in the 8-mg groups.
- Pooled safety analysis from PHOTON, PULSAR and CANDELA trials showed a similar safety profile of 8-mg aflibercept compared to its 2-mg counterpart.
- PHOTON and PULSAR trials were the first to demonstrate that 8-mg aflibercept can allow DME and nAMD patients to be treated immediately with every 12- or 16-week dosing after their initial monthly doses and experience clinically meaningful outcomes.

The discovery of anti-vascular endothelial growth factor treatments has been revolutionary in the world of ophthalmology and has paved the evolution of treatments for many retinal diseases. Aflibercept (Eylea, Regeneron), which was FDA-approved in 2011, is a VEGF decoy receptor and is effective in managing various retinal pathologies, including neovascular age-related macular degeneration, macular edema secondary to retinal vein occlusion and diabetic macular edema. Administered as an intravitreal injection of a 2-mg dose (0.05 mL of 40 mg/mL solution), the efficacy and safety profile of aflibercept has been demonstrated in multiple large-scale trials.

FDA approved in August 2023, Eylea HD is aflibercept administered intravitreally as an 8-mg dose (0.07 mL of 114.3 mg/mL solution), a four-times higher molar dose compared to its regular counterpart (2 mg). Recommended dosing frequency is every four weeks for the first three doses and every eight to 12 weeks (for DME) or eight to 16 weeks (for nAMD) thereafter. The approval was based on the two pivotal, multicenter, randomized, double-masked trials: PHOTON and PULSAR,[1,2] the data of which were presented in 2023 at ARVO, ASRS and EURETINA meetings. Here, we'll review the key findings of these studies.

PHOTON

The PHOTON trial compared 8-mg and 2-mg aflibercept in treatment of DME over a two-year period (96 weeks, n=658). Treatment arms consisted of:

- 2 mg every eight weeks after five initial monthly injections (2q8)
- 8 mg every 12 weeks after three initial monthly injections (8q12)
- 8 mg every 16 weeks after three initial monthly injections (8q16)

Despite fewer injections than the 2-mg arm (fewer initial monthly loading injections, and fewer total number of injections),

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the 8-mg groups maintained comparable improvements in vision and central retinal thickness (CRT) to the 2-mg group (*Figure 1*).[3] Eighty-nine and 84 percent of patients were maintained on ≥12- and ≥16-week dosing intervals, respectively, throughout the two-year period, while sustaining their anatomic and vision improvements (*Figure 2*).[3] Furthermore, as patients receiving 8-mg aflibercept were able to extend their dosing intervals in the second year (up to 24 weeks) by meeting pre-specified criteria, 44 percent met the requirements for ≥20-week intervals, including 27 percent who were eligible for 24-week dosing intervals.[3] At 96 weeks, the mean number of injections were 13.8 for the 2q8 group, 9.5 for the 8q12 group and 7.8 for the 8q16 group.[3]

Subsequent subgroup analysis revealed similar BCVA gains from baseline between 8-mg and 2-mg groups regardless of age, sex, race and ethnicity.[4] An interesting finding from ensuing univariable and multivariable analyses was that patients with more severe disease at baseline, specifically lower BCVA (BCVA ≤58 ETDRS letters) or higher central retinal thickness (CRT ≥474 µm), were more likely to need *shortening* of their intervals (down from 12- or 16-week) due to disease progression.[5] However, despite the interval shortening, these patients were still able to achieve comparable BCVA and CRT improvements.

PULSAR

The PULSAR trial compared 8 mg and 2 mg aflibercept in treatment of nAMD over a two-year period (96 weeks, n=1,009). Treatment arms consisted of:

- 2 mg every eight weeks after three initial monthly injections (2q8)
- 8 mg every 12 weeks after three initial monthly injections (8q12)
- 8 mg every 16 weeks after three initial monthly injections (8q16)

Similar to PHOTON's results, PULSAR demonstrated durable vision gains and reduction in central subfield thickness (CST)

