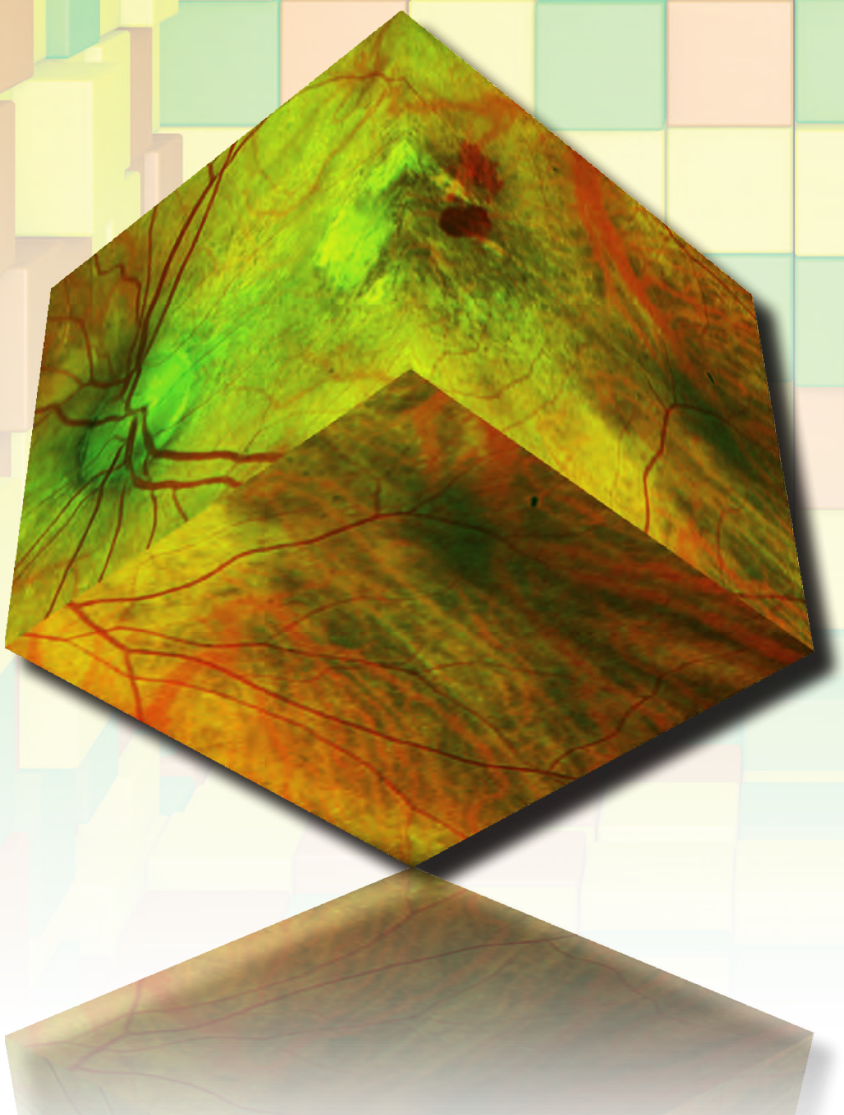
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20TH ANNIVERSARY

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Study design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multicenter, 2-year, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE every other month, sham monthly, or sham every other month for 2 years. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by FAF. SYFOVRE was also assessed in GALE, a 3-year, open-label extension study evaluating the incidence and severity of ocular and systemic AEs, and change from baseline in total area of GA lesion(s) in the study eye (mm^2).[1,3,5]

AE=adverse event; AMD=age-related macular degeneration; FAF=fundus autofluorescence; GA=geographic atrophy.

References: 1. Syfovre. Package insert. Apellis Pharmaceuticals, Inc.; 2025. **2.** Data on file. Apellis Pharmaceuticals, Inc. **3.** Wykoff CC, Holz FG, Chiang A, et al; OAKS, DERBY, and GALE investigators. Pegcetacoplan treatment for geographic atrophy in age-related macular degeneration over 36 months: data from OAKS, DERBY, and GALE. *Am J Ophthalmol.* 2025;276:350–364. **4.** Izervay. Package insert. Astellas Pharma US, Inc.; 2025. **5.** Heier JS, Lad EM, Holz FG, et al; OAKS and DERBY study investigators. Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials. *Lancet*. 2023;402(10411):1434–1448.

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, in patients with active intraocular inflammation, and in patients with hypersensitivity to pegcetacoplan or any of the excipients in SYFOVRE. Systemic hypersensitivity reactions (e.g., anaphylaxis, rash, urticaria) have occurred.

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.



Only SYFOVRE has 5 years of clinical trial data—longer than any other FDA-approved treatment for GA.[1-4]

Patients treated with SYFOVRE achieved a reduced rate of GA lesion growth vs sham pooled in clinical trials at Year 2,* with long-term data out to 5 years. Help your patients look forward to what's next, instead of what's left behind.[1,2]

*At Year 2, SYFOVRE reduced GA lesion growth by **18% and 22%** with monthly dosing and **17% and 18%** with every-other-month dosing vs sham pooled.[1]

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SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL

- **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 following page.

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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.
Hypersensitivity
SYFOVRE is contraindicated in patients with hypersensitivity to pegcetacoplan or to any of the excipients in SYFOVRE. Systemic hypersensitivity reactions (e.g., anaphylaxis, rash, urticaria) have occurred.

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
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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.

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. Systemic reactions: anaphylaxis, rash, and urticaria.

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-20Dec2024-3.0

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RT NEWS

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LARGE GLOBAL STUDY SHOWS SMOKING INCREASES RISK OF OPHTHALMIC DISEASE

Results of a global database study published in April in *Clinical Ophthalmology* found a significant association between smoking status and risk of multiple vision-threatening ophthalmic diseases, including cataract, glaucoma, diabetic retinopathy, AMD, retinal vascular occlusion, uveitis, and ischemic optic neuropathy.[1] The study also identified quantitative risk estimates to help inform counseling on smoking cessation.

The retrospective cohort study was conducted using the TriNetX electronic health records platform (n = 12,183,254), and patients were categorized into smokers (n = 304,823) and nonsmokers (n = 11,878,431). The researchers used propensity score matching to balance the two groups for demographic features and vascular risk factors. The incidence rates of the targeted diseases were compared over a 10-year period using risk ratios (RR).[1]

The results showed that smokers exhibited a significantly higher 10-year risk for all studied ophthalmic outcomes ($P < .0001$). The strongest associations were observed for posterior subcapsular cataract (RR = 2.60), uveitis (RR = 2.43), and retinal vascular occlusions (central retinal artery occlusion: RR = 2.35; central retinal vascular occlusion: RR = 2.16). Increased risks were also found across glaucoma subtypes (RR = 1.57-2.47), AMD (RR = 1.85), and diabetic retinopathy (RR = 1.21).[1]

The authors concluded in their paper that ophthalmologists should consider incorporating smoking history into risk stratification and screening programs, as well as emphasize the potential ocular effects of smoking as a modifiable risk factor.[1]

1. Gad El Sayed M, Vu Pham N, Bandaru D, et al. Smoking and risk of vision threatening complications: a global database analysis. [published online ahead of print April 2, 2026.] *Clin Ophthalmol*.

STUDY OF LENS IMPLANT FOR AMD MOVES TO PHASE 2

OnPoint Vision announced plans to initiate phase 2 of its clinical trial evaluating the AccuraSee Intraocular Pseudophakic Capsular Lens Magnifier (IOPCL MAG) device for the treatment of patients with AMD.[1]

The study will assess the safety and efficacy of the IOPCL MAG as a secondary implant in the capsular bag of patients with AMD who already have a 6-mm acrylic posterior chamber IOL. The device is specifically designed for pseudophakic patients with low vision due to inactive AMD at least 6 months following cataract surgery.[1]

The IOPCL MAG features a neutral optic (plano power) design with a central +10.0 D and 1.8-mm optical zone. The device is intended to improve functional vision by providing magnification of near images when implanted unilaterally.[1]

Phase 2 follows the successful completion of a phase 1 first-in-human Investigational Device Exemption study conducted in the United States under a separate early feasibility study.

1. OnPoint Vision expands clinical trial for investigational lens targeting AMD patients. Eyewire+. April 14, 2026. Accessed April 23, 2026. eyewire.news/news/onpoint-vision-expands-clinical-trial-for-investigational-lens-targeting-amd-patients

NOVEL WET AMD DRUG SHOWS POSITIVE PHASE 3 RESULTS

Ocular Therapeutix shared positive data from post-hoc analyses of its phase 3 SOL-1 clinical trial evaluating Axpaxli (OTX-TKI) for the treatment of wet AMD. Axpaxli is a bioresorbable intravitreal hydrogel incorporating axitinib and is designed for sustained drug delivery.

The drug met its superiority primary endpoint and showed benefits across multiple secondary endpoints.[1] For patients treated with Axpaxli, the median time to a ≥ 30 µm increase in central subfield thickness (CST) was 39 weeks versus 16 weeks for those treated with 2 mg aflibercept (Eylea, Regeneron), and the median time to a ≥ 75 µm increase was 46 weeks versus 24 weeks, respectively. Treatment with Axpaxli also reduced the risk of worsening anatomic outcomes by 30% for ≥ 30 µm CST increase ($P = .0028$) and 50% for ≥ 75 µm increase ($P < .0001$). Moreover, patients treated with Axpaxli maintained the vision gains achieved during the initial loading phase through week 52, and those with poorer baseline vision saw gains of +11.8 ETDRS letters compared with

MEETING COVERAGE: VBS IN WONDERLAND



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+8.5 ETDRS letters in the aflibercept group.[1]

Among patients who did not require rescue injection, 75% remained injection-free by week 36. The safety profile was well-tolerated, with reports of vitreous floaters that resolved in an average of 20 weeks and did not affect vision.[1]

In addition, the first patient was enrolled in the SOL-X extension trial to evaluate the long-term safety and durability of Axpaxli over an additional 3 years.[2]

1. Ocular Therapeutix reports additional positive phase 3 data for Axpaxli in wet AMD. Eyewire+. April 13, 2026. Accessed April 23, 2026. eyewire.news/news/ocular-therapeutix-reports-additional-positive-phase-3-data-for-axpaxli-in-wet-amd
2. Ocular Therapeutix enrolls first patient in long-term SOL-X trial for Axpaxli in wet AMD [press release]. Eyewire+. April 29, 2026. Accessed May 4, 2026. tinyurl.com/mr2f8xr9

PHOTOSWITCH THERAPY FOR RP SHOWS EARLY PROMISE IN PHASE 1

According to a recent study, a small azobenzene photoswitch molecule (KIO-301) designed to confer light responsiveness to retinal ganglion cells was evaluated for safety and feasibility in a phase 1, first-in-human trial of patients with advanced retinitis pigmentosa (RP). The therapy met its primary endpoint of safety and tolerability at 30 days, with no serious adverse events or dose-limiting toxicities observed, including no intraocular inflammation.[1]

In the study, KIO-301 was administered via an intravitreal injection to 12 eyes of six patients with RP. All ocular adverse events were mild and related to the procedure. In addition to safety, exploratory assessments revealed light-evoked blood-oxygen-level-dependent signal changes in the visual cortical regions following dosing, which showed temporal patterns compatible with pharmacodynamic activity.[1]

The authors concluded that these findings support the feasibility of photoswitch therapy and warrant further evaluation in a large clinical trial.[1] ■

1. Casson RJ, Daniels E, Barras CD, et al. Intravitreal photoswitch therapy in advanced retinitis pigmentosa: a phase 1 open-label trial. [published online ahead of print April 14, 2026]. *Nat Med.*

