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Retina 2023

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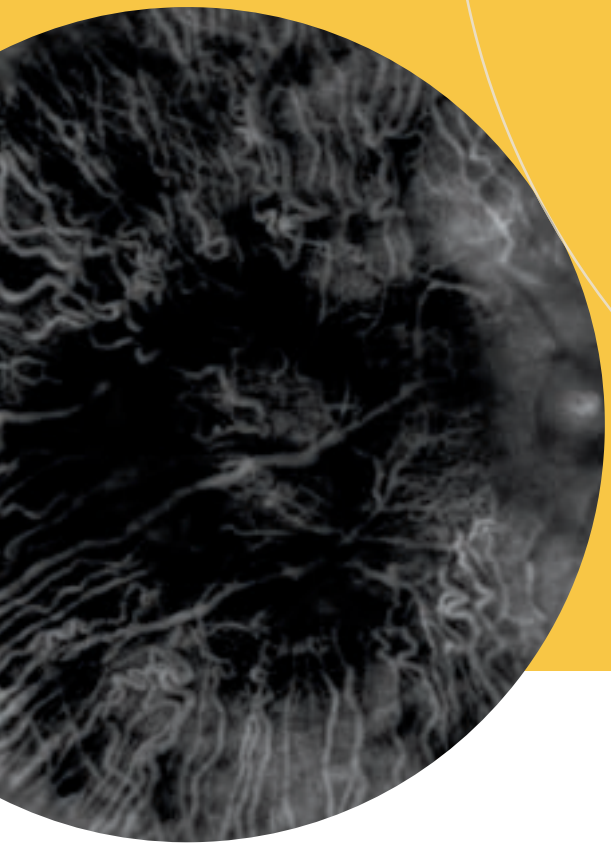


Protecting Sight. Empowering Lives.®

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL

GA unravels so much

Save retinal tissue by slowing progression[1–3]

INDICATION

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

IMPORTANT SAFETY INFORMATION

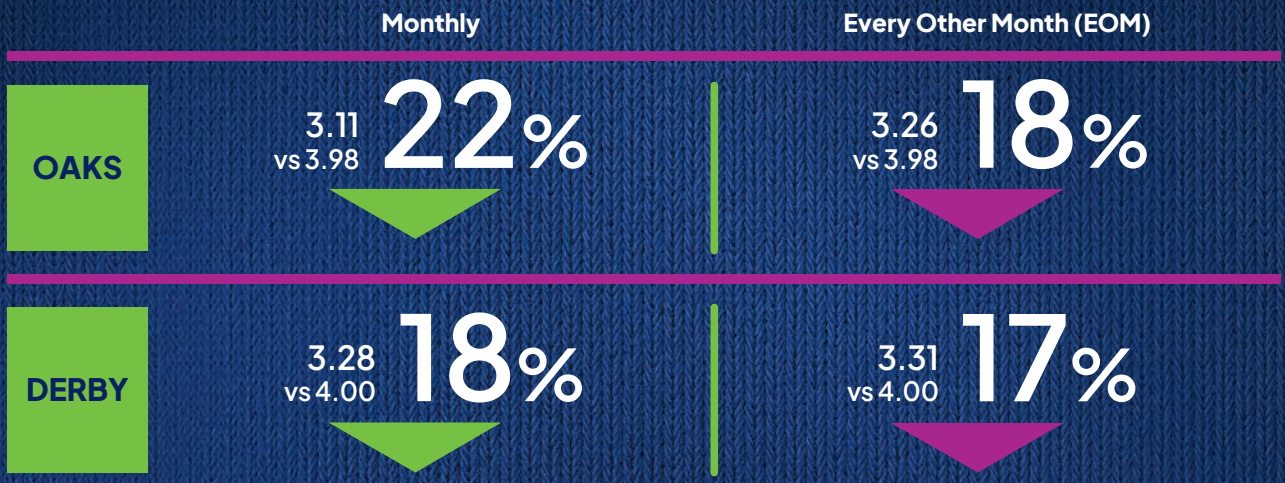
CONTRAINDICATIONS

- 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.
- **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.

SYFOVRE achieved continuous reductions in mean lesion growth rate* (mm^2) vs sham pooled from baseline to Month 24[1]



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

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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

ADVERSE REACTIONS

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

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 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.

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

Apellis

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

INDICATIONS AND USAGE

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CONTRAINDICATIONS

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Active Intraocular Inflammation
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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.

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 neovascular AMD, endophthalmitis, and retinal detachments. 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-17Feb2023-1.0

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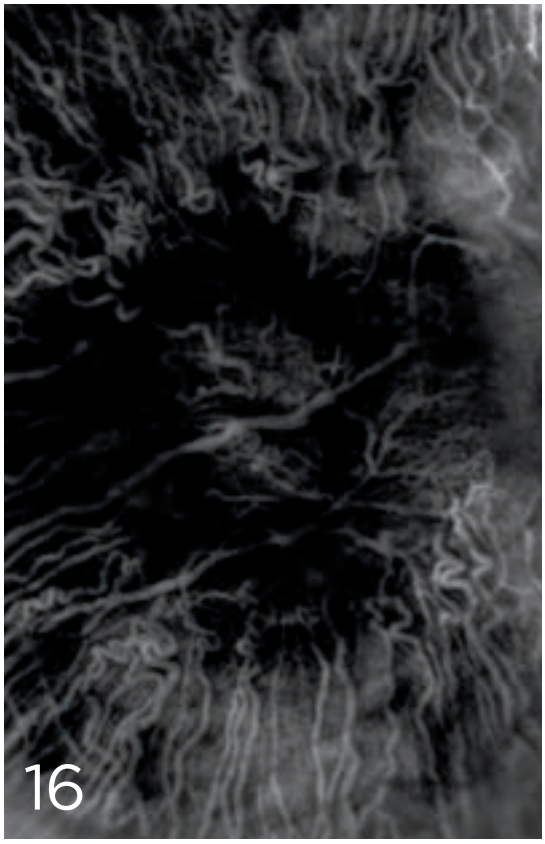

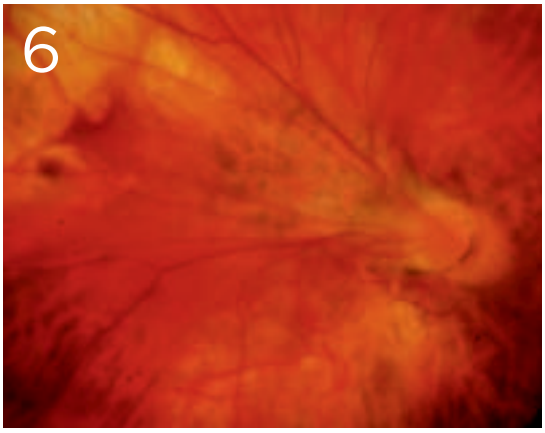

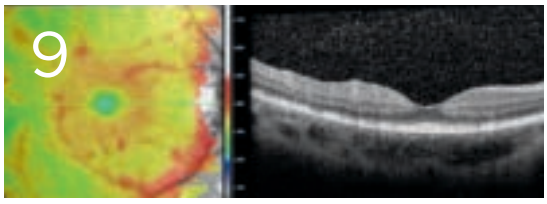

EyeNet Selections
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REPRINTS FOR
RETINA SUBSPECIALTY DAY
AT AAO 2023

COVER PHOTOGRAPH
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When Babies With ROP Grow Up

Ophthalmologists have long considered retinopathy of prematurity (ROP) to be a strictly neonatal disease. However, a paradigm shift has occurred. Advances in care and treatment of preemies have allowed babies to live longer, and laser ablation and intravitreal anti-VEGF therapy have led to improvements in ocular outcomes. Years later, ophthalmologists are identifying significant late sequelae. Now, ROP is considered a lifelong disease that requires routine follow-up.