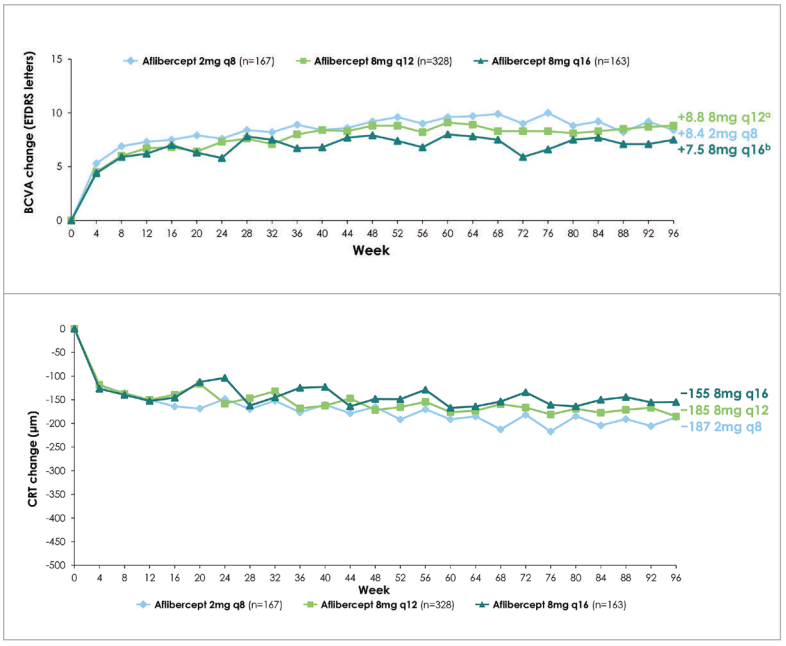

Figure 1. Mean change in best-corrected visual acuity from baseline (top), and central retinal thickness (bottom), in patients with diabetic macular edema with different aflibercept doses and intervals across two years (96 weeks), as per the PHOTON trial.
[a]*p*<0.0001 (one-sided test for non-inferiority at four-letter margin vs. 2 mg q8 group).
[b]*p*=0.0044 (one-sided test for non-inferiority at four-letter margin vs. 2 mg q8 group.
(Adapted from Do DV. Aflibercept 8 mg for diabetic macular edema: 2-Year results of the Phase II/III PHOTON trial. Presented at the American Society of Retina Specialists 2023 annual meeting, July 28-August 1, 2023.)

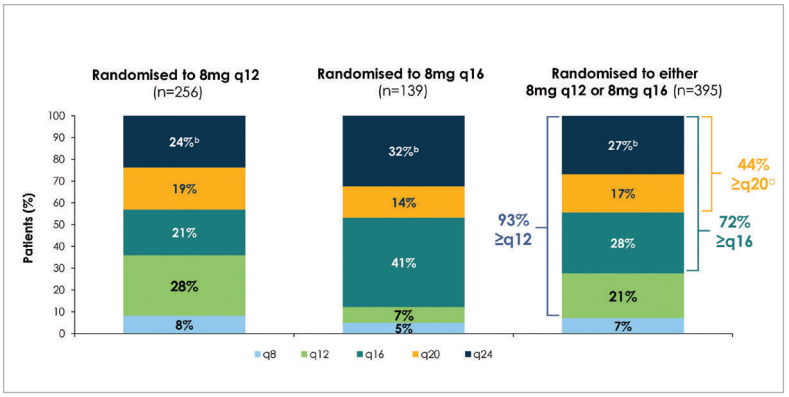

Figure 2. Proportion of patients with diabetic macular edema with their last assigned aflibercept dosing and treatment intervals (in number of weeks) at the end of two years (96 weeks), as per the PHOTON trial.
[a]Treatment intervals were extended in Year 2 if patients had <5-letter loss in BCVA from Week 12 and CRT <300 µm (or <320 µm on SPECTRALIS). ***(Adapted from Do DV. Aflibercept 8 mg for diabetic macular edema: 2-Year results of the Phase II/III PHOTON Trial. Presented at the American Society of Retina Specialists 2023 annual meeting, July 28-August 1, 2023.)***

with 8-mg aflibercept at extended dosing intervals that are comparable to the 2-mg group (*Figure 3*), with 88 percent treated on ≥12-week dosing interval at the end of two years *(Figure 4)*.[6] As with PHOTON, patients receiving 8-mg aflibercept in the PULSAR trial were able to extend their dosing intervals in the second year by meeting pre-specified criteria, and 71 percent met the extension criteria for ≥16-week dosing intervals, including 47 percent for ≥20-week intervals and 28 percent for 24-week intervals.[6] At 96 weeks, the mean number of injections was 12.8 for the 2q8 group, 9.7 for the 8q12 group, and 8.2 for the 8q16 group.[6]