Eyewire+ Pharma Update

- **AAVantgarde Bio** completed recruitment of approximately 150 patients in the global STELLA natural history study for Stargardt disease. Insights from the study are expected to support development of the gene therapy candidate AAVB-039.
- **Oculis** completed the final patient visit in its phase 3 DIAMOND trials for OCS-01, an eye drop for diabetic macular edema (DME), with topline results expected in June 2026. In addition, the company announced new findings from its DME AWARE Delphi study, showing that a majority of DME patients remain untreated or inadequately treated, highlighting significant care gaps and the limitations of current therapies.
- **MeiraGTx** entered into an agreement with Johnson & Johnson to acquire botaretigene sparoparvovec (bota-vec), an investigational therapy for X-linked retinitis pigmentosa. MeiraGTx intends to immediately pursue global regulatory filings for approval of bota-vec.
- **Eclipse Life Sciences** completed patient enrollment in its phase 2 BETTIS-1 trial evaluating EC-104, a sustained-release fluocinolone acetonide implant for DME. Topline data are expected in fall 2026.
- **Genentech/Roche** secured FDA approval for extended use of faricimab (Vabysmo), allowing treatment of macular edema due to retinal vein occlusion beyond 6 months.
- **Merck** initiated the pivotal phase 2b/3 MALBEC trial to evaluate MK-8748, a dual-action bispecific antibody targeting Tie2 activation and VEGF inhibition, for wet AMD.
- The FDA granted 510(k) clearance for **Bausch + Lomb's** Bi-Blade+ vitrectomy cutter and Adaptive Fluidics update, expanding capabilities of the Stellaris Elite system. In addition, the company recently launched the Bi-Blade+ vitrectomy cutter in Europe.
- **Regeneron** secured FDA approval to extend the dosing intervals to up to 20 weeks for 8 mg aflibercept (Eylea HD).
- **i-Lumen Scientific** received FDA Investigational Device Exemption approval to begin enrollment in the United States for its i-SIGHT2 pivotal study evaluating a noninvasive bioelectric stimulation therapy for patients with intermediate to advanced dry AMD.
- **Lineage Cell Therapeutics** reported 36-month data from the phase 1/2a trial of RG6501 (OpRegen), a cell therapy for geographic atrophy. Findings show sustained visual acuity gains and retinal structural improvements following a single administration.
- **Atsena Therapeutics** shared positive 6-month data from Part B of the phase 1/2/3 LIGHTHOUSE study of ATSN-201, an investigational gene therapy for X-linked retinoschisis. Interim data show foveal schisis closure in 67% of treated adults, with no comparable changes in untreated eyes and no serious adverse events.
- **Bayer** has entered into an agreement to acquire **Perfuse Therapeutics**, gaining full rights to PER-001, a phase 2 therapy candidate for glaucoma and diabetic retinopathy.

Want more retina news from *Eyewire+*?

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THE AMD SPACE RACE



For anyone who grew up obsessed with space and dreamed of becoming an astronaut, this has been your year. For the first time since 1972, we sent astronauts to the moon. While they didn't land this time, they did slingshot around the dark side of the moon and return safely—renewing the interest in space exploration that had lain dormant in many of us.

To top off the revived space mania, the movie adaptation of Andy Weir's space thriller novel *Project Hail Mary* hit box offices with a bang, grossing nearly $580 million within the first 5 weeks in theaters. If you haven't read the book or seen the film, we highly recommend them, because they capture not only the sense of awe and adventure that comes with space exploration, but the hard work required to make it happen. The detailed mathematical calculations, careful understanding of scientific formulas, and feats of engineering they depict aren't for everyone, but we bet retina specialists will gravitate toward those parts of the story.

That's because we ourselves are doing our own version of these feats of engineering to develop the novel therapies that are poised to change our treatment paradigms—our own little retina space race. To those of us who have been around long enough, some of the drug delivery systems and novel mechanisms of action we are investigating now could be right out of a science-fiction novel. We could only dream of gene therapy, bioerodible hydrogel implants, and optogenetics 20 years ago, yet we are already awaiting phase 3 data for some of these treatments.

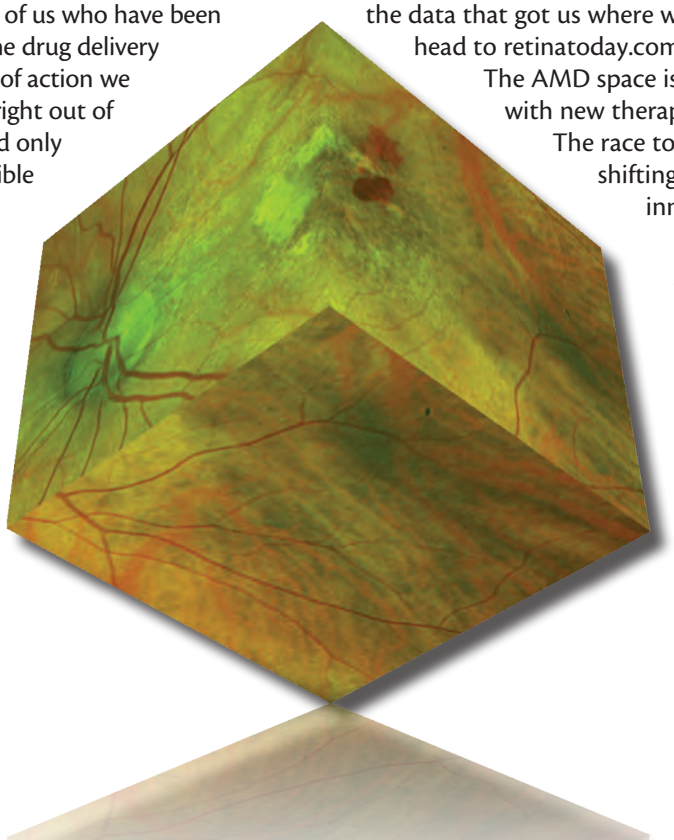
So, while we are all stuck in our injection clinics or worrying over some less-than-ideal data readouts, remember all the monotonous tasks (and failed missions) required to get the space shuttle to and from the moon without a hitch, and take heart: It's all part of the scientific process.

In this issue, we share the hope garnered by our robust and futuristic pipeline, as well as the successes that have already improved our care for patients with wet and dry AMD. To start, we (L.V. and R.L.A) sat down with Carl D. Regillo, MD, and Durga S. Borkar, MD, MMCi, to discuss the many novel therapies under investigation for wet AMD, including tyrosine kinase inhibitors and gene therapy.

With second-generation treatments in our armamentarium and more on the way, the already complex decision tree for AMD is only getting more difficult. Thus, Jennifer Adeghate, MD, PhD, and her team provide an update on step therapy and the various advocacy efforts, while Sean Adrean, MD, and Wesley Han, BS, walk us through the pearls and pitfalls of treating concurrent geographic atrophy (GA) and wet AMD.

Eleonora M. Lad, MD, PhD, and Kelly Donovan, MD, PhD, highlight novel imaging biomarkers that are helping us track progression in GA, and Luis Acaba-Berrocal, MD, and Anton Orlin, MD, provide a how-to for treating intermediate AMD with photobiomodulation (another therapy that sounds like it could have been lifted from science fiction).

To round out our coverage, Dimitra Skondra, MD, PhD, and her team share finding on the influence of diet on long-term AMD outcomes, and researchers at the Doheny Eye Institute have contributed three wonderful reference charts of landmark AMD clinical trials to help ground us in the data that got us where we are (to view those charts, head to retinatoday.com).



The AMD space is evolving at the speed of light with new therapies and delivery approaches. The race to meet patient needs amid the shifting economics of care has driven innovation further than some of us thought possible. But just as Ryan Gosling set out to save humanity with wildly unlikely and increasingly complicated math, science, and engineering, we are equally dedicated to saving patients' vision, one unlikely scientific success at a time. ■

- Allen C. Ho, MD
- Robert L. Avery, MD
- Lejla Vajzovic, MD

RETINA: THEN AND NOW

As part of our 20th anniversary, *Retina Today* is digging into the archives to reflect on how much the profession has changed.

MAY/JUNE SPOTLIGHT: CRVO, BRVO, AND DME

In 2006, Michael S. Ip, MD, contributed an article on *The Future of CRVO, BRVO, and DME Therapies* (follow the QR code to read the original article). He noted that "not many existing treatments produce profound improvements in visual acuity," and the only effective therapy for diabetic macular edema (DME) was laser photocoagulation.

Here, he reflects on the advances in our armamentarium for macular edema due to central retinal vein occlusion (CRVO), branch retinal vein occlusion (BRVO), and diabetic retinopathy over the last 20 years, and the innovations poised to change the treatment paradigm once again.

RETINA TODAY (RT): How were you treating RVOs and DME in 2006?

Dr. Ip: We were treating RVO and DME primarily with laser photocoagulation, or observation in the case of CRVO. Intravitreal corticosteroids were also an option, and level 1 evidence regarding their use came out following the release of the DRCR Retina Network's Protocol B dataset and the original SCORE dataset.[1,2]

RT: How has the therapeutic landscape evolved over the last 2 decades?

Dr. Ip: The introduction of anti-VEGF therapy came with the release of the BRAVO, CRUISE, RIDE, and RISE data for ranibizumab (Lucentis, Genentech/Roche) for RVO and DME, as well as the release of DRCR Retina Network's Protocol I.[3-6] The Copernicus, Galileo, VIVID, and VISTA trials for 2 mg aflibercept (Eylea, Regeneron) soon followed.[7-9]

These trials established anti-VEGF therapy as a standard of care for RVO and DME, which provides excellent results with overall excellent safety (Figure). Since then, we have added 8 mg aflibercept (Eylea HD, Regeneron) and faricimab (Vabysmo, Genentech/Roche) for both indications. For DME, the port delivery system with ranibizumab (Susvimo, Genentech/Roche) offers an extended treatment effect.

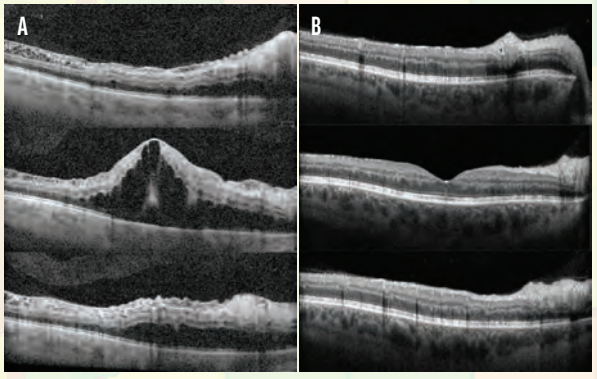


Figure. This patient presented with a CRVO in the right eye with a VA of 20/150 (A). In 2006, this patient would have been observed. In 2026, the patient was treated with a single intravitreal injection of faricimab, leading to a profound improvement in vision (VA of 20/30) at the 1-month follow-up (B).

RT: What new therapies are you hoping to see?

Dr. Ip: Although repeat injections are generally safe and highly effective, I hope to see more durable therapies to help reduce the treatment burden for patients with these chronic conditions. Novel intravitreal therapies are under development that may block different molecular pathways, leading to a more durable treatment effect. Gene therapies using a biofactory approach to release anti-VEGF also look promising. Some researchers are even evaluating very early RVO treatment with intravenous approaches to reduce erythrocyte aggregation to prevent progression to long-term complications.

Time will tell if these new approaches will join our list of options to treat macular edema from RVO and diabetic retinopathy. ■

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ONE TO WATCH

RT Retina Today

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Jordan D. Deaner, MD



Dr. Deaner's advice: Being a vitreoretinal surgeon is difficult, but we don't choose this career path because it's easy! Don't be intimidated by the tough cases, but rather embrace them as opportunities to continue to learn and grow.

WHERE IT ALL BEGAN

I grew up in the small, rural town of Stoystown, Pennsylvania. My mother is a third-generation nurse, my father a sixth-generation funeral director, and my older sister, for a time, became the seventh. From an early age, I was drawn to the sciences. My childhood room was filled with microscopes, telescopes, chemistry kits, and anatomy books. However, my mother guided me toward medicine as a career. I earned a Bachelor of Science in Chemistry at the University of Pittsburgh and spent significant time in a synthetic organic chemistry lab. Although the work was intellectually stimulating, I realized I wanted my life's work to have a more direct effect on the people around me. Medicine fused my love of science and service.

MY PATH TO RETINA

I went to medical school at the Sidney Kimmel Medical College of Thomas Jefferson University in Philadelphia. Initially, I planned to pursue internal medicine with the goal of specializing in critical care or infectious disease. During a rotation with the Retina Service, I watched as the retina fellow astutely diagnosed a patient with cytomegalovirus retinitis and, subsequently, HIV/AIDS. I was awestruck that a brief look into the eye could reveal so much. I left that rotation determined to become a vitreoretinal surgeon. Little did I know that this early encounter would serve as a foreshadowing of my path toward also becoming a uveitis specialist.