"The problem we're seeing, though, is that when these patients get into their teenage years, they move on to adult specialists who may not necessarily be comfortable treating pediatric retinal diseases, including ROP," said Mary Elizabeth Hartnett, MD, at Stanford University in Palo Alto, California. As a result, a large portion of this population may not receive the care they need, she said. "So, all of us—from comprehensive ophthalmologists to retinal surgeons—need to better understand ROP in all of its presentations."

Lifelong Retinopathy: Clinical Features

"We used to think of ROP as a disease of prematurity and even sometimes gave parents the impression that their child was safe from ROP once they grew out of the at-risk window," said Peter Campbell, MD, MPH, at Oregon Health & Science University in Portland. "However, as more and more infants survive to adulthood, we're finding that many of them have potentially vision-threatening retinal disease, even without a known history of severe ROP."

Parsing what is abnormal. As is the case with other retinal diseases, sometimes there are no long-term complications, even if the retina looks abnormal, said Dr. Campbell. For example, the retinal vessels might appear a little more dilated and tortuous, the optic nerve might be a little thin, or the anterior segment a bit shallow.

What to look for. On the other hand, patients can develop forms of myopia as well as be at risk for a multitude of late sequelae and sight-threatening conditions regardless of whether they received prior neonatal treatment, said Dr. Hartnett, and the challenge is we don't know which patients will develop future complications from prematurity.

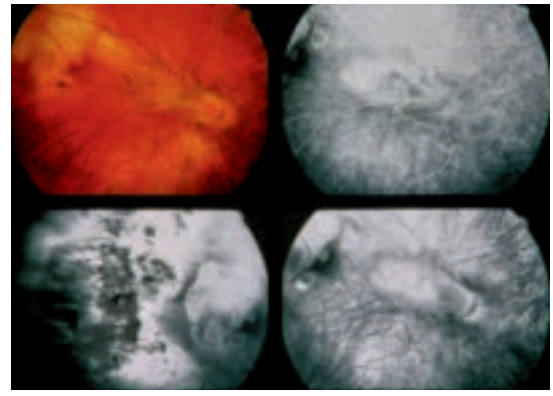
Among the most common long-term complications of the anterior segment are the following:

- increased lens thickness,
- angle-closure and other forms of glaucoma,
- a highly curved cornea,
- early development of cataracts,
- strabismus, and
- amblyopia.

Posterior segment complications include:

- rhegmatogenous, tractional, and/or exudative retinal detachments,
- retinoschisis,
- retinal folds and tears,
- abnormal foveal development,
- persistent avascular retina, and
- other retinal vascular disorders.

Cortical visual impairment. In addition to structural changes that can interfere with VA, ROP patients can have other neurologic and ophthalmologic manifestations of prematurity as they age, said Dr. Hartnett. "Although it's not completely understood, cortical visual impairment is one of the most common causes of bilateral visual impairment worldwide and affects children born prematurely," she said. This neurological form of visual impairment is a result of damage to the visual processing centers of the brain and, even in seem-



AGING AND ROP. *Fundus photos from a 35-year-old who developed ROP as an infant.*

Originally published in May 2023

BY MIKE MOTT, INTERVIEWING **PETER CAMPBELL, MD, MPH, KIMBERLY A. DRENSER, MD, PHD,** AND **MARY ELIZABETH HARTNETT, MD.**

ingly healthy eyes, it can result in photophobia, deficient color vision, and other visual field defects. In addition, some evidence suggests that some abnormalities related to cortical visual impairment may exist at the level of the retina, she said.

"We are still learning a lot about the incidence of sight-threatening disease in this population and what happens as patients age," Dr. Campbell said.

Age-Based Nuances

"We're in an era now where ophthalmologists are seeing adolescents and adults across the three generations of ROP treatment," said Kimberly A. Drenser, MD, PhD, a retina specialist in Royal Oak, Michigan. There are specific nuances to be aware of for each age group that will help ophthalmologists to identify and monitor ex-ROP patients, she said.

The "before" times. Baby Boomers can be distinguished by their age and their past medical care, said Dr. Drenser. These older adults have a different presentation from later generations of children who had ROP, she said. Because they were considered miracle babies at the time—born before newer technologies were available—they are aware of and generally disclose their history, so they are fairly easy to identify.

The ablation years. In 2004, laser photocoagulation became the standard of care for type 1 ROP after the Early Treatment for Retinopathy of Prematurity study reported the efficacy of laser ablative therapy in high-risk eyes.[1] Targeting the peripheral avascular retina that incites VEGF production, laser ablation presented several advantages over prior cryotherapies, including precise delivery with less ocular trauma.

Because of the scarring involved in ablative therapy, these eyes are generally easy to identify in adolescents and adults, said Dr. Drenser. "Most ophthalmologists, even if they are not retina specialists, will recognize these laser scars and ask the patient if they were born premature," she said.

And because the therapy has been common practice for almost two decades, ophthalmologists have a general sense of what to expect as children age, said Dr. Drenser. "As the eye elongates and the vitreous changes, these patients tend to have higher levels of myopia and can have some atypical vitreoretinal traction," she said. "But our most recent retrospective analysis has shown that this ablation generation has the least risk of retinal tears and detachment."

The anti-VEGF era. Over the past 10 years, treatment has shifted from laser photocoagulation to intravitreal anti-VEGF injection. Compared with ablation, anti-VEGF treatment is less time-consuming and less technically challenging, and it subjects infants to less stress than the laser procedure, which requires deep sedation or anesthesia, said Dr. Campbell.

Persistent avascular retina. Although anti-VEGF permits some ordered intraretinal vascularization to develop in the peripheral avascular retina, not all the peripheral avascular retina becomes vascularized in all infants. Therefore, patients treated with anti-VEGF agents can be at significant risk of persistent avascular retina as they age, said Dr. Campbell. This thinned, avascular tissue can lead to atrophic retinal holes, lattice degeneration, and retinal tears and detachment.

"This is a critical issue," said Dr. Drenser, "because some studies are showing that up to 90% of kids treated with anti-VEGF are not regrowing and developing normal retinal tissue and will have some degree of avascular retina moving forward." And unlike the ablated population, this anti-VEGF group has an increased risk of morbidity that increases with every year of life because of how the avascular retina weakens and atrophies over the course of time, she said.

As to why incomplete retinal vascularization occurs, more research is needed, said Dr. Campbell. "In the laser era, once you treated a baby, there was no significant avascular retina," he said. "Either you had vascularized retina or you had lasered retina. In the anti-VEGF era though, the disease regresses and you have the opportunity for progressive vascularization, but this is occurring variably in some patients, and we don't know exactly why."

And yet, Dr. Hartnett said, peripheral avascular retina existed in some ROP patients who had regression of disease without laser treatment in the time before anti-VEGF treatment. "Some developed retinal detachments, but we don't know how many with peripheral avascular retina had long-term sequelae. More research is needed," she said.

The untreated. This begs another important question, said Dr. Campbell. How often does nonvascularization occur in "normal" untreated ROP patients who did not previously meet type 1 criteria? "Many times, we've told parents that their baby is no longer at risk of ROP and that they should just follow up with us for strabismus and amblyopia moving forward," he said. "However, there are now several studies suggesting that up to one-third of patients with spontaneously regressed ROP—patients we didn't used to worry about —have potentially clinically significant persistent avascular retina as they age."[2,3]

Anecdotally, Dr. Campbell is seeing more teenagers and young adults from this population present for vitreoretinal care—presumably because, today, more people who were born prematurely are living to adulthood than once was the case. "But we just don't know how common it is to have complications from persistent avascular retina in this population and what to do about it," he said. Many pediatric ophthalmologists and retina specialists are choosing to laser persistent avascular retina as a preventive measure because of just how challenging it is to follow such patients and to reduce any future risk of reactivation, he added.

Anti-VEGF unknowns. There are certainly other unknowns regarding the use of anti-VEGF, said Dr. Hartnett, specifically the effects of intraocular VEGF suppression on the rest of the body. "We do know that anti-VEGF agents cross into the bloodstream and suppress systemic VEGF levels to varying degrees," she said. "We don't yet know how that impacts neuronal health in the retina or leads to clinically significant complications involving other organ systems."