Subgroup analysis showed consistent BCVA gains from baseline between 8 mg and 2 mg groups regardless of baseline BCVA, CST, choroidal neovascular membrane type (classic or occult) or race.[7] Furthermore, post-hoc analysis revealed similar baseline BCVA, CST and CNVM size across all groups that maintained ≥12-week dosing intervals versus those that required interval shortening, which suggests the need for interval shortening may not be influenced by those baseline characteristics.[8] A separate subgroup analysis comparing patients with polypoidal choroidal vasculopathy (PCV) to the overall population showed comparable improvements in BCVA and CST across all three treatment arms up to 48 weeks.[9] Furthermore, no significant difference was found between PCV group and overall population with respect to being able to be maintained on a ≥12-week interval.[9]

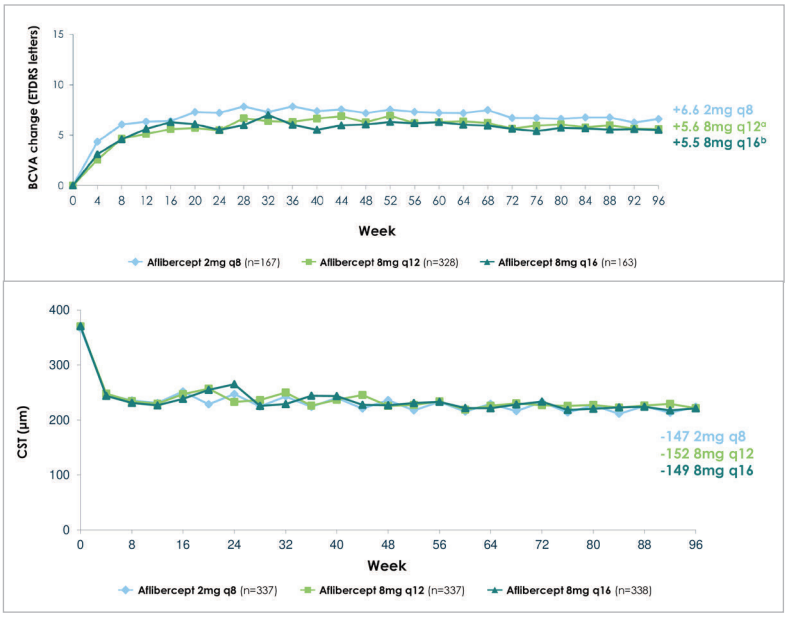

Figure 3. Mean change in best-corrected visual acuity (BCVA) from baseline (top), and central subfield thickness (bottom), in patients with neovascular age-related macular degeneration (nAMD) with different aflibercept doses and intervals across two years (96 weeks), as per the PULSAR trial. [a]*p*=0.000 (nominal)(one-sided test for non-inferiority at four-letter margin vs. 2mg q8 group). [b]*p*=0.0007 (nominal)(one-sided test for non-inferiority at four-letter margin vs. 2mg q8 group). *(Adapted from Lanzetta P, et al. Intravitreal aflibercept 8 mg injection in patients with neovascular age-related macular degeneration: 60-Week and 96-Week Results from the Phase III PULSAR trial. Presented at the European Society of Retina Specialists 2023 annual meeting, October 5-8, 2023.)*

Safety

One of the proposed advantages of Eylea HD was that it provides a new treatment option that builds upon the established efficacy and safety profile of 2-mg aflibercept. Both PHOTON and PULSAR demonstrated a similar safety profile of the 8-mg aflibercept to the 2-mg aflibercept through the two years of the respective trials.[3,6] Most common adverse reactions in the 8-mg aflibercept groups were cataract, conjunctival hemorrhage, increased intraocular pressure, ocular discomfort/pain/irritation, vision blurring, vitreous floaters, vitreous detachment, corneal epithelial defect and retinal hemorrhage.[3,6]