SUPPORT ALONG THE WAY

I've been incredibly fortunate to have exceptional mentors throughout my journey. In addition to James P. Dunn, MD, and Sunir J. Garg, MD, who introduced me to uveitis during residency, I'm deeply grateful to Allen C. Ho, MD; Carl D. Regillo, MD; and Julia A. Haller, MD, for their unwavering support. During my uveitis fellowship at Cole Eye Institute, I was mentored by Sunil Srivastava, MD; Sumit Sharma, MD; and Daniel F. Martin, MD. At the Duke Eye Center, where I completed my vitreoretinal surgery fellowship, I am especially thankful to Glenn Jaffe, MD, and Dilraj Grewal, MD, for their mentorship in both uveitis and vitreoretinal surgery, as well as to Lejla Vajzovic, MD, and Sharon Fekrat, MD, who challenged me to become the very best surgeon.

AN EXPERIENCE TO REMEMBER

My most cherished moment was receiving the Wills Eye Hospital Golden Apple Residency Teaching Award in 2025. Having been blessed with extraordinary teachers throughout my life, I feel a deep obligation to return that to my colleagues, residents, and medical students. To know that I have fulfilled that role, even in a small way, fills me with profound joy. ■

Jordan D. Deaner, MD, is a uveitis specialist and vitreoretinal surgeon at Mid Atlantic Retina, Wills Eye Hospital and an assistant professor of Ophthalmology at Sidney Kimmel Medical College of Thomas Jefferson University in Philadelphia. He serves as co-director of the Uveitis Unit and the Director of the Uveitis Fellowship Program at Wills Eye Hospital. Dr. Deaner is a consultant for Abbvie, ANI, Bausch + Lomb, Eyepoint, Genentech/Roche, and Regeneron and is on the Speakers Bureau for ANI and Bausch + Lomb. He can be reached at jdeaner42@gmail.com.

AMD COULD BE ON THE EDGE OF AN APPROVAL TIDAL WAVE



Which pivotal studies succeed—and in what number—will shape the trajectory of retina beyond 2026.

BY PETER K. KAISER, MD

When *Retina Today* updates its related macular degeneration (AMD) pipeline poster each year, I join the editorial team to review which elements need to be adjusted. One year, we re-drew the illustration of the complement cascade to make it more accurate. Another year, we added a color-coding system to the wet AMD pipeline candidate list to reflect which molecules targeted which receptors. In yet another year, we depicted the process by which gene therapy penetrates a cell to create a biofactory of therapeutic proteins. Each and every year, we added candidates to the list of pipeline products.

These tweaks slowly changed the face of the poster in service of creating a more perfect resource.

But this year, we did it all. New look, new illustration, new complement system schematic. And we actually cut some candidates rather than merely expanding the list. Think of it like pruning a bush: by removing candidates that have stalled in limbo for years, we made space for healthier candidates to grow.

We added badges to candidates that are undergoing pivotal clinical trials at the time of publication. Given the US FDA's new rules (which may consider sufficient a single pivotal study rather than a pair of studies), we might expect to see even more candidates with this badge in the coming years. Seeing the pivotal study badge peppered on both the wet AMD side and the dry AMD side of the poster, one has to wonder if we're on the edge of an approval explosion that could alter the treatment landscape.

Tyrosine kinase inhibitors (TKIs) in particular are in the spotlight. If FDA approval is granted to one or both candidates currently in the pre-approval period, shifts in practice patterns seem inevitable. We recommend keeping a close eye on these two molecules—while keeping the other eye, of course, on other candidates' trials, lest a press release announcing their results sneaks up on you.

We simplified the complement cascade schematic on the dry AMD side of this year's poster. The previous iterations, while accurate, were cluttered. This year's edition trims the cascade to only those areas targeted by a pipeline candidate. Don't let its simplicity fool you (the complement cascade remains exceedingly complex), but do enjoy the ease of this year's layout. ■

As always, we thrive on feedback. If you have ideas for next year's poster or want to include a technology not listed here, email Executive Director of Special Projects, Cara Deming, at cdeming@bmctoday.com.

> "SEEING THE PIVOTAL STUDY BADGE PEPPERED ON BOTH THE WET AMD SIDE AND THE DRY AMD SIDE OF THE POSTER, ONE HAS TO WONDER IF WE'RE ON THE EDGE OF AN APPROVAL EXPLOSION THAT COULD ALTER THE TREATMENT LANDSCAPE."

PETER K. KAISER, MD

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FELLOWS'FOCUS

STARTING RETINA FELLOWSHIP: FOUR STRATEGIES FOR SUCCESS




Make the most of this pivotal time in your retina career.

BY JUSTIN C. MUSTE, MD, AND DAVID FELL, MD

Transitioning from residency to retina fellowship marks an exciting and demanding phase of your career. It's a time of rapid growth, technical mastery, and intellectual challenge, where you lay the framework for your professional growth well into the future.

With this in mind, we offer four strategies to help ensure success as you begin your fellowship journey.

STRATEGY NO. 1: LEARN LIKE A BEGINNER AGAIN

Much like the beginning of residency, there will be frustrating times in fellowship when you fail at tasks you feel you should have mastered already, and other times when knowledge and technical skill come together seamlessly. Stay humble and lean into the feeling that you are starting all over again in a positive way. Try to avoid getting frustrated, and learn to take small wins as they come.

Ask questions—and lots of them. Observe how each attending approaches the same case differently. Reflect after every clinic and surgery on what went well and what could be improved upon. Resist the urge to rush toward autonomy; instead, focus on deliberate learning.

Approaching each day with curiosity and plenty of patience for yourself can only help to smooth the inevitably rocky learning process.

STRATEGY NO. 2: BUILD SYSTEMS EARLY

Fellowship can feel like a whirlwind of clinic notes, surgical cases, research projects, and lectures. A strong organizational system will protect your time and sanity.

Use a consistent task-tracking method—whether digital or paper—to capture to-dos as soon as they arise. Block protected time for note review, case preparation, and research tasks each week. Keep a concise surgical log from day 1. Small daily habits prevent chaos later, especially when you're juggling multiple attendings' schedules and clinical sites.

Record and review your (and your attendings') cases. You never know when valuable learnings will come up unexpectedly during surgeries, and reviewing last week's cases will always make you more prepared for the week ahead.

STRATEGY NO. 3: PROTECT YOUR ENERGY AND PERSPECTIVE

At some point in your training, you will hear the cliché: "Fellowship is a marathon, not a sprint." And there is truth to that; fellowship years are intense. It's easy to let the inertia of the day to day carry you forward and build a routine that resembles sleep, work, sleep, work, etc. But remember, the clock keeps ticking on your life outside of work as well.

With this in mind, schedule small, non-negotiable routines to help keep your life full outside the clinic, such as exercise, meals with friends, time outdoors, or even a hobby unrelated to medicine. Factoring such activities into your schedule will give you time and perspective away from work to reset, refresh, and come back stronger.

Maintaining your mental and physical health doesn't detract from your training; it enhances it by keeping you sharp, compassionate, and resilient.

STRATEGY NO. 4: CHOOSE RESEARCH PROJECTS THAT WILL TEACH YOU SOMETHING

As a fellow, you'll likely have more opportunity to participate in research than you did in medical school and residency, but you'll have far less time. Consider selecting opportunities that deepen your understanding of retinal disease and clinical decision making. Seek out a mentor

(Continued on page 20)

OPHTHALMIC ONCOLOGY PERSPECTIVES AT ARDS



During the 54th annual meeting, Tara A. McCannel, MD, PhD, explored the utility of prognostic biopsy and the psychological ups and downs that come with a cancer diagnosis.

BY JAMES P. WINEBRAKE, MD

The 54th annual Aspen Retinal Detachment Society meeting, held February 28 – March 4, 2026, in Snowmass, Colorado, was a feat of education with lectures on everything from surgical delivery of gene therapy and AI to diagnosing uveitis and surgical approaches to schisis detachments. This year, Tara A. McCannel, MD, PhD, delivered two lectures that offered a comprehensive framework for managing uveal melanoma: one grounded in the molecular science of risk stratification, the other in the psychology behind the diagnosis (Figure).

PROGNOSTIC BIOPSY IN UVEAL MELANOMA

Dr. McCannel opened with a case of a 56-year-old man with choroidal melanoma whose cytogenetic biopsy results—monosomy 3, chromosome 1p loss, and 6p gain—suggested an approximately 50% 5-year metastatic mortality risk. Twenty years later, the patient is alive and metastasis-free. The case served as a reminder that probabilistic data cannot predict individual outcomes.

She traced the origins of prognostic biopsy to a 1990 paper by Valerie White, MD, which first linked monosomy 3 to metastatic death.[1] Dr. McCannel began performing prognostic biopsy routinely and presented her early experience at the Retina Society in 2005, where she encountered significant opposition. The field has since shifted substantially with a growing body of literature published in the past 2 decades.

Limitations and Risks

Dr. McCannel devoted substantial attention to the limitations of prognostic biopsy. Tumor heterogeneity, sampling error, and inter-platform discordance all compromise accuracy. A 2015 study by the Augsburger group found that 16% of patients biopsied at two separate tumor sites received discordant gene expression profile results.[2] Her group also documented that 20% of Class 1A patients harbored monosomy 3 by molecular testing, and that choroidal metastases from systemic primaries can return Class 1 or Class 2 results—underscoring that gene expression profiles cannot substitute for clinical and pathologic diagnosis.



ABOUT THE SPEAKER

TARA A. MCCANNEL, MD, PHD

- Director, Ophthalmic Oncology Center, University of California, Los Angeles Stein Eye Institute of the David Geffen School of Medicine, Los Angeles

She raised concern about using biopsy results to determine whether to treat a lesion. With the number of practicing ocular oncologists increasing, many are seeing fewer new melanomas. Dr. McCannel disagreed with the practice of deferring treatment of growing lesions pending a Class 2 result and performing multiple repeat biopsies for triaging purposes, arguing this contributes to larger tumors, higher radiation doses, greater vision loss, and higher mortality.

When counseling patients, she deliberately downplays the biopsy result, framing it as one factor that may influence surveillance frequency rather than a definitive verdict. She avoids quoting survival percentages and emphasizes that outcomes are multifactorial. For example, a 2020 analysis demonstrated that marital status is an independent prognostic variable in uveal melanoma, underscoring how much remains unexplained by tumor biology alone.[3]

REFRAMING MINDSETS IN OCULAR CANCER AND VISION LOSS

Dr. McCannel's second lecture addressed the psychological dimensions of uveal melanoma care. Using the case of a 48-year-old woman presenting with photopsias and decreased vision, she catalogued the catastrophic thoughts that typically accompany a cancer diagnosis: fear of financial and functional loss, anticipatory



Image courtesy of Kevin Caldwell Photography

Figure. Dr. McCannel tackled the humanistic aspects of ocular oncology, including the implications of a prognostic biopsy and the patient's mindset during the cancer journey.

dread of the future, and hypervigilance to new systemic symptoms, to name a few. She noted that referring physicians, often themselves distressed, may inadvertently amplify these fears through language emphasizing blindness, organ loss, and therapeutic futility.

She grounded these observations in published data. A 2016 survey study found that nearly half of more than 2,000 respondents considered vision loss the worst possible health outcome.[4] A 2024 *JAMA* meta-analysis of more than five million patients found that visual impairment is associated with significantly elevated rates of suicidal ideation.[5] Her central arguments were: 1) It is not visual impairment itself that causes harm, but the fear surrounding it, and 2) That mindset is modifiable.