These are hard questions to answer because of many variables, said Dr.

Hartnett. For example, the infants who develop ROP tend to be small in terms of overall development and are already at a high risk of neural cognitive insufficiency and other complications—which makes it even more difficult to test any effects of anti-VEGF treatment.

Caring for Kids as They Age

Detection difficulties. When ex-ROP patients walk into the clinic, they may not even be aware that they were born prematurely. "It's a perfect storm," said Dr. Drenser, "because many of these children reach prethreshold type 2 ROP but never require treatment, and now they're running around years later with incomplete retinal development." On top of that, a substantial number of kids who were born prematurely develop prethreshold type 1 and are treated with anti-VEGF, she said. But both of these groups are unablated so their eye care team may not recognize them as premature when they enter adulthood.

Thus, general ophthalmologists and adult-only retina specialists need to be ready to change treatment course. These eyes are abnormal in subtle ways that place patients at risk if they go unrecognized, said Dr. Drenser.

"For example, a young adult may walk into your office with some peripheral abnormalities or perhaps a detachment," said Dr. Drenser. "But because you don't recognize them as an ex-premature kid, you refer them to an adult vitreoretinal surgeon. It's only then, during surgery, that the specialist sees an anatomy that's extremely different—compared to a typical myopic adult—and one that requires a very different surgery."

Medical mysteries call for histories and imaging. It can take some sleuthing on the physician's part to determine if a patient had ROP as a baby, said Dr. Campbell. That's why all ophthalmic practices should be asking about a history of premature birth as part of the patient intake process.

Ophthalmologists should also set a low threshold when it comes to performing a widefield angiogram or referring a patient to a retina specialist if they have any suspicions. "The pathology in these eyes can be very subtle," said Dr. Campbell. "And without fundus photography, it can be difficult to appreciate avascular retina on clinical examination alone."

Ongoing care. In the end, many patients are going to do well. Children are able to adapt and use other senses, even if they have some visual impairment, said Dr. Hartnett. But because ROP is a lifelong disease, patients should have annual comprehensive eye exams at the very least. And this needs to continue even when children enter adulthood and are responsible for seeking appointments themselves, she said. Also, she notes, adults who had ROP are at increased risk for other ocular conditions including glaucoma.

Until then, parents of these adolescents and young adults need to be educated about the importance of continued care, said Dr. Drenser. Children born prematurely have a lot of doctors' appointments, so it's understandable that parents may forget to follow up with ophthalmology care—but, she said, "because we're seeing more and more relatively young adults with essentially normal visual function develop severe vitreoretinal pathology, we need everyone on board to get these patients seen."

1 Good WV. *Trans Am Ophthalmol Soc.* 2004;102:233-248.
2 Haniff AM et al. *J AAPOS.* 2022;26(1):29-31.
3 Ling XC et al. *Ophthalmol Sci.* Published online Feb. 6, 2023.

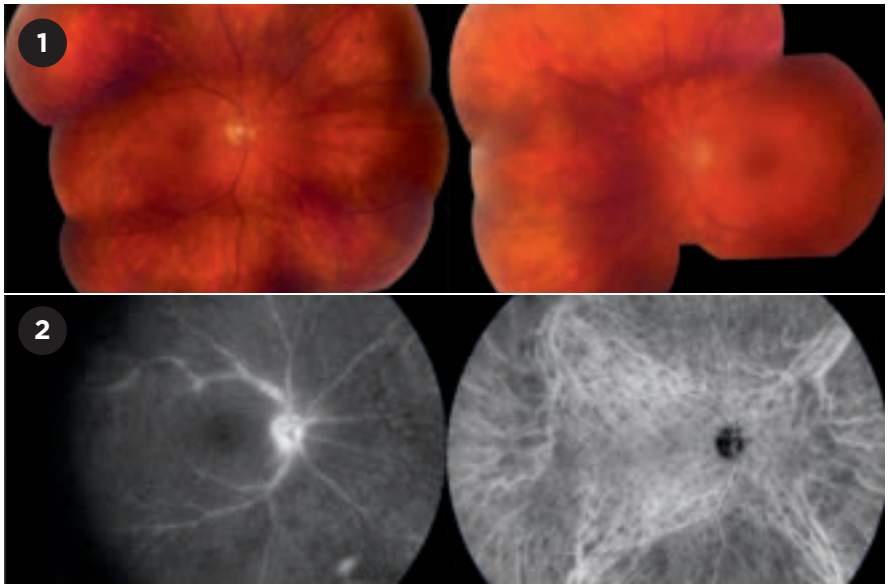
Dr. Campbell is Edwin and Josephine Knowles professor, and associate professor of Ophthalmology at the Casey Eye Institute at Oregon Health & Science University in Portland. *Relevant financial disclosures: None.*
Dr. Drenser is a retina specialist with Associated Retinal Consultants in Royal Oak, Mich., and director of the Pediatric Retinal Disease Molecular Genetics Laboratory, Oakland University William Beaumont School of Medicine, on the Rochester campus. *Relevant financial disclosures: None.*
Dr. Hartnett is the Michael F. Marmor, M.D. Professor of Retinal Science and Disease, director of Pediatric Retina, and professor of Ophthalmology at the Byers Eye Institute at Stanford University in Palo Alto, Calif. *Relevant financial disclosures: None.*
For full disclosures, see this article at aao.org/eyenet.

Clinical Follow-Up of Birdshot Chorioretinopathy

Birdshot chorioretinopathy (BSCR) is a bilateral, chronic, posterior uveitis characterized by cream-colored lesions primarily in the posterior pole. It is typically accompanied by vitritis, retinal vasculitis, and cystoid macular edema (CME). BSCR is rare, affecting approximately 8% of patients with posterior uveitis.[1] It has a slight female preponderance and usually manifests in the fourth or fifth decade of life. There is a strong association between BSCR and the HLA-A29 allele.

Ocular symptoms can precede the diagnosis by several years and include shimmering photopsias, floaters, nyctalopia, and blurred vision. However, visual acuity (VA) is often preserved even with end stage disease. Given the chronic nature of BSCR, management usually requires long-term immunosuppression.

Disease monitoring traditionally has been conducted with visual field testing and full-field electroretinography (ERG), but these modalities are cumbersome and detect only the sequelae of intraocular inflammation, making them impractical for real-time disease-management decisions. A beneficial alternative approach to disease monitoring is based on OCT with enhanced depth imaging (OCT-EDI), widefield fundus autofluorescence (FAF), and, if indicated, fluorescein angiography (FA) and indocyanine green angiography (ICGA).



SIGNS. *(1) Classic funduscopic appearance of BSCR: ovoid cream-colored lesions. (2) FA and ICGA (late frame) of the right eye. Note the large-vessel vasculitis (left) and multiple hypocyanescent lesions (right).*

Originally published in February 2023

BY **TIMOTHY M. JANETOS, MD, MBA,** AND **DEBRA A. GOLDSTEIN, MD.** EDITED BY BENNIE H. JENG, MD.

Determining the Diagnosis

A consensus document on BSCR diagnosis was released in 2006.[2] The diagnostic criteria are bilateral disease, low-grade inflammation of the anterior chamber (≤1+ cell), low-grade vitreous inflammation (≤2+ vitreous haze), and at least three peripapillary cream-colored lesions (Fig. 1). It is important to note that these classic lesions may not necessarily be present until the patient has experienced symptoms for several years. Other findings that support the diagnosis include HLA-A29 positivity, retinal vasculitis, and CME. The exclusion criteria are significant keratic precipitates, posterior synechiae, and a diagnosis of any other infectious, inflammatory, or neoplastic condition that can lead to multifocal choroiditis.