Pooled safety analysis performed with data across PHOTON, PULSAR and CANDELA, which was a Phase II, multicenter, randomized, single-masked study comparing 8-mg and 2-mg aflibercept doses for nAMD,[10] also revealed comparable safety profiles between the 8 mg and 2 mg groups of aflibercept, with low incidence of intraocular inflammation.[11] Serious adverse events were infrequent and consistent between the two doses: retinal detachment (0.4 percent and 0 percent); increased IOP (0.2 percent and 0 percent); and vitreous hemorrhage (0.2 percent and 0 percent) for aflibercept 8 mg and 2 mg, respectively.[11] There were no cases of endophthalmitis or occlusive retinal vasculitis.[11] There are limitations of the study in that it's

a pooled analysis and the data was limited to available data for the PHOTON, PULSAR and CANDELA trials, but the overall safety of 8-mg aflibercept appears to be consistent with the known safety profile of aflibercept 2 mg from previous clinical trials.

BOTTOM LINE

The PHOTON and PULSAR trials demonstrated comparable visual and anatomical improvements between the 8-mg and 2-mg aflibercept groups in treating DME and nAMD, respectively.[3,6] These benefits were sustained in the 8-mg group throughout the two years of trial duration despite the longer treatment intervals of every 12 or 16 weeks, which allowed for fewer total injections. Just as important, in both PHOTON and PULSAR, as well as the pooled safety analysis of PHOTON, PULSAR and CANDELA, the rate of adverse reactions in the 8-mg aflibercept group was infrequent and consistent with the known rate for the 2-mg aflibercept.[3,6,10,11]

Being able to unite improved clinical outcomes with reduction in treatment burden, all while not compromising safety, is an area of ongoing interest, and can make a significant impact in patient care. The 8-mg aflibercept clinical trials were the first to demonstrate that DME and nAMD patients can immediately be treated with every 12- or 16-week dosing intervals after their initial monthly doses and still experience clinically meaningful outcomes, while having a similar safety profile of the previously established profile of 2-mg aflibercept.

There are more questions that need to be addressed, such as the optimal dosing regimen, potential long-term implications of higher volume (0.07 mL) injections, as well as comparative data to other anti-VEGF agents, including recently approved faricimab (Vabysmo, Genentech). More research is warranted, and as the use of Eylea HD becomes more commonplace, more data is certainly expected, but the presented data thus far looks promising in improving patient care.

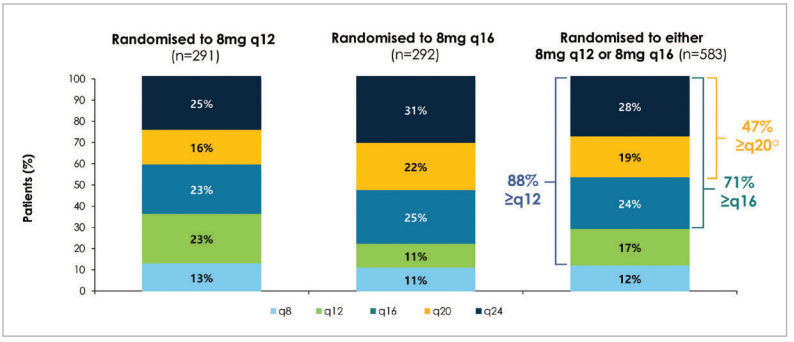

Figure 4. Proportion of patients with neovascular age-related macular degeneration with their last assigned aflibercept dosing and treatment intervals (in number of weeks) at the end of two years (96 weeks), as per the PULSAR trial.
[a]Dosing intervals were extended in Year 2 if participants met the following criteria: 1) less than 5-letter loss in BCVA from Week 12 AND 2) no fluid at the central subfield AND 3) no new foveal hemorrhage or neovascularization. *(Adapted from Lanzetta P, et al. Intravitreal aflibercept 8 mg injection in patients with neovascular age-related macular degeneration: 60-week and 96-week results from the Phase III PULSAR Trial. Presented at the European Society of Retina Specialists 2023 annual meeting, October 5-8, 2023.)*

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Management options for PVR

What you need to know as a vitreoretinal surgeon.