The Science of Mindset

Dr. McCannel drew on three bodies of research to support a mindset-based approach to patient care. Carol Dweck's work on growth versus fixed mindset demonstrated that children who view challenges as learning opportunities perform better and recover more readily from setbacks than those who view ability as fixed.[6] Crum et al demonstrated that beliefs produce concrete physiologic changes: Hotel workers who were told their daily tasks constituted meaningful exercise showed measurable reductions in weight and blood pressure within 4 weeks.[7] In a second study, subjects who believed they were consuming a high-calorie shake suppressed the hunger hormone more than those told the identical shake was low-calorie.[8]

A 2023 randomized trial by Zeidman et al evaluated a seven-module mindset intervention in newly diagnosed nonmetastatic cancer patients and found significantly improved quality of life, coping, and engagement in the intervention group.[9] Dr. McCannel described a parallel pilot study at her own institution using mindset-oriented video education for uveal melanoma patients.

Clinical Translation

Dr. McCannel advocated for precise language, favoring "vision change" over "vision loss," the latter of which carries an implicit finality that can undermine resilience. She describes vision as a binocular, brain-mediated experience rather than a Snellen acuity, and reassures patients that the brain adapts with remarkable fidelity to altered visual input. She cautioned against allowing OCT findings to define a patient's visual identity, noting that the macula represents only a fraction of the retina and functional sight. She called for clinicians to perform a personal mindset inventory before attempting to shift their patients', noting that mindsets are learned and can be intentionally revised.

Discussion centered on the clinician's informal role as a therapist, the importance of teaching empathy alongside technical skill, and the risks of peer support communities that overrepresent poor outcomes. Dr. McCannel encouraged pausing during clinic to model humanistic pearls to trainees.

Course Director Timothy G. Murray, MD, MBA, closed with a reflection that a fellow's tears at a diagnosis can move a patient more than any clinical counsel, a reminder that our humanity is the core to our work as physicians. ■

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SAVE THE DATE:
55th Annual Aspen Retinal Detachment Society Meeting
February 27 – March 3, 2027, Snowmass, CO

FIBRIN GLUE IN RETINA SURGERY





This tried-and-true tool may be a valuable tamponade alternative.

BY LAWRENCE CHAN, MD; TANNER FREDIANI, MD; AND GAURAV K. SHAH, MD

Fibrin glue, a biologic tissue adhesive that recreates the final step of the coagulation cascade, has been a common tool in ophthalmic surgery for decades. It consists of fibrinogen and thrombin, and when the two components are combined, they quickly polymerize into a fibrin clot. That clot forms a temporary scaffold that adheres tissues together.[1] Fibrin glue is often used in anterior segment surgery, such as conjunctival closure in strabismus surgery, conjunctival autografts in pterygium surgery, sealing wounds and perforations in corneal surgery, and amniotic membrane transplantation for ocular surface disease.[2-6]

The use of fibrin glue in vitreoretinal surgery is more recent and still evolving. Surgeons have used it as a localized hemostatic agent in the setting of trauma, iatrogenic retinal breaks, and diabetic neovascularization, and as a form of retinopexy/tamponade to treat rhegmatogenous retinal detachment (RRD).[7-13]

Here, we share the surgical steps and considerations for using this tool in your retina OR (Video).

THE PROBLEM WITH TRADITIONAL TAMPONADES

Tamponade agents such as gas (eg, air, SF_6, C_3F_8), silicone oil, and perfluoro-n-octane (PFO) are effective, but they come with several constraints and potential complications. They often require postoperative positioning, can significantly reduce vision for weeks or months, prevent patients from flying or traveling to high elevations, carry risks such as elevated IOP, and, in the case of silicone oil, require a second surgery for removal.[14,15]

WHEN TO CONSIDER GLUE

Using fibrin glue shifts the strategy from filling the eye to mechanically seal a break toward directly sealing the break itself without the need for tamponade. Using this strategy, the eye could be filled with balanced salt solution at the end of the case, resulting in clearer postoperative vision—which is particularly helpful for monocular patients—and allowing for air travel or driving to high elevations. In addition, fibrin glue self-dissolves in approximately 1 to 2 weeks, which is enough time for the chorioretinal adhesion from laser to form.

Patients with RRD who may benefit from fibrin glue include those who are poor candidates for gas tamponade, such as those who are monocular, unable to tolerate postoperative positioning, or who must travel by air or to high elevations. Others who may do well with fibrin glue include those with RRDs involving inferior retinal breaks and complex proliferative vitreoretinopathy requiring large retinectomies or giant retinal tears, where stabilization of the retinal edges is needed to prevent slippage (Figure 1).

Patients who can benefit from fibrin glue's hemostatic properties include those with uncontrolled bleeding from

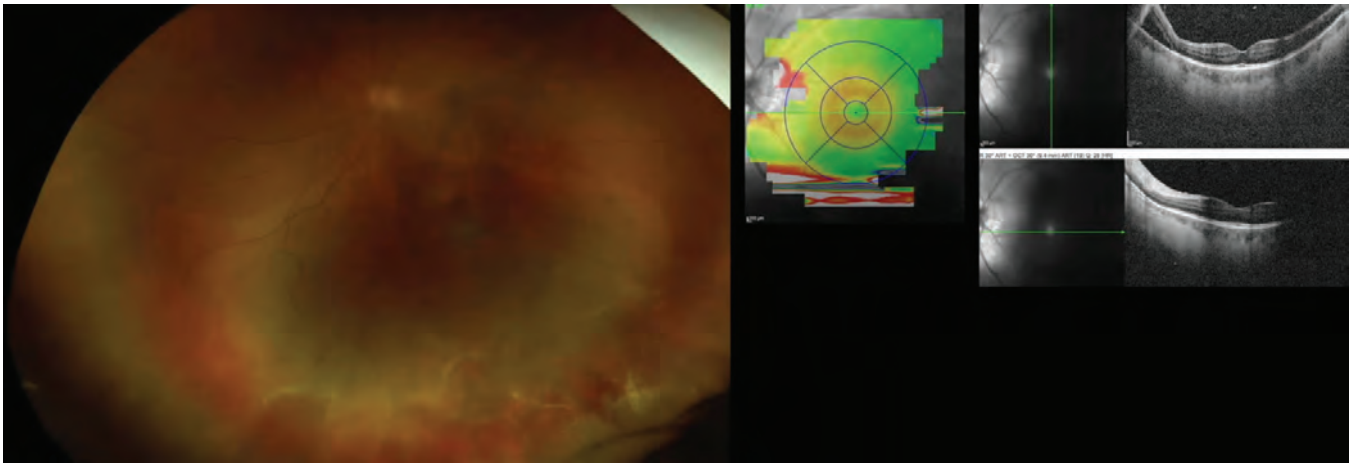


Figure 1. A 41-year-old man presented with a persistent inferior RD after scleral buckling surgery. In lieu of a traditional long-lasting tamponade, the surgeon applied fibrin glue.

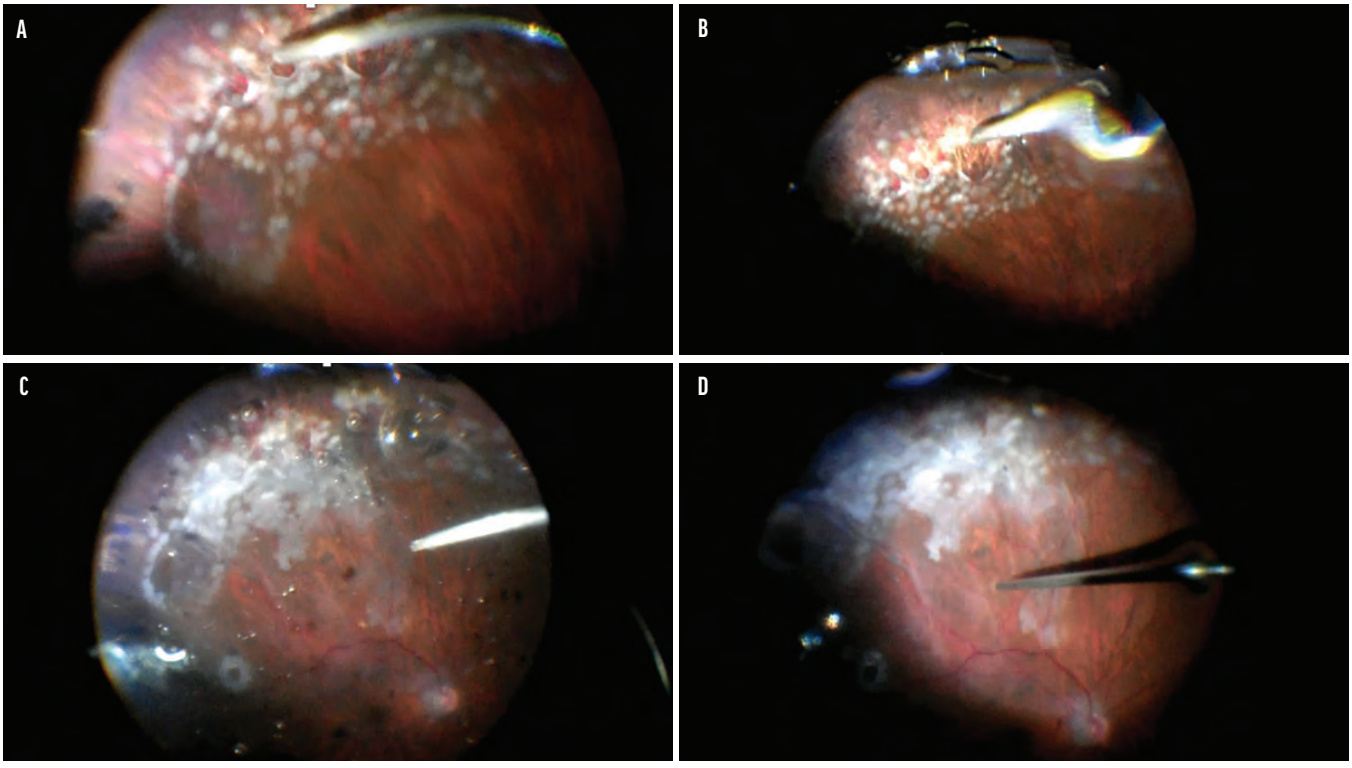


Figure 2. When applying fibrin blue, surgeons must instill the thick component (A) followed by the thin component (B). In this patient's case, the retina remained reattached when tested under fluid (C), and fluid-air exchange was repeated (D).

neovascularization (eg, proliferative diabetic retinopathy/tractional RDs) and bleeding from trauma, anticoagulation, or intraoperative iatrogenic causes.

Fibrin glue has also been successfully used to assist with macular hole closure and optic disc pit-related macular detachments.[7,11,16]

THE SURGICAL STEPS

The early steps are similar to a standard RD repair: core vitrectomy, induction of posterior vitreous detachment (if needed), meticulous peripheral shaving, flattening of the retina with fluid-air exchange or drainage through the break or a retinotomy, and endolaser around the break(s).

The retinal surface must be carefully dried under air, which is an important condition for the fibrin glue to work. The thick component of the glue is applied first, followed by the thin component shortly after (Figure 2). It is important to avoid using excessive amounts of glue. Only a drop at a time is necessary for each of the thick and thin components, and you can always apply more if needed. The polymerization occurs within seconds and is evident when the glue turns opaque.

The eye may need to be tilted toward the target area to minimize the amount of glue migrating posteriorly to the disc and macula. Sometimes, forceps can be used to pick up the partially formed coagulum from the posterior pole and move it back to the target area.