Imaging. Several imaging modalities may help to establish the diagnosis. ICGA can depict the birdshot lesions as multiple scattered hypocyanescent spots (Fig. 2). Often, the number of spots detected by ICGA is much greater than that seen clinically. FA may reveal vasculitis of large veins or smaller vessels, which may have a fern-like appearance. OCT also can be used to

identify characteristics of late-stage BSCR, such as diffuse retinal thinning, a thin choroid, and loss of the ellipsoid zone (EZ) with hyperreflective outer retinal foci.[3]

Monitoring the Disease

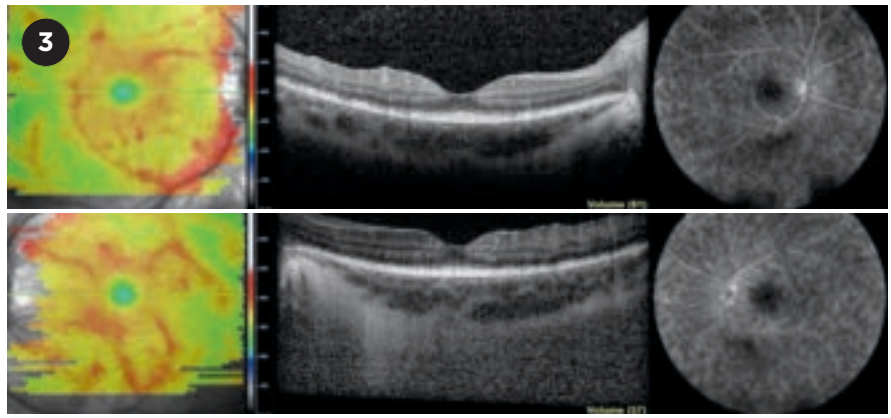
The following approach to patient monitoring is recommended.

Signs and symptoms. There is no replacement for a thorough clinical history and exam. Symptoms are key; for example, patients with disease activity often describe shimmering photopsias, which improve or resolve with treatment. VA, however, is not an appropriate indicator for monitoring disease activity, as patients can have end-stage disease with significant retinal atrophy but still maintain good central VA, providing false reassurance to providers. Certainly, a decline in VA warrants investigation and should raise suspicion for CME.

Other indicators of disease activity include vitreous inflammation or clinically apparent retinal vasculitis. Vasculitis of the larger vessels may be seen as subtle venous pinching at the vascular arcades, warranting further investigation with FA. However, in many cases, especially those involving smaller retinal vessels, the vasculitis associated with BSCR is subclinical and identifiable only by FA. Thickness mapping on OCT of the macula can reveal retinal thickening, especially at the vascular arcades, which may clue the clinician to active vasculitis (Fig. 3).[4]

OCT-EDI and FAF. OCT-EDI to evaluate the choroid is invaluable for monitoring disease activity.[5] Choroidal thickness and reflectivity have been extensively studied in BSCR. Compared with age-matched controls, the choroid is thinner in quiescent disease. During active disease, choroidal thickness increases and may be accompanied by a hyporeflective choroid with loss of vascular markings, which may denote inflammatory infiltration (Fig. 4). Hyporeflective foci within the choroid have also been identified as active lesions, but they do not always correlate with the clinically apparent birdshot lesions.

OCT and FAF can be used to identify EZ disruption in BSCR. Acute EZ disruption may occur, and associated diffuse punctiform hyper-autofluorescence (hyper-FAF) may be detected by FAF (Fig. 4).[3,6] Left untreated, EZ disruption may lead to further outer retinal atrophy. If the disruption is extramacular, OCT (nasal to the optic nerve) and widefield FAF can be useful for detecting changes.



VASCULITIS. *OCT-EDI and FA of another patient with BSCR shows diffuse fern-pattern vasculitis of the small vessels. The en face OCT thickness map showed thickening (red) of the vasculature in the macula, suggesting active vasculitis, which was confirmed by FA. Although OCT did not show CME, it detected discontinuity and disruption of the EZ.*

FAF can additionally reveal various BSCR patterns.[7] For example, chronic BSCR often includes multiple patterns of hypo-FAF, such as peripapillary, lichenoid, and macular hypo-FAF in the case of resolved CME. These are linked to chronic atrophy of the outer retina and the retinal pigment epithelium.

About ICGA. Although the number and size of lesions on ICGA can decrease with treatment and in some cases may be the main marker of disease activity, this is a relatively difficult marker to routinely follow, and, in many cases, lesions remain despite treatment.[8]

Therefore, OCT-EDI and widefield FAF are the optimal modalities for routine monitoring of disease activity. Additional testing (e.g., ICGA, FA) may be helpful for monitoring responses to changes in therapy and to check the status of characteristics identified by OCT, such as increased retinal thickness.

Treatment and Prognosis

BSCR generally requires long-term therapy, which may be systemic or local.

Systemic therapy. Long-term immunomodulatory therapy (IMT) is the preferred option for many patients. Although there are no randomized controlled studies of BSCR treatments, ample cohort studies have demonstrated disease control and quiescence with use of IMT. Moreover, this therapy can stabilize the VF and lowers the risk of long-term choroidal thinning.[9]

Many IMT regimens have been used to treat BSCR, including antimetabolites, cyclosporine, anti–tumor necrosis factor (TNF) agents, and interleukin (IL)-2 and IL-6 receptor blockers. The only systemic IMT approved for uveitis treatment is the TNF inhibitor adalimumab. All systemic therapies except for adalimumab are used off label.

Local therapy. Given that BSCR is strictly ocular (not systemic), long-acting steroid implants may be a viable alternative to systemic IMT for patients who have contraindications to IMT or prefer only local treatment.

Long-acting steroid implants include the .59-mg fluocinolone acetonide intravitreal implant (Retisert; Bausch + Lomb), the .19-mg insert (Iluvien; Alimera Sciences), and the .18-mg insert (Yutiq; EyePoint Pharmaceuticals). Retisert has demonstrated high resolution rates for retinal vasculitis and clinical inflammation and has allowed for successful weaning from systemic IMT.[10] However, all patients with Retisert implants will require cataract surgery, and many will need glaucoma surgery to control IOP.[10]

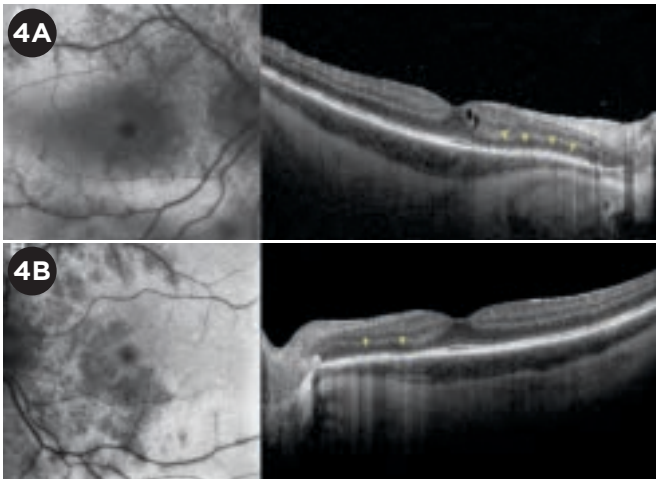
Courtesy of Debra A. Goldstein, MD

Case Study: BSCR in a 57-Year-Old Woman

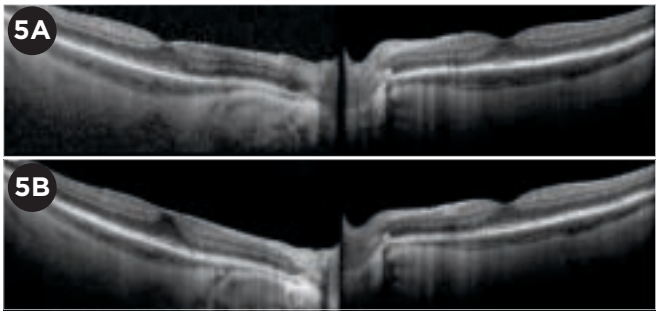
A 57-year-old White woman experienced photopsias and floaters in both eyes in 2017 and underwent vitrectomy in 2019 to address floaters in her left eye. The photopsias and floaters persisted, and BSCR was diagnosed in June 2019. Methotrexate treatment (15 mg/week) was started in November 2020, and the disease was monitored with ERG. In June 2021, the methotrexate dosage was increased to 25 mg/week because ERG detected further deterioration. Despite this, the symptoms continued.