By Ryan S. Huang MSc, MD(C), Tina Felfeli, MD Efrem D Mandelcorn, MD, FRCSC

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Proliferative vitreoretinopathy continues to be a concern in retinal detachment surgery, presenting significant challenges in achieving optimal surgical outcomes. Despite advancements in surgical methods and a deeper comprehension of PVR's pathophysiology, postoperative anatomical and visual results remain suboptimal.[1] This has prompted the exploration of various adjunctive pharmacological therapies in conjunction with surgical intervention.

Current mainstay

PVR is predominantly implicated in postoperative RD complications, arising from the proliferation and contraction of cellular membranes within the vitreous, leading to tractional RD and persistent retinal folds.[2] The Retina Society Terminology Committee's classification (A-D) delineates PVR severity, ranging from minimal to massive, based on retinal changes. Subsequent revisions have enhanced this classification, incorporating the anatomic location and contraction type to better guide treatment strategies.[3]

The cornerstone of PVR treatment involves surgical intervention, primarily via pars plana vitrectomy accompanied by membrane peeling.[4]

The operative strategy for addressing PVR closely mirrors that of standard primary RDs, with the key distinction being the greater degree of retinal traction in PVR due to the presence of membranes and bands as opposed to vitreous gel. Consequently, surgeons may adapt their techniques to meticulously separate these membranes to facilitate retinal reattachment. In instances where a scleral buckle wasn't placed during the initial repair of a primary RD, its insertion might be beneficial in the subsequent vitrectomy for PVR. Nonetheless, the necessity for a scleral buckle may be obviated if an extensive inferior retinectomy is anticipated.

The overarching aim of PVR surgery is the meticulous removal of epiretinal and subretinal membranes, which often necessitates bimanual surgical maneuvers to delicately handle the retina and its adherent membranes. In most cases, silicone oil is preferred for long-term internal tamponade, although perfluoropropane (C_3F_8) gas can be an alternative for less severe presentations.[5]

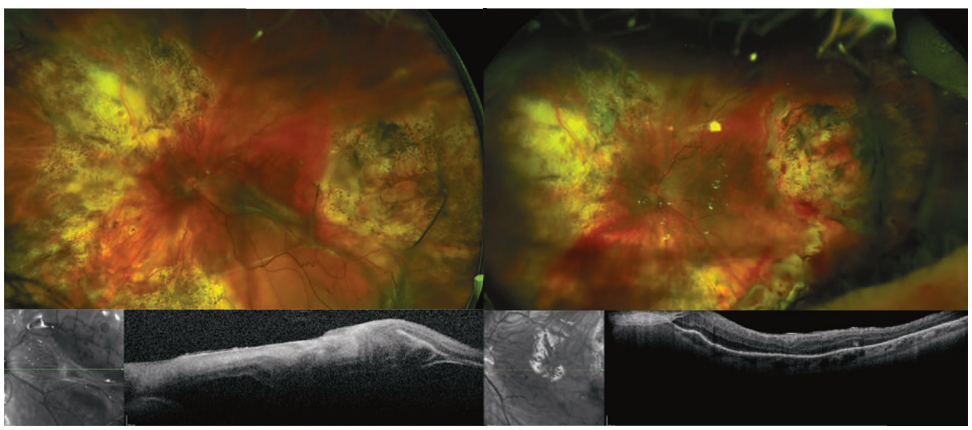

Figure 1. Preoperative view shows temporal retinal detachment with marked peripheral chorioretinal scarring, proliferative vitreoretinopathy, subretinal bands in the macula and a star fold with adjacent retinal break. Corresponding optical coherence tomography shows disorganized retinal laminations with tractional elevation.

Figure 2. Postop, the scleral buckle appears to support the area of inferior traction. Previous areas of macular proliferative vitreoretinopathy and subretinal bands have been released with no significant traction on the retina. Optical coherence tomography shows relief of macular traction with resolution of subretinal bands and fluid.

BIOS

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Despite surgical advances, the prevalence of PVR post-RD repair hasn't significantly diminished, with most cases manifesting within three months postoperatively.[6] In addition, postoperative outcomes following pars plana vitrectomy remain suboptimal, amplified by the recurrence of RD due to PVR.[7] Considering these challenges, the investigation of new pharmacological agents aims to enhance both anatomical and functional results in PVR treatment.