PITFALLS OF FIBRIN GLUE IN THE RETINA

The techniques described here are off-label applications of fibrin glue. Potential complications include displacement of the glue posteriorly, subretinal migration, and epiretinal membrane or proliferative vitreoretinopathy formation because fibrin can act as a scaffold. Intraocular inflammation is also possible because fibrin glue is a biologic product. There is a theoretical risk of viral or bacterial transmission because the glue is derived from pooled plasma, although modern processing techniques minimize this risk.[17]

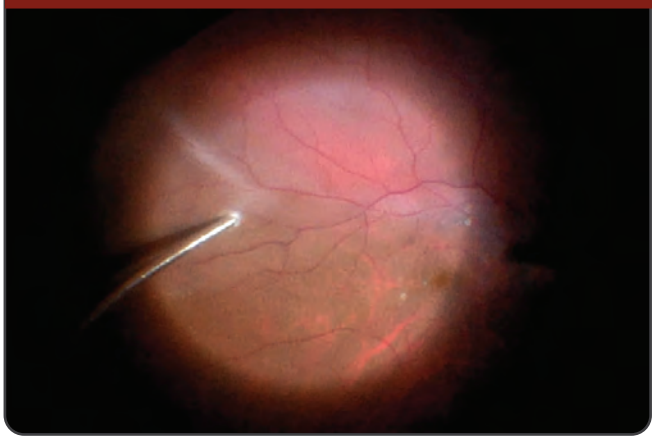
USE WITH CARE

Fibrin glue's ability to provide localized adhesion, hemostasis, and temporary support without the limitations of gas or oil make it an appealing option in select cases. Used judiciously, this tool, already a mainstay in most ORs, can be a valuable adjunct in the retina OR, offering flexibility when traditional tamponades are infeasible or less desirable. ■

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WATCH IT NOW

Video. Fibrin Glue-Assisted RD Repair



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(Continued from page 15)

NEW PODCAST!
THE FELLOW EYE: EPISODE 4

— NEW RETINA RADIO —
THE FELLOW EYE

Co-hosts David Fell, MD, and Justin C. Muste, MD, sit down with Allen C. Ho, MD, and Curtis Heisel, MD, MBA, to discuss the gene therapy landscape in retina and how fellows can get involved.

who can advise on feasibility and offer suggestions on who to work with. Perhaps you could write about a unique complication, present a case you found interesting, or investigate the outcomes of a procedure that did not go quite so well. In an increasingly AI- and data-driven world, you could focus on studies that teach you practical skills such as data analysis, imaging interpretation, or surgical outcomes assessment.

Finally, you could seek out a research project that is designed to help you narrow down an area of interest or set you up to pursue another fellowship.

It's important to set realistic goals: One or two well-executed papers or presentations are more valuable than many unfinished abstracts. To echo the above points, focus on honing the process—design, data collection, writing—so you can carry those skills forward into your career.

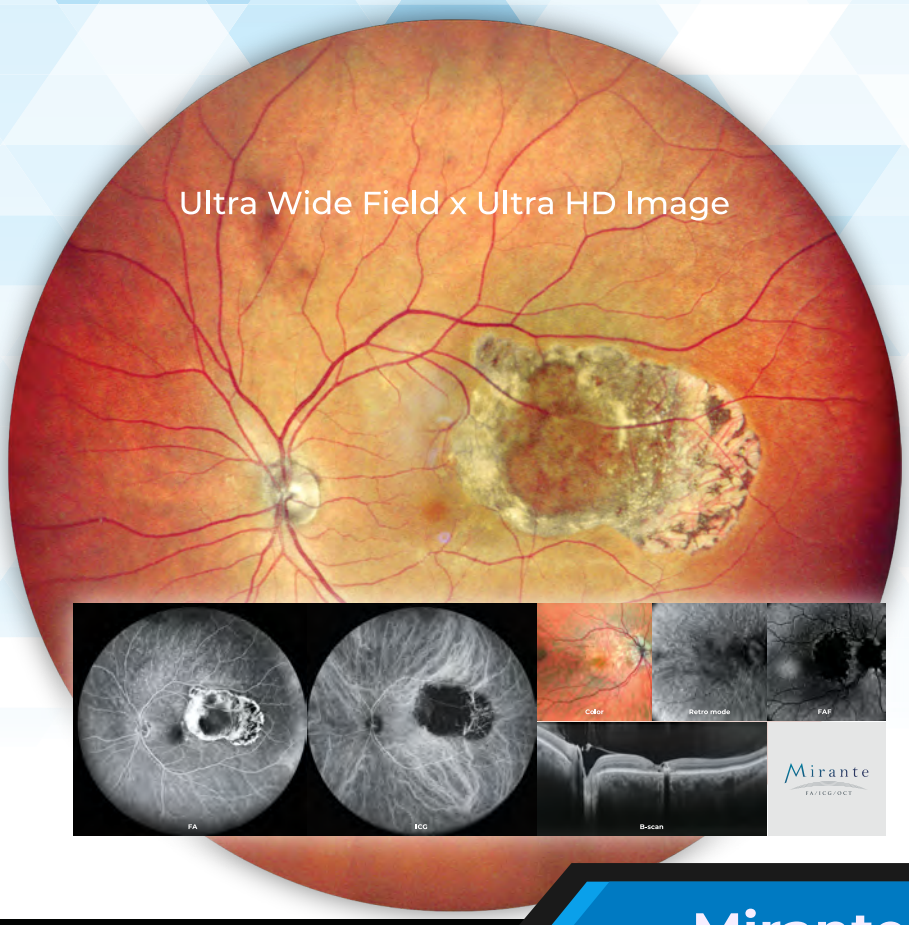
FORM GOOD, SUSTAINABLE HABITS

Fellowship is a time to transform from a competent resident into a confident, thoughtful retina specialist. The growth will be fast, but not always linear, and it will certainly continue beyond fellowship. Approach each challenge with the right mindset; remember, you are just a few years away from being solo and relying on the professional habits you've built to sustain you. ■

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March 13, 2023
2023-0009

NOVEL MOAS IN WET AMD

The pipeline is full of therapies that hold promise for extending treatment efficacy.

A discussion with Lejla Vajzovic, MD, FASRS; Robert L. Avery, MD; Carl D. Regillo, MD, FASRS; and Durga S. Borkar, MD, MMCi



The advent of anti-VEGF agents, coupled with OCT imaging, transformed the care of our patients with wet AMD. We now have amazingly effective therapies to preserve and even restore vision for these patients (Figure), with second-generation agents providing even more durability. Now, clinicians and researchers are working to extend efficacy to reduce treatment burden with novel sustained delivery platforms, gene therapies, and various mechanisms of action.

Here, experts discuss the many novel therapies with diverse mechanisms of action and delivery methods working their way through the pipeline that hold promise for extending treatment efficacy for patients with wet AMD.

LEJLA VAJZOVIC, MD, FASRS: HOW MIGHT NOVEL DELIVERY METHODS EXTEND DURABILITY OR REDUCE TREATMENT BURDEN FOR OUR PATIENTS WITH WET AMD?

Robert L. Avery, MD: First, we are already using higher molar doses of our first-generation anti-VEGF agents. For example, compared with the legacy ranibizumab 0.5 mg (Lucentis, Genentech/Roche) and aflibercept 2 mg (Eylea, Regeneron), we now have aflibercept 8 mg (Eylea HD, Regeneron) and faricimab 6 mg (Vabysmo, Genentech/Roche). The higher doses allow for longer durability.

There's significant variability in the need for treatment among patients with wet AMD, and with OCT and these newer drugs, we can extend many patients out and treat them when needed.

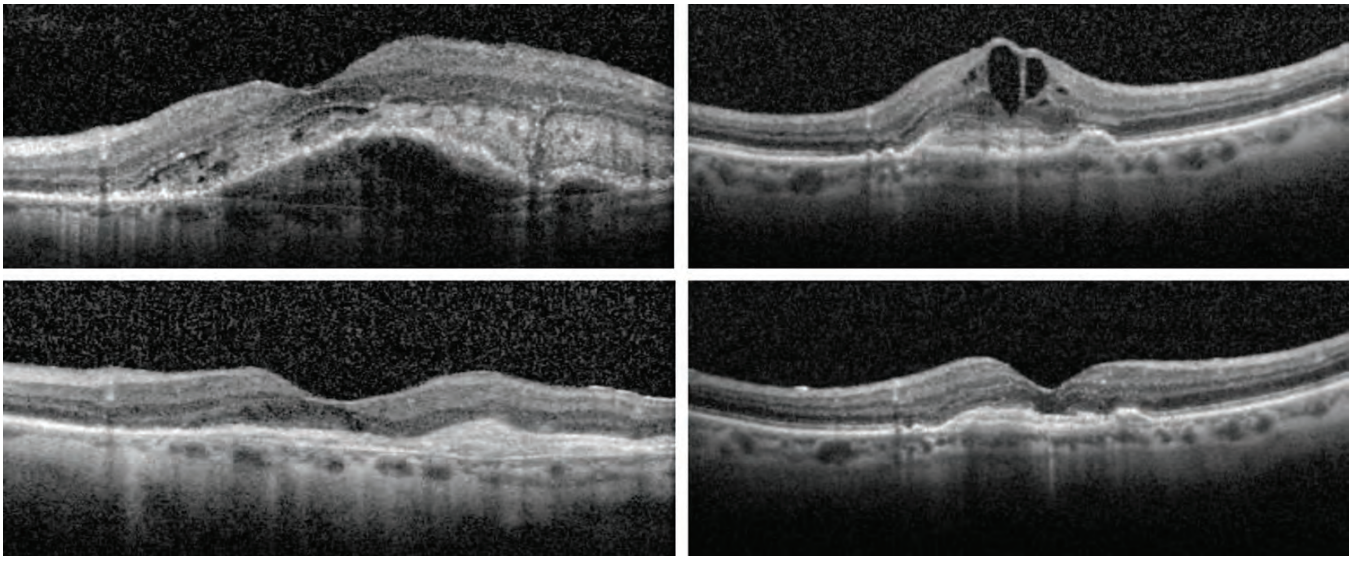
Second, higher doses of other drugs and newer mechanisms of action are being developed. Ollin Therapeutics has a compound, OLN324, that is smaller than a full-length antibody, and significantly higher molar doses are being tested. In early trials, it seems to have a better drying effect than even some second-generation anti-VEGF agents.[1]

As for drug delivery, researchers have found ways to put these molecules into slow-release polymers. Small molecules such as tyrosine kinase inhibitors (TKIs) can go into hydrogels. I am excited to see the phase 3 results from several companies with TKIs coming out soon.

However, the macromolecules are harder to integrate into a polymer, as they are more likely to denature and aggregate. Still, Re-Vana has a photocrosslinked polymer that shows promise for enabling anti-VEGF agents to work even when embedded in a slow-release device.

KEY TAKEAWAYS

- Novel drug delivery approaches hold promise for extending treatment efficacy for patients with wet AMD, including gene therapy and tyrosine kinase inhibition.
- Extending treatment durability should also decrease visit burden for patients with wet AMD, maybe with the help of new imaging tools such as home OCT.
- Several hurdles remain, including the risk of inflammation, the potential for the denaturization and aggregation of macromolecules, and cost.
- Other novel approaches include tweaking the VEGF-A and angiopoietin-2 blockades, interleukin-6, WNT agonism, and direct Tie2 agonism.



Images courtesy of Carl D. Regillo, MD, FASRS

Figure. OCT images of two cases of wet AMD before (above) and after (below) three monthly injections of a first-generation anti-VEGF agent with excellent resolution of exudation.

There are also other ways of forming antibody biopolymer conjugates, which are covalent links of an antibody to a large polymer. Kodiak Sciences is working on tarcocimab and KSI-501, both antibody biopolymer conjugate drugs, with KSI-501 binding both VEGF and interleukin-6. By binding an antibody to a polymer with a huge molecular weight, you have longer retention in the vitreous and a longer half-life.

Finally, some companies such as Optigo are binding anti-VEGF agents covalently to a molecule that binds vitreous components, such as collagen or hyaluronic acid. These agents can linger in the vitreous, using the existing vitreous as their polymer, so to speak, and have great durability.

Multiple exciting options are on the horizon for us to deliver these drugs that have been so revolutionary in our treatment of retinal diseases, and all these different mechanisms have a lot of promise.

Carl D. Regillo, MD, FASRS: We have a sustained delivery platform that's FDA approved and commercially available, the port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche). It is well established that this sustained delivery approach provides effective therapeutic levels of ranibizumab for at least 6 months in most patients with wet AMD. We now have more than 7 years of follow-up showing outstanding visual outcomes with excellent maintenance of the vision gains that you get in the induction phase with anti-VEGF biologic injections that carry through for years to follow in the maintenance phase.

Not only is this sustained delivery available now, but the concept of sustained delivery bodes well for any slow release of an anti-VEGF agent in the pipeline, such as anti-VEGF biologic gene therapy or small molecules (eg, TKIs) incorporated into injectable sustained-release drug delivery polymer platforms.