The patient presented to our uveitis service in July 2021. At that time, best-corrected VA was 20/40 in her right eye and 20/20 in her left eye. Noteworthy findings of the clinical exam were mild inflammation of the anterior chamber and 2+ anterior vitreous cell. FA did not show any vasculitis. OCT-EDI demonstrated EZ disruption in the right eye, worse than in the left eye, along with moderate choroidal infiltration and thickening (Fig. 4). Trace CME was found in the right eye via OCT. The patient received an intravitreal dexamethasone implant in her right eye and began treatment with systemic adalimumab. The choroidal infiltration, CME, and EZ disruption improved subsequently (Fig. 5). Final VA was 20/25+2 (right eye) and 20/20 (left eye).

Takeaway messages. There were several clues that this case of BSCR had not been treated adequately. Foremost, the symptoms were persistent, and there was clinical evidence of vitreous cell. Second, there was disruption of the EZ in both eyes and a thickened choroid. Third, CME was noted by OCT. No single symptom or sign guided the treatment. Rather, it was the combination of the patient's symptoms, clinical exam results, and OCT-EDI findings that dictated the need to escalate therapy.



INITIAL VISIT. *FAF and OCT-EDI images of the patient's right eye (4A) and left eye (4B), obtained at the initial consultation. FAF demonstrated areas of peripapillary and scattered hypo-autofluorescence and punctate hyper-autofluorescence. OCT-EDI showed a thickened infiltrated choroid, with patchy areas of outer retinal and EZ disruption (arrowheads denote areas of greatest prominence). CME was apparent in the right eye. VA at this visit was 20/40 in the right eye and 20/20 in the left eye.*



FOLLOW-UP VISIT. *Follow-up OCT-EDI images. (5A) One month after injection of a dexamethasone implant into the right eye, the CME and choroidal infiltration had resolved, and reconstitution of the EZ had begun. (5B) Seven months into adalimumab treatment, there was further evidence of resolution of choroidal infiltration and reconstitution of the EZ, as well as epiretinal membrane formation in the right eye. VA at this visit was 20/25+2 in the right eye and 20/20 in the left eye.*

The Iluvien implant has been specifically studied in BSCR and has produced good control of retinal vasculitis and CME in patients with this condition. However, many cases have required systemic IMT to resolve choroidal infiltration, indicating that lower-dose implants may not necessarily be sufficient to control the disease.[11] There are currently no studies evaluating the utility of the Yutiq implant in BSCR.

Both Retisert and Yutiq are FDA approved to treat noninfectious intermediate uveitis, posterior uveitis, and panuveitis. Iluvien is not FDA approved to treat any type of uveitis.

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Dr. Janetos is a uveitis fellow and **Dr. Goldstein** is director of the uveitis service as well as the Magerstadt Professor of Ophthalmology. Both are at Northwestern University Feinberg School of Medicine in Chicago.

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See disclosure key, page 5.

Courtesy of Debra A. Goldstein, MD

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL

GA unravels so much

Save retinal tissue by slowing progression[1–3]

INDICATION

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

IMPORTANT SAFETY INFORMATION

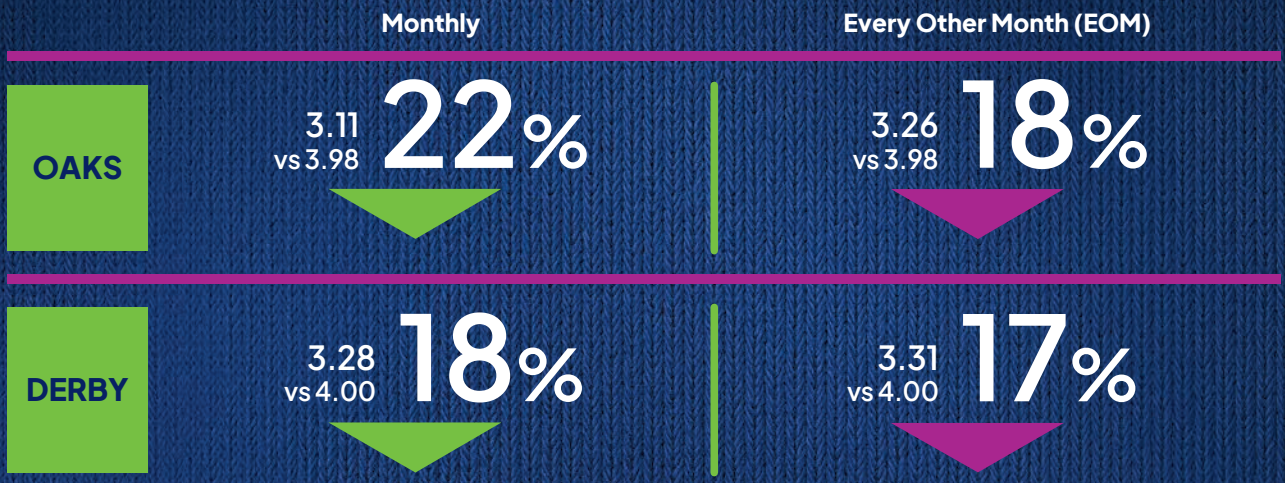
CONTRAINDICATIONS

- 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.
- **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.

SYFOVRE achieved continuous reductions in mean lesion growth rate* (mm^2) vs sham pooled from baseline to Month 24[1]



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

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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

ADVERSE REACTIONS

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

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 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.

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

Apellis

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

INDICATIONS AND USAGE

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

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Neovascular AMD
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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.

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 neovascular AMD, endophthalmitis, and retinal detachments. 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.
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SATURDAY, NOV. 4

Reimagining Management of Retinal Disease with Anti-VEGF Therapy

Speaker: Lloyd Clark, MD

Presented by Regeneron and designed for U.S. retina specialists.