In the ongoing search for effective management of PVR, no pharmacological agents have yet received approval for use as adjuncts to surgical treatment. The pathogenesis of PVR, characterized by inflammation, cellular proliferation and fibrosis has guided the investigation of various drugs, including corticosteroids, methotrexate and other antiproliferative agents, with promising results in preclinical studies that are now advancing to clinical trials *(Table 1)*.

Corticosteroids

Corticosteroids were among the first pharmacological interventions investigated, primarily due to their extensive anti-inflammatory and antiproliferative properties, diverse administration routes and minimal evidence of retinal toxicity.[8] Preclinical studies have illustrated the potential of corticosteroids in mitigating PVR. Notably, one group of researchers conducted research on a rabbit model, observing that a 2-mg dose of triamcinolone acetonide significantly reduced the occurrence of PVR-associated RD from 90 percent to 56 percent.[9]

Despite these encouraging preclinical outcomes, clinical trials have yielded inconsistent results. A particular trial evaluating the adjunctive use of triamcinolone in 75 eyes with RD and advanced PVR undergoing vitrectomy with silicone oil tamponade found no significant difference between treated patients and controls.[10] Emerging evidence from sustained-release systems suggests they can maintain therapeutic drug concentrations for extended periods, although a two-year randomized trial found no significant difference in anatomical success or visual acuity when comparing dexamethasone implants to placebo in PVR patients.[11] While preclinical data on corticosteroids for PVR management are promising, clinical application has produced mixed results, emphasizing the need for further research to define their role in PVR therapy.

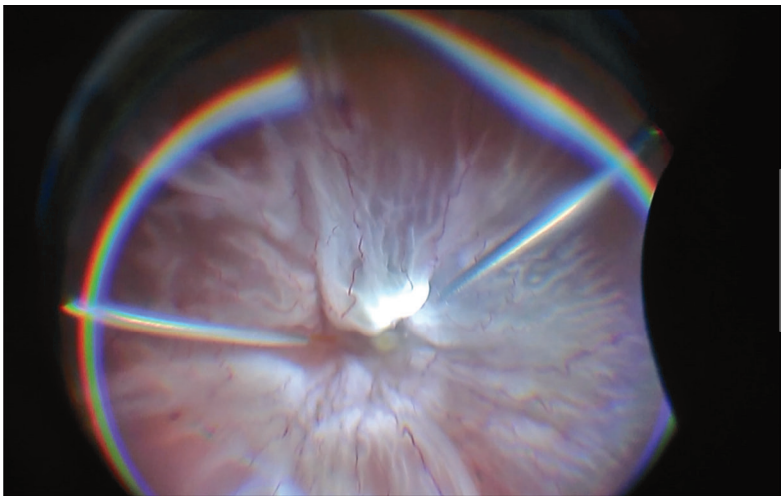

Figure 3. When dealing with proliferative vitreoretinopathy, Perfluoro-n-octane can stretch out or loosen up the retina. Also, it lets the surgeon judge the possibility to reattach the retina using a direct PFO-to-oil exchange. ***(John Kitchens, MD)***

Antiproliferative and antineoplastic agents

Methotrexate (MTX), a folate antagonist with antiproliferative and anti-inflammatory effects, has been under investigation for its potential in managing PVR.

Laboratory studies have indicated that MTX can inhibit the proliferation and migration of retinal pigment epithelium cells and induce apoptosis without the photoreceptor toxicity associated with other agents like 5-fluorouracil (5-FU).[12]

Clinically, MTX has been tested in various dosages and delivery methods, including intraoperative and postoperative intravitreal applications. However, the benefits of MTX haven't always been statistically significant. For example, a randomized study found a lower but not statistically significant rate of retinal redetachment in patients receiving intravitreal MTX compared to controls.[13] Despite this, a study involving high-risk eyes

demonstrated a considerable reduction in PVR incidence with MTX treatment during surgery, suggesting a potential prophylactic effect.[14]