Durga S. Borkar, MD, MMCi: The key will be how we integrate some of these new therapies into practice. We think a lot about extended durability and decreasing treatment burden, but we also need to decrease visit burden for our patients with some of these drugs. We will need to incorporate other technologies such as home OCT, if that becomes widely available, to decrease the amount of times our patients must come into the clinic.

DR. VAJZOVIC: WHAT DO CLINICIANS NEED TO KNOW ABOUT VARIOUS GENE THERAPIES UNDER INVESTIGATION?

Dr. Borkar: Our clinical trials show that anti-VEGF agents work well for most patients, but our real-world data suggest we're likely undertreating many patients for a variety of reasons. Pharmacokinetic studies and anatomic outcomes in central subfield thickness show the seesaw pattern in routine care. This is where gene therapy comes into play.

Most investigational therapies in the wet AMD space are ocular biofactories, which use an adeno-associated viral (AAV) vector to continuously produce an anti-VEGF protein. ABBV-RGX-314 (sura-vec, Regenxbio/Abbvie) has promising results both for subretinal and suprachoroidal administration of an AAV8 vector encoding an anti-VEGF fab that's similar to ranibizumab. The phase 3 subretinal trials, ATMOSPHERE and ASCENT, should have pivotal data later this year. The company also has a phase 2 suprachoroidal program, AAVIATE. The different modes of delivery are important when considering incorporating gene therapy into routine clinical care, where it might be most accessible to patients in the office, rather than taking them to the OR.

Additionally, there are two intravitreal gene therapies under investigation from Adverum (ixo-vec) and 4DMT (4D-150), both delivering an AAV vector encoding

aflibercept, although the 4DMT vector is a synthetic capsid. Both companies have shown promising results with initial concerns about inflammation with intravitreal administration. Finding the appropriate doses and initiating antiinflammatory treatment at the onset is important.

Lastly, and a little earlier in development, is NG101 (elisigen, formerly Neuracle Genetics), which is also an AAV8 vector that's designed for a low-dose delivery of aflibercept.

One or more of these options may hopefully become available to soon to help us manage this chronic disease in a way that's more sustainable for our patients.

DR. VAJZOVIC: HOW DO YOU SEE TKIS FITTING INTO OUR LONG-TERM MANAGEMENT OF WET AMD?

Dr. Regillo: Most TKIs offer an intravitreally delivered sustained delivery platform. These are small molecules that must be packaged in such a way that there's slow release or sustained delivery over at least several months. There are two candidates in phase 3 now: OTX-TKI (Ocular Therapeutix) and EYP-1901 (Eyepoint Pharmaceuticals). Both are intravitreal, but they differ in the type of TKI molecule and the associated bioerodible polymer. Based on early phase 1/2 data, they appear to be similar in terms of good wet AMD disease control for about 6 months or more in most patients along with having a good safety profile.

Sustained delivery approaches, in general, not only have the potential to decrease treatment burden, but they also hold the promise of better real-world vision outcomes because any sustained delivery method is going to be more forgiving to variable patient follow-up or missed appointments. If a patient skips a visit or two because of health issues, their vision likely won't be affected as much because there is still some degree of therapeutic effect in the eye to keep the disease in check. For patients who need anti-VEGF biologic injections on a frequent basis to control disease, it would be great if we could offer them something that's much more durable in the maintenance phase of therapy. With TKIs, the preliminary data show that most patients can be extended to at least 6 months. Later this year and in early 2027, we're going to see all the phase 3 study results for both these drug candidates. I call it the year of the TKIs.

DR. VAJZOVIC: WHAT ARE SOME OF THE CHALLENGES INVESTIGATORS FACE WITH THESE NEW THERAPIES POTENTIALLY COMING ON THE MARKET?

Dr. Avery: The first is inflammation. We have been spoiled with our early agents, which are shockingly benign without a lot of inflammation. As we evolved our therapies with second-generation agents and higher concentrations, we started to see more inflammation. We must weigh the benefits of treatment with the risk of inflammation that comes with many investigational therapies.

The intravitreal gene therapies come with more concern for inflammation compared with the surgical subretinal delivery approach, but the trade-off is going to the OR versus an in-office injection. In addition, companies are developing lower intravitreal doses to minimize the risk of inflammation.

The second concern with many of the extended-delivery platforms is denaturization and aggregation of the macromolecules. If the polymer is dissolvable, such as a hydrogel, patients may see floaters. It's not a big problem, and it won't stop the potential adoption of these therapies, but it's something to take into account.

The third issue will be cost. The cost of the original anti-VEGF agents has dropped considerably over the years, and that will be a factor when new therapies hit the market. In addition, step therapy and other insurance coverage issues will come into play as well, limiting initial use of the new agents.

Dr. Regillo: As we get into an era of more choice with novel therapies, there will be potential trade-offs in terms of side effects. For example, with intravitreal gene therapy, patients will need to be monitored for intraocular inflammation and may need to use steroid drops to suppress inflammation for long periods of time. Other novel approaches that require a surgical procedure to administer—such as the PDS or subretinal gene therapy—may face surgical adverse events and related safety issues. As new options become available, the conversations with patients will become much more involved to discuss a broader array of treatment choices with very different risk-benefit profiles.

Dr. Borkar: When thinking about the risks and benefits with these potential new therapies, we will also have to decide what treatment is best for each patient because there are no head-to-head data. Most of the trial data compares with standard of care, and we don't know how many of these treatments compare with each other and who responds better to one versus another. It's going to be a challenge to generate that data outside of a trial setting



FURTHER READING

Anti-VEGF and Beyond: Expanding Therapeutic Options for Wet AMD

A 2025 review of clinical trials evaluating novel therapies for wet AMD.

By Matthew Elitt, MD, PhD; Pariyamon Thaprawat, BS; and Nita Valikodath, MD, MS



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to help us understand which patients would do well with each of these therapies.

Dr. Vajzovic: We will definitely need more personalized treatment strategies and imaging biomarkers to understand which drug might be the best fit for each patient with AMD.

DR. VAJZOVIC: WHAT OTHER NOVEL THERAPIES ARE UNDER INVESTIGATION IN THE WET AMD SPACE?

Dr. Regillo: We are continuing to tweak the VEGF-A blockade by making the molecules smaller for better penetration or greater molar concentration, increasing binding affinity, or increasing drug half-life through novel mechanisms such as binding to the native components of the vitreous gel including heparan or hyaluronic acid. There are also new or different mechanisms of action. We're all familiar with faricimab, which is both a VEGF-A and angiopoietin-2 (Ang-2) blocker. Other companies are exploring enhanced Ang-2 blockades or direct Tie2 stimulation. Interleukin-6 is also being explored as a target for wet AMD, as is WNT agonism as a stand-alone or combination approach.

Dr. Avery: Direct Tie2 agonism, as opposed to Ang-2 blockade, is particularly interesting with MK-8748 (Tiespectus, Merck); so far, it's showing a very nice effect in AMD, and it may be able to work in the relative absence of Ang-1. I'm also interested in the research on antifibrosis agents or agents that may be able to minimize the atrophy that is developing after the choroidal neovascular membrane is treated.

It seems that we've gone about as far as we can go with respect to visual improvement with anti-VEGF agents. There's room for better durability, but to get better vision, it may take other mechanisms such as fibrosis and atrophy, which seem to cause a lot of the visual loss once we've stopped the leakage with anti-VEGF agents.

Dr. Vajzovic: It's a very exciting time for those of us in retina. It's important that we begin to think about how all these therapies coming to the market in the future can help us take care of our patients better. ■

Editor's note: This manuscript has been edited from the original transcript for clarity and space purposes.

1. Wykoff CC. Randomized phase 1b trial of OLN324 vs faricimab-first-time results of the JADE trial. Presented at Angiogenesis, Exudation, and Degeneration 2026; February 7, 2026. Virtual.

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ANTI-VEGF STEP THERAPY: AN UPDATE

Despite ongoing advocacy efforts, this payer policy persists, putting vision at risk.

By Lucas McGuire, BS; Baseer Ahmad, MD; and Jennifer Adeghate, MD, PhD





In ophthalmology, step therapy has become increasingly relevant with anti-VEGF injections for various indications such as wet AMD, diabetic macular edema (DME), and retinal vein occlusion (RVO). Following the 2019 Centers for Medicare and Medicaid Services (CMS) decision permitting Medicare Advantage plans to impose step therapy for Part B drugs, many insurers adopted a bevacizumab (Avastin, Genentech/Roche)-first approach. Although bevacizumab is effective for many patients, alternatives such as ranibizumab (Lucentis, Genentech/Roche), aflibercept 2 mg/8 mg (Eylea/Eylea HD, Regeneron), and faricimab-svoa (Vabysmo, Genentech/Roche) are FDA-approved for intravitreal use and can provide superior outcomes for certain patients (Figures 1–3).

We reviewed the developments in this space between 2019 and 2024, beginning with the CMS policy change that permitted step therapy for Medicare Advantage Part B drugs. We included US-based policy articles, clinical studies directly related to ophthalmology, and advocacy statements from the AAO and the American Society of Retina Specialists (ASRS).

Here, we highlight our findings, including the clinical outcomes, safety concerns, and evolving practice patterns that have emerged under step therapy, as well as potential next steps from an advocacy standpoint.

SAFETY CONSIDERATIONS AND PRACTICE PATTERNS

Step therapy introduces several safety risks that extend beyond administrative burden and can have direct implications for patient outcomes. For example, a 2024 multicenter study found that nearly 60% of prior authorization requests for anti-VEGF therapy led to treatment delays, despite a 96% eventual approval rate.[1] These delays required a median of 100 minutes of staff time per request and, more importantly, postponed time-sensitive treatment of conditions, such as wet AMD

KEY TAKEAWAYS

- Following the 2019 Centers for Medicare and Medicaid Services decision permitting Medicare Advantage plans to impose step therapy for Part B drugs, many insurers adopted a bevacizumab (Avastin, Genentech/Roche)-first approach to intravitreal anti-VEGF therapy.
- Step therapy introduces several safety risks that extend beyond administrative burden and can have direct implications for patient outcomes.
- DRCR Retina Network Protocol T data show that treatment with aflibercept 2 mg (Eylea, Regeneron) led to improved resolution of edema compared with bevacizumab at 1 and 2 years for patients with lower presenting visual acuity (20/50 to 20/320).
- Advocacy efforts in ophthalmology highlight the persistence of step therapy and the challenges of influencing federal and state policy.

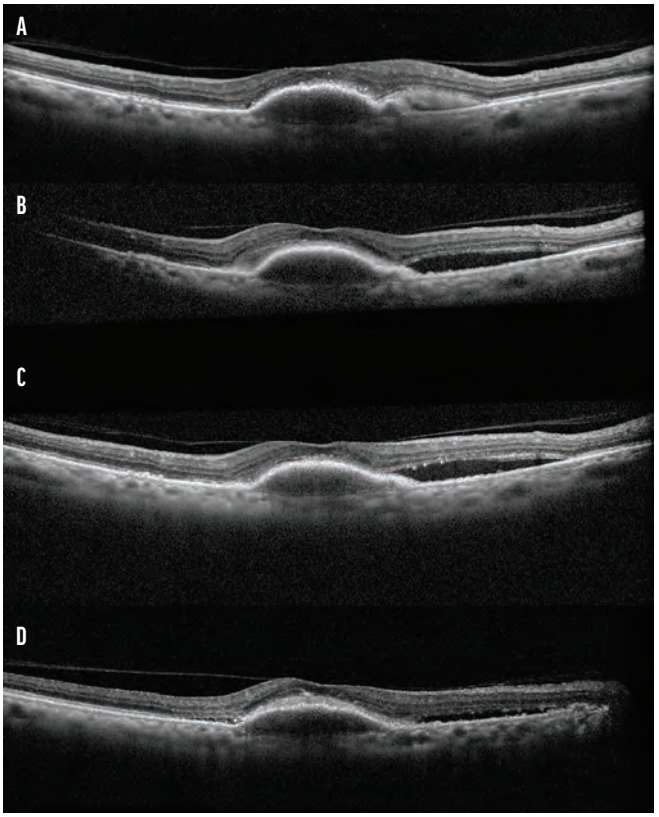


Figure 1. Sequential OCT images of the right eye of a patient with wet AMD illustrate the disease course under step therapy: baseline imaging prior to initiation of bevacizumab with subretinal hemorrhage (A); persistent/worsening fluid after 4 months of continued bevacizumab (B); no improvement 3 months later (C); improvement in subretinal fluid 6 months after transitioning to aflibercept (D). BCVA remained 20/100 throughout.

and DME, for which even short interruptions can result in irreversible vision loss.[1] Furthermore, in busy retina practices, this additional administrative burden diverts resources away from direct patient care.