SUNDAY, NOV. 5

Discover a Different Treatment for the Signs and Symptoms of Dry Eye Disease

Speakers: John Sheppard, MD, MMSc, FACS, and Priya Mathews, MD

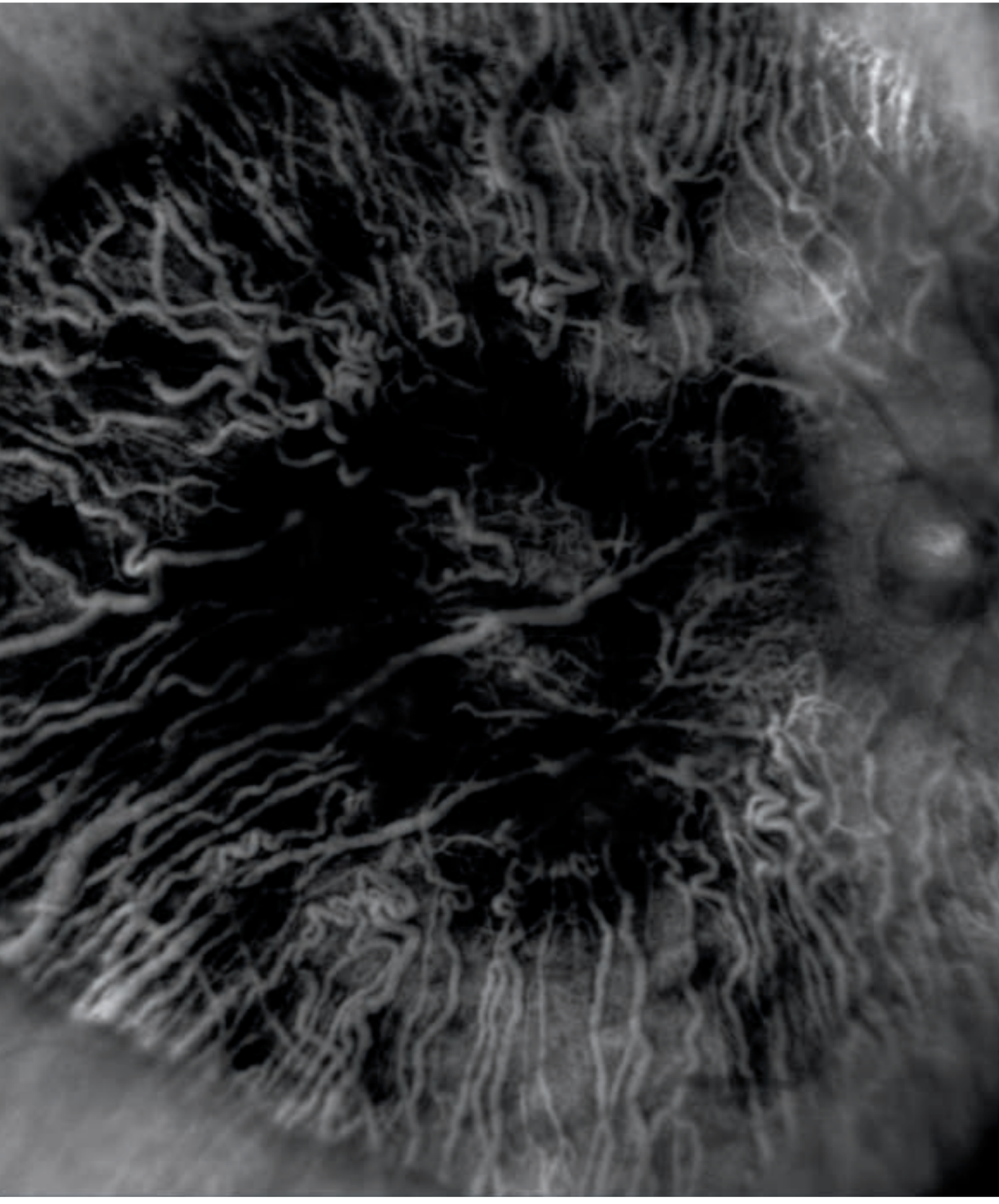
Presented by Viatris, Inc. and designed for U.S. eye care specialists.

MONDAY, NOV. 6

An Approved Treatment for Geographic Atrophy: An Expert Exchange

Speakers: Jorge A. Fortun, MD, and Jaclyn L. Kovach, MD, FASRS

Presented by Apellis and designed for U.S. retina specialists.



Novel Therapies and New Biomarkers for Geographic Atrophy

The first two drugs showing promise in slowing the progression of geographic atrophy are poised for FDA approval. Will this signal a new era in patient care?

By Rebecca Taylor, Contributing Writer

UNTIL RECENTLY, CLINICIANS HAVEN'T had a viable option to treat geographic atrophy (GA). This absence of treatment has presented a considerable gap in patient care, considering that the disease poses a significant risk of blindness.

Now, two new therapeutics appear to show success in slowing the growth rate of GA lesions. These treatment advances are based on evidence that genetic changes associated with the complement genes and the complement cascade play a role in age-related macular degeneration (AMD). Other advances in the GA field include high-resolution OCT imaging and deep-learning algorithms that have revealed subtle biomarkers, which have helped fine-tune the diagnostic criteria for GA and define the targets for new therapies.

New Terminology, New Role for OCT

"The field is moving toward a new definition of GA that employs OCT," said Eleonora Lad, MD, PhD, at Duke University Medical Center in Durham, North Carolina. While fundus autofluorescence (FAF) and color fundus imaging have been the gold standard for diagnosing GA, "we feel that OCT is best because it allows 3D and high-resolution visualization to diagnose atrophy more accurately," she said.

Recently, the Classification of Atrophy Meetings (CAM) group, a collaboration among international experts in retinal imaging, published two reports: one suggested new terminology based on OCT findings,[1] while the other validated these terms as biomarkers for future research.[2]

New terms: iRORA and cRORA. These new terms refer to early features of retinal cell death based on the anatomic layers affected, including the retinal pigment epithelium (RPE). iRORA, for Incomplete RPE and Outer Retinal Atrophy, refers to pre-GA lesions, while cRORA refers to Complete RPE and Outer Retinal Atrophy. The CAM group noted that the term "nascent GA" should be used for "a subset of AMD-associated iRORA in the absence of past or current neovascularization to signify that the progression toward GA has begun."[1]

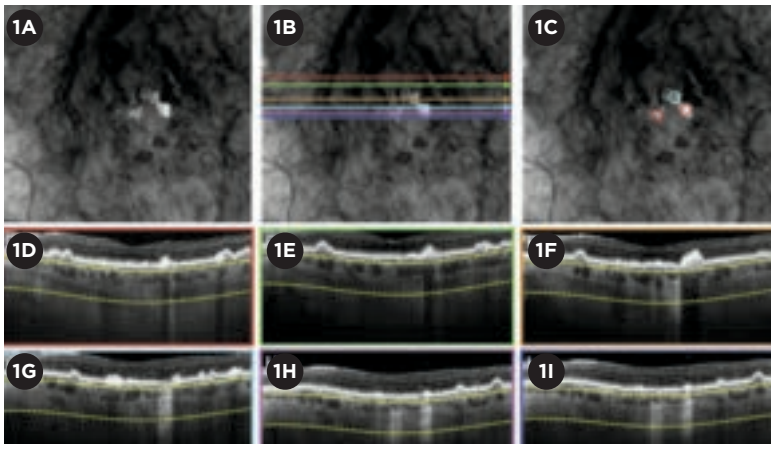
The CAM group defines cRORA as having an area of choroidal hypertransmission of 250 µm or more in diameter, an area of disrupted or attenuated RPE of 250 µm or more in diameter, and overlying photoreceptor degeneration without an RPE tear. In turn, iRORA is defined as including these OCT signs but with smaller lesions.

Why OCT is key. The OCT imaging modality drives the diagnosis of cRORA and iRORA. "GA is a color-imaging diagnosis, while cRORA is diagnosed based on OCT, which is far more sensitive," said Philip J. Rosenfeld, MD, PhD, at the Bascom Palmer Eye Institute in Miami.

"Both cRORA and iRORA are defined using horizontal OCT B-scans, which show loss of the outer retina and RPE, as well as the presence of hypertransmission defects, which means light is getting into the choroid that would normally be blocked by the RPE," Dr. Rosenfeld said. In

Originally published in February 2023. [Editors' note: Since original publication of this article, both drugs have been FDA approved.]

addition to using single B-scans as recommended by the CAM group, "another strategy is to use a collection of densely spaced B-scans and an en face imaging strategy to diagnose cRORA," he added.[3] "While all GA is cRORA, all cRORA may not be diagnosed as GA if it isn't detectable on color fundus imaging," he said, given variances in sensitivity of different imaging modalities.



BIOMARKER. *(1A) Hypertransmission defects (hyperTDs) on en face SS-OCT. (1B, 1D-1I) Color-coded lines that correspond to colored borders on B-scans used by graders. (1C) Red circles = hyperTDs; blue circle = an area initially identified as two lesions when, in fact, it was a single hyperTD.*

In Search of Better Biomarkers

Beyond BCVA. "The new paradigm is to recognize that BCVA is not a good biomarker for GA trials," said James T. Handa, MD, at the Wilmer Eye Institute in Baltimore. "Functional endpoints will be invaluable for future clinical trials to assess treatment validity, but the field hasn't identified them."

Researchers are diving deep into OCT analyses for subtle changes that reflect disease activity, Dr. Handa said. "There's evidence, for example, that the ellipsoid zone [EZ] line becomes less visible, suggesting loss of mitochondria in the photoreceptors, and mitochondrial dysfunction is a known pathogenic factor in AMD," he said. "So if you could integrate functional assays with structural changes, you'd have more robust findings than structural or functional assays alone in clinical trials."