Daunomycin, an anthracycline known for its role in inhibiting cell proliferation and migration, has been evaluated for its effectiveness in PVR management through animal studies.[15,16] Its use as an adjunct to vitrectomy in patients with advanced PVR was assessed in a recent study showing a higher rate of retinal reattachment compared to controls, albeit with non-significant differences in visual acuity and requiring fewer additional surgeries.[17] Research has also delved into the potential of low-molecular-weight heparin (LMWH) and 5-FU in PVR prevention, with a notable randomized trial demonstrating a decreased incidence of postoperative PVR and fewer re-operations in the treatment group, although no change in visual acuity was observed.[18] Another trial, however, didn't replicate these significant findings, indicating variability in treatment outcomes.[19]

Retinoic acid, an inhibitor of RPE cell growth, has been shown in a study to significantly improve retinal attachment and ambulatory vision, and decrease macular pucker formation, compared to a placebo.[20] In addition, mitomycin C and a host of other antiproliferative compounds have displayed promising results in preclinical stud-

Retinoic acid, an inhibitor of RPE cell growth, has been shown in a study to significantly improve retinal attachment and ambulatory vision, and decrease macular pucker formation, compared to a placebo.[20]

Table 1. Summary of evidence of pharmacological agents in the management of PVR

Adjunctive Treatment	Current Evidence
Corticosteroids	
Triamcinolone acetonide	In animal model, reduced incidence of PVR-related RD from 90 to 56 percent with optimal dosage of 2 mg.[9] In RCT, no significant differences in adjunctive intraoperative triamcinolone efficacy.[10] In observational study, mixed results; retina attached in 10 out of 13 eyes, variable visual benefits.[27]
Prednisolone	In RCT, visual improvement and 87.5-percent success in retinal reattachment.[28]
Dexamethasone	In an animal model, didn't mitigate the severity of experimental PVR.[29] In RCT, significant anatomical and functional results from dexamethasone implant.[11]
Antiproliferative and Antineoplastic Agents	
Methotrexate	*In vitro* study, decreased RPE cell proliferation and migration, induced cell apoptosis, no toxicity to photoreceptor cells.[12] In observational studies, varying results, with some showing reduction in PVR incidence and others showing no significant benefit.[30,31] In RCT, a lower, but not statistically significant, redetachment rate in MTX group.[13]
Daunomycin	In an animal model, effective in preventing RD.[16] In RCT, slight improvement in complete retinal reattachment, lower number of reoperations needed.[32]
LMWH and 5-FU	In an animal model, reduce rate of tractional RD.[33] In RCT, significant decrease in incidence of postoperative PVR and in reoperation rate.[18]
Retinoic acid	*In vitro* study, inhibits growth of RPE cells.[34] In RCT, promising results in terms of retinal attachment and reduciton of macular pucker formation.[20]
Mitomycin C	In an observational study, there was a beneficial effect in reduction of post-traumatic PVR rate, and improvement in anatomical and functional results.[22]
Anti-VEGF Agents	
Ranibizumab	In an animal model, effective in reducing bioactivity of vitreous and preventing PVR.[23]
Bevacizumab	In an observational study, no significant difference in BCVA, retinal reattachment rate or epiretinal membrane formation.[25] Meta-analysis, not effective in lowering retinal redetachment rate or improving visual acuity.[26]

RD: retinal detachment, PVR: proliferative vitreoretinopathy, RPE: retinal pigment epithelium, RCT: randomized controlled trial, BCVA: best-corrected visual acuity, LMWH: low-molecular-weight heparin, 5-FU: 5-fluorouracil, Anti-VEGF: antivascular endothelial growth factor.

ies, though their clinical efficacy and safety remain to be confirmed in human trials.[21,22] Presently, topotecan is under Phase II clinical investigation for its antifibrotic and antiproliferative effects in PVR-related RD.