In addition, with rigid fail-first protocols, patients are often required to receive three monthly bevacizumab injections before a switch can be approved. Because injections cannot be given more frequently than every 4 weeks, clinicians face an inflexible treatment window. To complicate matters further, some payers have mandated that if any of the three monthly payer-preferred drug injections fall outside a 4- to 6-week window, the process must be restarted. In progressive diseases with potentially severe sequelae such as macular subretinal hemorrhage in wet AMD, waiting periods can be harmful, leaving patients at risk of irreversible vision loss.

Reliance on compounded bevacizumab also exposes patients to supply chain instability. The AAO and ASRS highlighted this risk as early as 2021 when outsourcing facilities faced sterility and regulatory issues, and the problem intensified in 2024 with the discontinuation of bevacizumab production from Optum Specialty Pharmacy, the facility responsible for 45% of bevacizumab repackaging in the United States.[2,3]

These disruptions underscored the fragility of a system dependent on a single, repackaged first-line drug, particularly when policy requires its use before alternatives can be offered. At the peak of those supply chain issues, many patients were unable to receive treatment due to the payer step therapy requirement for bevacizumab first, which was often unavailable.

Together, these issues demonstrate that step therapy not only increases administrative burden but also introduces structural vulnerabilities into care delivery. By limiting flexibility, delaying access, and depending on a fragile supply chain, step therapy protocols create risks that compromise both patient safety and practice efficiency.

CLINICAL OUTCOMES

Numerous comparative studies have been conducted since newer generation anti-VEGF agents have arrived on the market, highlighting how initial agent selection and treatment delays can affect outcomes.

The DRCR Retina Network Protocol T compared outcomes of aflibercept, bevacizumab, and ranibizumab in DME treatment and showed similar visual outcomes in patients with mild baseline vision loss at 2 years; however,

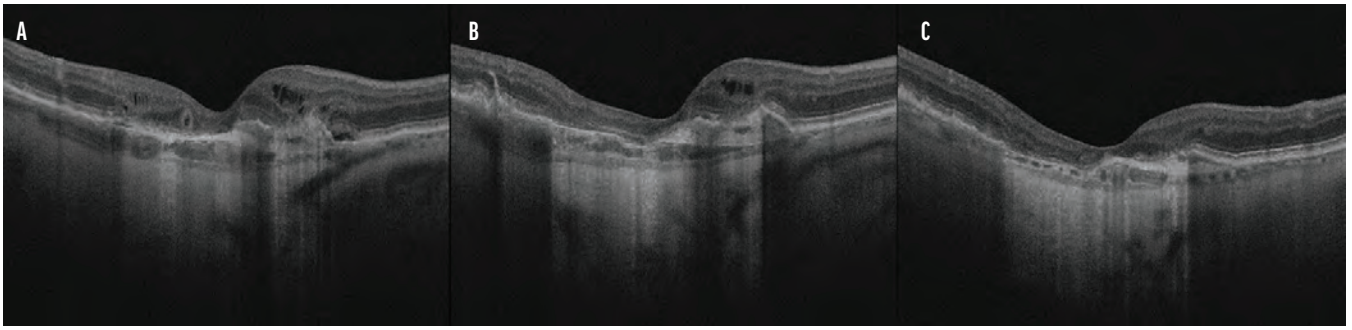


Figure 2. OCT images of the left eye of a patient with wet AMD after loss of response to long-term bevacizumab given every 10 weeks (A). Aflibercept was subsequently denied by the patient's insurance. Exudation remained stable on bevacizumab given every 6 weeks (B). Once step therapy was completed and aflibercept was approved, the exudation resolved 10 weeks after the second dose (C). VA remained stable at 20/40.

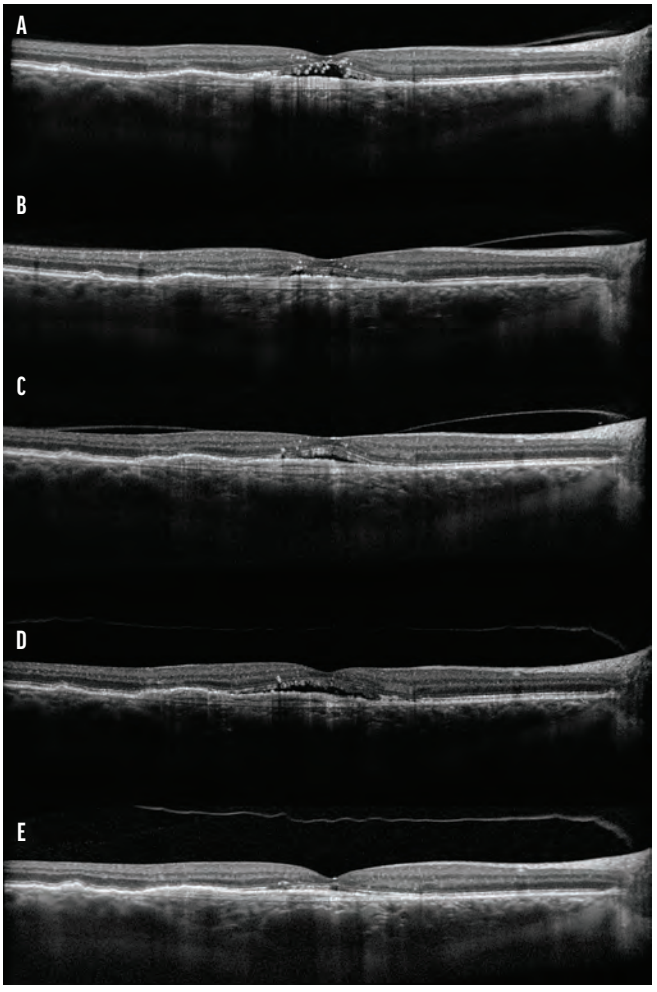


Figure 3. OCT images of the right eye of a patient with wet AMD demonstrate the sixth (A) and 17th (B) dose of bevacizumab administered every 4 to 6 weeks. After switching to aflibercept with dosing every 7 weeks, there was a slight increase in subretinal fluid at 4 months (C) and 9 months (D). The patient was then switched to faricimab, with good anatomic response after three doses (E). VA remained stable between 20/25 and 20/40 during this time.

treatment with aflibercept led to improved resolution of edema compared with bevacizumab at 1 and 2 years for patients with lower presenting visual acuity (20/50 to 20/320). Additionally, laser photocoagulation was less frequently required in the aflibercept group.[4] These findings suggest that a bevacizumab-first approach may disadvantage certain patients with more advanced disease.

Another randomized controlled trial directly compared bevacizumab-first therapy with aflibercept monotherapy. Although 2-year visual outcomes were similar, nearly 70% of patients in the step therapy group required switching to aflibercept to achieve comparable outcomes, and they underwent more injections overall.[5] This demonstrates that noninferior vision can come at the cost of a greater treatment burden, and a potential gap between what is acceptable from a payer perspective and what is practical clinically.

Cao et al compared aflibercept and bevacizumab in wet AMD using a treat-extend-pause/monitor approach.[6] Patients who received aflibercept injections were more often weaned off therapy at 1 year (43% vs 15%), required fewer injections, and achieved longer treatment intervals. Visual acuity was similar, but aflibercept showed less vision loss and better fluid resolution on OCT, supporting its role in reducing treatment burden and maintaining more consistent disease control.[6] For patients and providers, these differences translate into fewer visits, less treatment fatigue, and greater disease stability over time.

Li et al also found that faricimab-svoa demonstrated noninferiority in achieving improved central subfoveal thickness compared with other anti-VEGF therapies at extended dosing intervals.[7] This may ultimately reduce payer costs when considering the number of injections received in a year per patient.

Thus, while step therapy may not always compromise long-term visual acuity, it often increases treatment burden, prolongs therapy, and risks undertreatment in patients with severe disease.

ADVOCACY RESPONSES

Advocacy efforts in ophthalmology have highlighted both the persistence of step therapy and the challenges of influencing federal and state policy. In 2018, more than 200 organizations, including the AAO, warned that fail-first protocols would delay care and jeopardize outcomes.[8,9] The AAO later supported the Improving Seniors' Timely Access to Care Act to curb prior authorization and step therapy requirements in Medicare Advantage plans.[10]

Despite the push to streamline prior authorization and reduce barriers to care, these measures have produced only incremental change.

Advocacy has led to small regulatory adjustments to existing step-therapy policies. In November 2021, CMS issued new guidance prohibiting Medicare Advantage plans from mandating the use of bevacizumab-bvzr (Zirabev, Pfizer) or bevacizumab-awwb (Mvasi, Amgen)—biosimilars not FDA-approved for ophthalmic use—as substitutes for repackaged bevacizumab. However, CMS maintained that FDA-approved biosimilars could be used in step therapy programs. While this acknowledged the safety concerns raised by the AAO and ASRS, it stopped short of addressing the broader risks inherent in bevacizumab-first policies, such as cost-centricity and minimal long-term safety data on biosimilars.[11,12]

The ASRS and AAO directed advocacy efforts when clinical care was disrupted by bevacizumab supply shortages. Their 2024 petition followed the discontinuation of Optum Specialty Pharmacy's bevacizumab production and underscored how policies mandating a single, repackaged drug could leave patients without timely treatment, particularly if step therapy is required.[3] Despite

TO ENSURE EQUITABLE ACCESS AND OPTIMAL CLINICAL OUTCOMES, FUTURE POLICIES MUST BE GUIDED BY CLINICAL NUANCE, REAL-WORLD OUTCOMES, AND COLLABORATIVE DIALOGUE BETWEEN PROVIDERS, PAYERS, AND POLICYMAKERS.

these advocacy efforts, CMS policies remained unchanged.

Overall, advocacy has raised awareness and achieved modest safeguards, but the lack of decisive federal action continues to leave patients vulnerable. Without stronger policy alignment, reliance on state-level reforms and piecemeal adjustments may perpetuate fragmented access to sight-saving therapy.

WHAT YOU CAN DO

Despite years of coordinated advocacy efforts in ophthalmology, policy inertia at the federal level has left clinicians and patients navigating treatment algorithms that may not reflect current clinical standards, or account for patient-specific risk.

Although some randomized and real-world data show that step therapy can result in comparable long-term outcomes for select patients, these findings must be contextualized against the practical burdens of care delays, administrative requirements, and rigid scheduling restrictions. In the clinic, requiring clinicians to rely on first-generation anti-VEGF agents leaves many populations (including seniors) vulnerable to compliance issues and loss to follow up.

To ensure equitable access and optimal clinical outcomes, future policies must be guided by clinical nuance, real-world outcomes, and collaborative dialogue between providers, payers, and policymakers. Continued advocacy, combined with transparent data collection and evidence-based reform, will be essential to aligning step therapy with the principles of patient-centered care. ■



FURTHER READING

Prior Authorization Burden for Anti-VEGF Therapies

By Ella H. Leung, MD; Saira Khanna, MD; Michael M. Lai, MD, PhD; Charles C. Wykoff, MD, PhD, FASRS, FACS; J. Michael Jumper, MD; Jill Blim, MS; and Sabin Dang, MD



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Ken is a real patient with GA, and Dr. Arshad Khanani is his retina specialist who treats his GA with IZERVAY.

Moments like this deserve your protection.

Ken loves to golf—Dr. Khanani loves to keep him golfing for longer.

Dr. Arshad Khanani is a compensated physician.

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 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, to permit prompt and appropriate management.

References: 1. Holz FG, Strauss EC, Schmitz-Valckenberg S, van Lookeren Campagne M. Geographic atrophy: clinical features and potential therapeutic approaches. *Ophthalmology*. 2014;121(5):1079-1091. **2.** Izervay. Package insert. Northbrook, IL: Astellas Pharma US, Inc.; 2026. **3.** Syfovre. Package insert. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2025. **4.** Astellas Pharma US, Inc. Izervay. Data on File.