Since dim-light vision is challenging for intermediate AMD patients, one promising functional endpoint is a low-luminance VA test, said Dr. Handa. Functional endpoints could be developed from other tests, including microperimetry testing for visual deficits, mesopic microperimetry to measure low-light vision loss, delayed dark adaptation, and contrast sensitivity testing, he added.

In addition, Dr. Lad pointed out, "New artificial intelligence [AI] algorithms can analyze multimodal imaging of all kinds to help correlate structure with function, which will become increasingly important for GA management." For instance, in a recent post hoc analysis of data from the phase 2 FILLY trial, researchers conducted an AI-based morphologic analysis of the efficacy of pegcetacoplan (Apellis) in treating GA.[4]

Key biomarker. Choroidal hypertransmission is one of the more robust, consistent biomarkers for GA, said Dr. Rosenfeld.

When atrophy is viewed using an en face strategy, "a bright spot measuring 250 µm in any dimension is referred to as persistent hypertransmission defect, and this has been shown to progress to typical GA," said Dr. Rosenfeld. "The advantage of en face imaging is that these hypertransmission defects can be seen in any en face dimension, and their growth can be measured just as we measure atrophy growth using FAF imaging."

It's a structural defect that's easy to grade, he said, adding, "Graders from Bascom Palmer and the CAM group showed 97% agreement and an overall positive predictive power of 99% in detecting these defects."

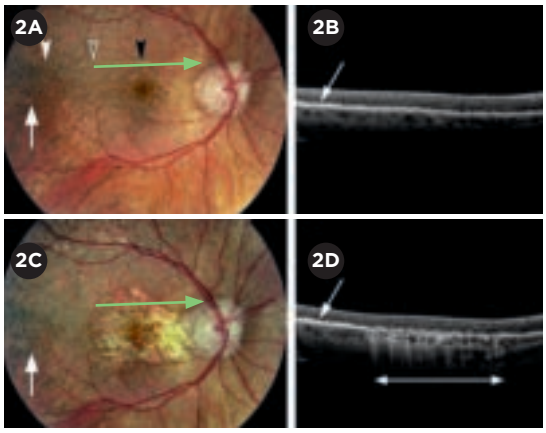
OCT modalities, such as OCT angiography (OCTA) and swept-source OCT (SS-OCT), can detect the earliest changes that lead to typical atrophy and identify which layers of tissue are damaged. "We can measure photoreceptor integrity around the atrophy, blood-flow deficits in the choriocapillaris within the macula, and basal laminar deposits [a type of drusen] around the atrophy," said Dr. Rosenfeld. "All of these measurements help predict the growth rate of atrophy and can be obtained from a single OCT scan."

Additional biomarkers. Other biomarkers associated with GA progression from earlier studies include lesion area, number, shape, location, and direction of growth relative to the fovea.[5]

Novel Therapies: Complement Inhibitors

Two new drugs target the complement system. If FDA-approved, both would require monthly intravitreal injections. *[Editors' note: Since original publication of this article, both drugs have been FDA approved.]*

"There are at-risk genes that are clearly causative or demonstrate an at-risk phenotype for AMD," said Dr. Rosenfeld. "The good news with these drugs is that we can slow down disease pro-



PROGRESSION. *Development of GA in eye with confluent subretinal drusenoid deposits (SDDs). (2A) Arrowheads = areas of SDDs; white arrow = area of no SDDs; green arrow = site of OCT scan in (2B). (2C) After 63 months, SDDs have spread (white and green arrows reference same areas in 2A). (2D) Hypertransmission under area of absent RPE (double arrow); more recently developed SDDs are apparent temporally (arrow).*

gression; the bad news is that we can't recover lost vision because the atrophy can't be repaired."

Pegcetacoplan. Pegcetacoplan inhibits complement component 3 (C3). In the phase 3 OAKS trial, researchers compared monthly and bimonthly pegcetacoplan with sham intravitreal injections at 12, 18, and 24 months.

The 12-month Apellis data are under review, said Dr. Lad, the OAKS trial's international principal investigator. "OAKS is the first large phase 3 trial in GA that met its primary endpoint," she said. "In the parallel phase 3 DERBY trial, pegcetacoplan reduced GA lesion growth versus sham, but statistical significance wasn't reached, [though] data from both studies were submitted to the FDA."

Both OAKS and DERBY used the same structural endpoint as the FILLY trial did: change in size of lesions from baseline.[6] (In FILLY, pegcetacoplan had a 29% and 20% reduction, as measured by FAF, after monthly and every-other-month [EOM] injections, respectively.) According to two-year data from Apellis, the OAKS investigators saw a reduction in lesion growth of 22% with monthly injections and 18% with EOM injections compared to sham. Results of DERBY showed a slightly lower effect: 19% with monthly injections and 16% with EOM.[7]

"Two-year data are positive," said Dr. Rosenfeld. "We can slow the progression of GA using this C3 inhibitor." But the results have yet to be peer-reviewed. "The devil is in the details, so it's hard to know more than what the [company's] press release states," said Dr. Handa. The drug seems to need 18 or 24 months to show results, Dr. Handa added. "You're asking patients to invest far into the future, but it's the best we have, so we'll probably use it in selected cases if approved."

Avacincaptad. Avacincaptad pegol (Iveric Bio) inhibits complement component 5 (C5). The drug was evaluated in two phase 3 studies, GATHER1 and GATHER2, both of which used the structural endpoint of growth rate in lesion size, measured by FAF at baseline, month 6, and month 12. According to the company, the mean rate of growth in GA area from baseline to month 12 was 35% for the 286 participants in GATHER1 and 18% for the 448 participants in GATHER2.[8]

"With GATHER2, the original trial design was quite savvy," Dr. Handa said. "Different-sized lesions grow at different rates, and the study randomized control and treatment groups with similar lesion features to compare apples to apples, which could make a substantive difference in recognizing a defined change after treatment."

Cautious optimism. "We may identify subtle differences between effectiveness and safety profiles of these two complement inhibitors as we gain more information from the clinical

Update July 2023: Adverse Events Reported for Pegcetacloplan

On July 15, the American Society of Retina Specialists (ASRS) alerted its members that it had received physician reports of intraocular inflammation, including six cases of occlusive retinal vasculitis, in patients treated with the drug Syfovre (pegcetacoplan injection), which was approved by the FDA in February 2023 for the treatment of geographic atrophy. The cause of the inflammation is not known and does not appear to be linked to a specific lot. The ASRS recommended close follow-up and reporting of adverse events after administration of the drug and noted that Apellis Pharmaceuticals is working with their committee to review these cases. In a filing to the U.S. Securities and Exchange Commission, Apellis wrote, "The reported vasculitis events have occurred at an estimated rate of approximately 1 in 10,000 injections, or 0.01% per injection."

To report, go to www.asrs.org/forms/4/asrs-adverse-event-report-form.

trials," Dr. Rosenfeld said.

Of note, however, complement inhibitors only slow, but do not stop, the progression of disease. "These drugs bend the curve of progression, and the hope is that over time the rate of progression slows and plateaus," said Dr. Rosenfeld. "The vast majority of my patients are excited because [these drugs present] an option not available before."

What about risk of exudation? Both of these complement inhibitors can trigger exudation—a further complexity in treating the dry form of advanced AMD. "Using SS-OCTA, we've identified abnormal vessels under the RPE long before exudation developed," said Dr. Rosenfeld. "The blood vessels start growing but aren't leaking, and we believe that growth is a good thing: those vessels are bringing the blood supply closer to the RPE and outer retina because the choriocapillaris has been damaged."

Does this represent a paradoxically healthy "bypass" mechanism? "It's the body's attempt to resupply the outer retina and RPE with nutritional and blood supply," he said. "It's only when those vessels start leaking that we run into problems."