Anti-VEGF agents

Recent research has underscored the influence of growth factors in the development of PVR, particularly noting the role of vascular endothelial growth factor A (VEGF-A) in activating the platelet-derived growth factor receptor α, a key player in PVR's etiology.[23]

Preclinical studies have assessed ranibizumab, an anti-VEGF medication that targets all VEGF-A isoforms, demonstrating its efficacy in reducing vitreous bioactivity and preventing PVR in animal models.[24]

However, the transition from animal to clinical studies hasn't met with similar success. Prospective studies, including one that evaluated the effects of repeated bevacizumab injections within a silicone oil medium on both the anatomical success and best-corrected visual acuity, haven't shown significant improvements in patients with PVR-induced RD.[25]

These findings align with a meta-analysis of 133 studies, which concluded that bevacizumab does not effectively reduce rates of retinal redetachment nor enhance visual outcomes in patients undergoing vitrectomy for PVR. This gap between promising animal research and less conclusive clinical results highlights the complexities of PVR treatment and the need for further investigation into effective therapies.[26]

Bottom line

Collectively, these findings highlight a landscape of potential, yet unapproved, adjunctive pharmacotherapies for PVR. The journey from promising preclinical results to clinical application remains fraught with variability, necessitating further rigorous research to establish efficacy and safety profiles before these therapies can be recommended as part of PVR management protocols. RS

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Recent research has underscored the influence of growth factors in the development of PVR, particularly noting the role of vascular endothelial growth factor A in activating the platelet-derived growth factor receptor α.

What does it mean to be an influencer?

In today's world, any retinal specialist can become an influencer.

By Jayanth Sridhar, MD

I was sitting on my couch watching the 2024 NBA Slam Dunk Contest while texting with my basketball-enthusiastic friends when Jaylen Brown of the Boston Celtics brought a fan from the audience to sit in a chair so he could jump over him while dunking. The graphic provided by Turner Sports identified this fan as "Kai Cenat." One of my friends (and fellow retinal surgeon) immediately group texted, "I must be finally too old because I have no idea who Kai Cenat is." A quick Google search revealed that he is an "online streamer and YouTuber," otherwise known as an influencer.

The Rise of Influencing

The term "influencer" predates the rise of social media. It refers to a person or entity whose behavior or statements trickle down to influence the behavior of followers. Celebrities such as Coco Chanel and Michael Jordan were influencing our spending habits decades before the first social media applications were released. The first online influencers were bloggers, but digital influencing skyrocketed with the release of Instagram in 2010. A picture is worth a thousand words and, as it turns out, billions of dollars. By 2013, Instagram included paid ads, and influencers could directly share products they've enjoyed and get paid for it.

Though influencing isn't new, what has changed with social media is the democratization of becoming an influencer. Anyone with a working smartphone and an idea can now collect a base of followers with interesting posts, pictures, livestreams and/or TikTok videos. Similarly, social media has leveled the playing field for medical influencers. The medical influencers of yesteryear were a small group of key opinion leaders who were at the top universities and/or medical practices, had access to the most clinical and research knowledge, and would speak at congresses and smaller regional meetings to educate the physician public. For retina, the intravitreal injection boom heralded a prodigious generation of influencers who were looked to for guidance on which drug to use, how to decide treatment initiation and cessation, and how to interpret clinical trial results in the context of real-world practice. Drug companies paid, and continue to pay, KOLs (me included) to deliver branded drug and disease-state lectures. Interests are aligned: greater adoption of newer medication may result in superior patient outcomes and supports the pharmaceutical industry's financial motivations.

Influencing the Retina Space

Democratization via social media exists in the retina space for budding influencers. Exciting surgical videos, podcast discussions of the literature, commentary on international meeting highlights, and reposting of results of peer-reviewed publications are just a few of the ways any retinal specialist can build a following. With followers comes *influence*, and with *influence* comes both responsibilities to be ethical and, whether they are fair or not, perceptions of clinical and academic competence. For a retinal specialist hoping to become a KOL, social media is now the most easily accessible route, as it doesn't rely on connections via mentors, institutional affiliations, or perceived pedigree based on training background.

For social media, influencing has been predicted to merge with AI, corporate interests and international politics into a murky and potentially dark field of computer-generated influencing, where bots may produce images and content of purported human beings who accumulate followers. Hopefully, we're able to stave off this dangerous tech from infiltrating the medical consciousness, as prescribing patterns should be kept sacrosanct. For now, enjoy those LinkedIn, Instagram and TikTok retina images and videos. Just remember to take it all with a grain of salt until we devise better ways to validate and cross-check digitally distributed content.

BIO

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

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

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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.

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