Dr. Rosenfeld pointed out, "Everyone with AMD starts with dry macular degeneration, and why some eyes progress to wet is a mystery. With anti-VEGF therapy, we can convert wet AMD back to dry, but if patients live long enough, they'll eventually lose vision from the progression of the dry AMD. With these new complement inhibitors, we'll have a treatment for GA, and if we treat early enough, we'll be able to preserve as much vision as possible." He added, "Exudation doesn't scare us anymore. Atrophy scares us."

"Patients need to be counseled that if they convert to wet AMD, they'll need two injections, one for wet, one for dry," Dr. Lad noted. "That's been well tolerated in studies, and my patients would accept this possibility because GA is such a debilitating disease."

[Editors' note: Current and emerging therapies for dry AMD provide hope and reinvigoration for patients with this previously untreatable disease. However, clinicians should remain vigilant about monitoring for potential known and unknown side effects, some of which may be rare and devastating; among these may be intraocular inflammation, vasculitis, and nonarteritic ischemic optic neuropathy events. Clinicians should also have a thorough benefit-risk discussion with patients when choosing current and future therapies.]

Dietary Impact on GA Development and Progression

There's new evidence that diet can help patients at risk for GA. Using data from the Age-Related Eye Disease Study 2 (AREDS2), NEI researchers found that a "Mediterranean-style" diet was associated with both a delay in progressing to GA and a slower growth of lesions themselves.[1]

"It's an observational study, but the effect size is pretty amazing," said Emily Y. Chew, MD, at the NEI. "The reduction in growth rate of the GA lesion is significant, when comparing those with high adherence to the Mediterranean-style diet to those with low adherence."

Risk reduction. Those with greater adherence to the diet experienced "about a 30% reduction in the risk of developing GA," Dr. Chew said. And in the subset of participants without large drusen, she added, "there was a 20% reduction in developing large drusen."

Thus, she said, "It seems that diet has an effect early on, and even if a patient already has intermediate AMD, it's never too late, and you can still reduce the rate of having late AMD."

When individual dietary components were assessed, the results showed that the single most important factor related to a lower risk of developing GA is a higher intake of fish, said Dr. Chew. The four factors related to delaying GA enlargement were a higher intake of whole fruits, less red meat, moderate alcohol, and a better ratio of monounsaturated to saturated fatty acids, she added. Her take on these findings: "We need to eat a healthy diet, period."

Dr. Chew noted the underlying genetic complexities inherent in AMD, saying that genes can be either problematic or protective, thus adding to or subtracting from the diet's effect. For example, she said, "If you have a protective gene for complement factor H and you also eat fish, it markedly reduces the risk of progressing to late AMD, particularly for GA."

Glycemic index. In other dietary news, "There's also strong preclinical laboratory research[2] to support a low–glycemic-index diet," Dr. Handa noted. "If sugar gets into the bloodstream too quickly, it causes structural changes to proteins and lipids that cause damage and contribute to AMD; epidemiologic data show that."

1 Agrón E et al. *Ophthalmol Retina.* 2022;6(9):762-770.
2 Rowan S et al. *Free Radic Biol Med.* 2020;150:75-86.

Going Forward: Continuing Challenges

In pursuit of earlier intervention. The holy grail in GA is earlier intervention.[2] "The greatest challenge retina specialists face right now is to treat at the intermediate stage to preserve vision and prevent the atrophy from forming," said Dr. Rosenfeld. "Intermediate macular degeneration is characterized by drusen, which are focal elevations of the RPE full of lipid and protein, but these patients often have good vision in normal lighting."

Enter AI. Early diagnosis remains a priority, although the absence of symptoms in the intermediate stage makes this difficult. Toward that end, the Collaborative Community on Ophthalmic Imaging, a consortium that includes NEI, FDA, and academic groups, is developing AI methodologies for earlier diagnosis of patients with AMD.[9]

"There's been an explosion of new AI methods for AMD screening and for prediction of conversion from intermediate to advanced stages," said Dr. Lad. Using a machine-learning analysis on a large dataset of intermediate AMD images, for instance, her group was able to "stratify patients into four risk levels, telling us which patients are more likely to progress to GA," she said. That work used biomarkers of disease progression in intermediate AMD based on spectral-domain OCT.[10]

Machine learning requires access to expert human graders of OCT, she added. "The next step will be deep-learning algorithms that use retinal images alone to predict progression. At Duke we have developed and are validating an AI algorithm based on OCT alone, without needing costly and time-consuming human gradings, that predicts progression from intermediate AMD to GA."

Still unknown. Multiple pathogenic pathways have been proposed for GA, said Dr. Handa, whose research focuses on molecular mechanisms of normal aging versus those seen in early AMD. "We don't have a prioritized rank of what's causing disease," he said. "Is it complement? Is it oxidative stress? Is it mitochondrial dysfunction? We don't know which is most important.

"We also don't know how much these pathogenic pathways interact," he added, "so if they're causing disease in parallel and you treat one pathway, you still have the other pathways causing disease, and a single therapy won't work."

Also unknown: the stage at which these pathways cause disease. "The phase 3 trials have all targeted complement, part of the innate immune response, which is typically one of the first lines of defense," said Dr. Handa. "Logically, you'd think [complement] would occur in early- rather than late-stage AMD, so it may not be the relevant target for GA." To make substantive breakthroughs would mean prioritizing known pathways of disease and validating new, FDA-approved functional and structural endpoints for studies, he added.

1 Jaffe GJ et al. *Ophthalmol Retina.* 2021;5(9):855-867.
2 Wu Z et al. *Ophthalmol Retina.* 2022;6(1):4-14.
3 Liu J et al. *Ophthalmol Science.* 2022;2(2):100162.
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10 Lad EM et al. *Ophthalmol Science.* 2022;2(2):100160.

Meet the Experts

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Philip J. Rosenfeld, MD, PhD Professor of ophthalmology at the University of Miami's Bascom Palmer Eye Institute. *Relevant financial disclosures: Apellis: C,PS; Carl Zeiss Meditec: C,S; Gyroscope Therapeutics: S; Stealth Biotherapeutics: S.*

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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.

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.

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 neovascular AMD, endophthalmitis, and retinal detachments. 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.

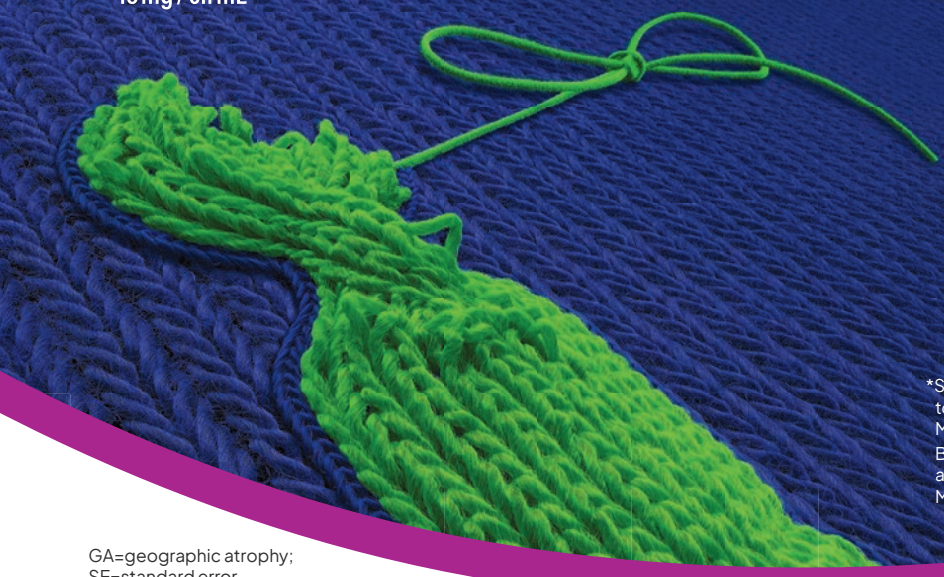
Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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

SYF-PI-17Feb2023-1.0

7/23 US-PEGGA-2200163 v3.0

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

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- **Intraocular Inflammation**
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- **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.