Protect healthy retinal cells for longer with IZERVAY[1,2]

Only IZERVAY showed statistically significant efficacy at one year in two Phase 3 trials[2,3]

In 2 clinical trials of 624 people, IZERVAY was proven to reduce the annualized rate of GA lesion growth by 18%-35% in one year compared to those who were not treated.[2]

Demonstrated safety through 2 years in the GATHER trials[2]

Consistent real-world safety across nearly 600k vials distributed.[2,4*]

izervay® (avacincaptad pegol intravitreal solution) 2 mg

Treat GA to help preserve vision for longer[1,2]

Scan to explore IZERVAY:
The #1 prescribed FDA-approved treatment for new GA patients[4†]

†Based on Symphony data from 3/24-12/25. May not represent entire population.

*As of 02/26. Based on samples and commercially distributed vials.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Neovascular AMD

- In the GATHER1 and GATHER2 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. Over 24 months, the rate of neovascular (wet) AMD or choroidal neovascularization in the GATHER2 trial was 12% in the IZERVAY group and 9% in the sham group. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

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.

ADVERSE REACTIONS

Most common adverse reactions (incidence ≥5% and occurred with frequency ≥2% vs. sham) reported in patients receiving IZERVAY for up to 24 months in GATHER2: conjunctival hemorrhage, blurred vision, increased IOP, wet AMD, punctate keratitis, and eye pain.

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

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MAT-US-IZE-2026-00244 03/26

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 800-707-4479.

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 dosage 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).

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 the GATHER1 and GATHER2 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. Over 24 months, the rate of neovascular (wet) AMD or choroidal neovascularization in the GATHER2 trial was 12% in the IZERVAY group and 9% in the sham group. 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 for up to 12 months pooled across the GATHER1 and GATHER2 studies are listed below in Table 1.

Table 1: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye up to 12 months

Adverse Drug Reactions	**IZERVAY N=292**	**Sham N=332**
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Blurred Vision*	8%	5%
Choroidal neovascularization	7%	4%
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.

Adverse reactions reported in ≥ 2% of patients who received treatment with IZERVAY for up to 24 months in the GATHER2 study are listed below in Table 2.

Table 2: Common Ocular Adverse Reactions (≥2%) and greater than Sham in Study Eye up to 24 months

Adverse Drug Reaction	IZERVAY N=225	Sham N=222
Conjunctival hemorrhage	17%	9%
Blurred vision[1]	14%	5%
Increased IOP	13%	1%
Choroidal neovascularization	12%	9%
Punctate keratitis[2]	10%	8%
Eye pain	7%	4%
Retinal hemorrhage	4%	3%
Vitreous floaters	4%	<1%
Ocular hypertension	4%	0
Blepharitis	3%	<1%
Corneal abrasion	2%	<1%

[1] Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently and blindness transient.

[2] Punctate keratitis includes punctate keratitis and keratitis.

Photopsia, optic ischemic neuropathy, vitreous hemorrhage, vitreal cells, vitritis, and endophthalmitis were each reported in ≤ 1% of patients treated with IZERVAY for up to 24 months across the GATHER1 and GATHER2 studies.

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 5.5 times and 3.4 times the human exposure, respectively, based on Area Under the Curve (AUC), following a single 2 mg intravitreal (IVT) dose (see Animal Data).

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 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 5.5 times the human AUC of 999 ng·day/mL (23976 ng·hr/mL) following a single 2 mg IVT dose.

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 3.4 times the human AUC of 999 ng·day/mL (23976 ng·hr/mL) following a single 2 mg IVT dose.

8.2 Lactation

There is no information regarding the presence of avacincaptad pegol in human milk, or the effects of the drug on the breastfed infant or on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child.

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.

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PREDICTING PROGRESSION TO GA USING IMAGING BIOMARKERS

Several OCT findings can help clinicians better understand a patient's risk of progression to sight-threatening disease.

By Kelly Donovan, MD, PhD, and Eleonora M. Lad, MD, PhD





The modern parameters for dry AMD disease staging were first outlined by the Beckman classification in 2013.[1] In 2017, the Classification of Atrophy Meeting provided an updated consensus on OCT-based classification of geographic atrophy (GA).[2] Dry AMD disease staging relies on a combination of dilated fundus examination, color fundus photography (CFP), fundus autofluorescence (FAF), and OCT. Disease progression is gauged by these same modalities, with OCT being the most reliable for assessing interval anatomic changes. FAF is particularly well-suited for tracking GA lesion topography over time, with active expansion of GA lesion(s) on FAF representing the key indication for considering anticomplement therapy.

Other structural and functional testing modalities are also under investigation as adjuncts for assessing the progression of dry AMD. For example, there is burgeoning interest in using OCT angiography to evaluate regional flow features of the choriocapillaris in different stages of dry AMD.[3] In addition, functional measurements can be used to quantify *sub-anatomic* AMD progression in patients, with studies validating functional metrics such as microperimetry, dark adaptation, contrast sensitivity, and low-luminance visual acuity.[4,5]

In clinic, the most granular assessment of retinal anatomy is derived from OCT, which has generated most modern imaging biomarker candidates. A variety of tomographic disease features have been reported, providing us with broad insight into the diversity of anatomic changes that can occur during the natural history of dry AMD. The ability to leverage these imaging biomarkers into risk stratification algorithms will improve our ability to counsel patients and direct clinical trial design.

While the dry AMD pipeline is overwhelmingly focused on curbing progression of established GA, it would be ideal to intervene prior to irreversible loss of retinal tissue. The confident prediction of areas of retina at high risk for progression to GA would facilitate testing therapeutic candidates for potential effect on the incidence of GA.

KEY TAKEAWAYS

- In the clinic, the most granular assessment of retinal anatomy is derived from OCT, which has generated most modern imaging biomarker candidates.
- Promising dry AMD imaging biomarkers include drusenoid lesions, intraretinal hyperreflective foci, loss of outer retinal integrity, choriocapillaris perfusion and thickness, and pigmentary changes.
- Eventually, the integration of multivariable risk calculators may provide composite progression estimates for patients, clinicians, and researchers.

TABLE. AMD BIOMARKER RISK ASSOCIATIONS

Biomarker	Hazard Ratio [95% CI]	Odds Ratio [95% CI]	Other	Prognostic Accuracy (AUC)[22]	Median Time to Conversion (years)[22]
Large drusen (> 125 µm)	6.26 [1.46-26.73]	5.53 [3.21-9.53]		59.7 [55.2-64.5]^	
Hyporeflective drusen core	2.85 [1.94-4.2]	3.84 [1.23-15.45][22#^]		50.9 [32.3-65]^	3.35^
	2.83 [1.89-4.26][21]	2.52 [1.59-3.98]			
Reticular pseudodrusen	1.8 [0.97-3.32] (not significant)	2.1 [1.16-3.81]		45.9 [27.6-60.8]^	
	1.95 [1.34-2.82][21]				
Drusenoid pigment epithelial detachment	2.36 [1.98-2.8][30]	4.19 [1.49-11.81]	62% of 37 eyes[13]	57.5 [38.1-73.3]^	4.81^
		6.66 [1.32-42.71][22#^]			
Serous pigment epithelial detachment			21% of 71 eyes[31]		
			50% of 20 eyes[12]		
Calcified drusen		6.36 [2.99–13.53][14]			
Drusen volume (≥ 0.03 mm^3)	2.08 [1.58-2.73]				
	1.74 [1.14-2.66][21]	4.3 [1.87-9.86]	RR 3.86 [2.40-6.21][32*]		
Intraretinal hyperreflective foci	9.97 [4.85, 20.49]	14.9 [2.7- 279.3][22]		61.6 [48.7-71]^	3.61^
	10.66 [4.96-22.89][21]	5.53 [3.21-9.53]			
External limiting membrane abnormality	17.34 [5.88-51.19]			54.4 [40.5-64.4]^	
Ellipsoid zone abnormality	6.1 [3.03-12.25]			58 [47-65.8]^	
Choroidal thickness		0.47 [0.28-0.8]			
Hypertransmission defect	80 [10.7-614][33]				
iRORA		29.60 [6.86-127.84]^			
Nascent geographic atrophy	78.1 [13.6-448.0][34]	28.27 [2.44-545.3][22#^]		65.1 [36.3-84]^	2.74^
Pigmentary changes on color fundus photography		20.5 [3.69-385.1][22#^]		63.6 [49.7-73.5]^	3.35^

Abbreviations: AUC, area under the curve; iRORA, incomplete retinal pigment epithelium and outer retinal atrophy; RR, relative risk. Note: All associated *P*-values are ≤ 0.05 unless otherwise noted. Risk associations are derived from Trinh et al unless otherwise cited.[6] Only studies not already included in meta-analysis are shown individually.

* When the fellow eye has advanced AMD

Adjusted odds ratio shown when available

^ Conversion to advanced AMD (geographic atrophy or macular neovascularization)

Here, we highlight a list of promising dry AMD imaging biomarkers and the associated risk of developing GA or advanced AMD (GA and/or macular neovascularization; Table). The predictive value of many of these markers has been evaluated by various groups over the years, including in a recent Cochrane-style meta-analysis by Trinh et al.[6]

DRUSENOID LESIONS

While the array of drusen and drusenoid lesion subtypes continues to grow,[7-9] only a subset has been shown to confer significant risk for progression to advanced dry AMD (Figure). They range widely in size (small < 63 µm, medium ≥ 63-125 µm, and large > 125 µm), location, morphology, and reflectance pattern. Drusen with hyporeflective or hollow cores have been associated with reduced choriocapillaris flow on OCT angiography.[10] Reticular pseudodrusen (RPD), or subretinal drusenoid deposits, are distinguishable by their subretinal location and typically have a distinctive reticular or "leopard spot" pattern on FAF.[8] Drusenoid and serous pigment epithelium detachments

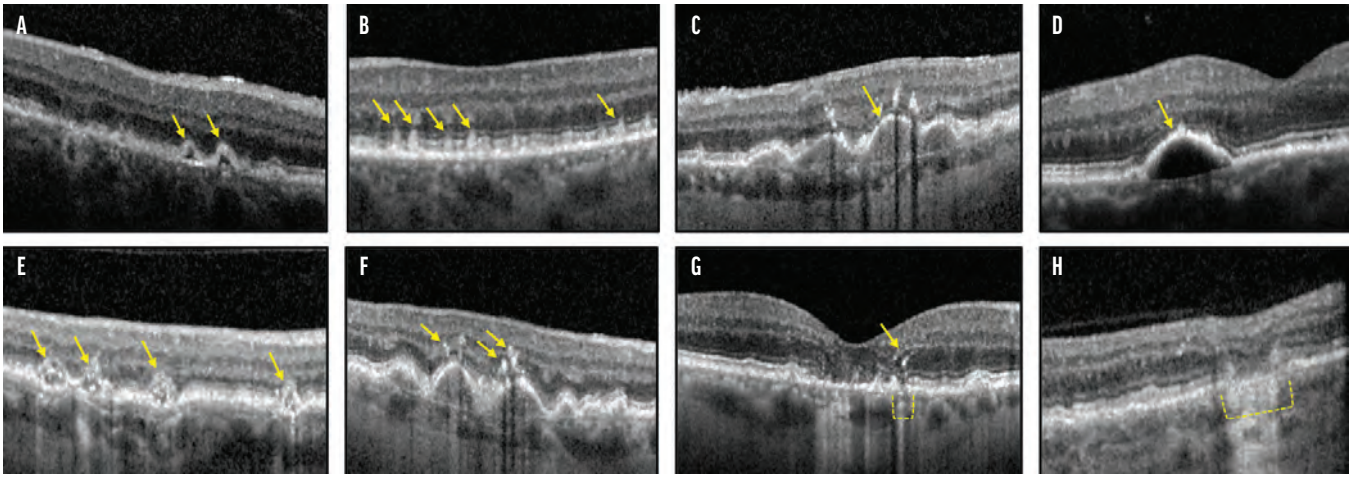


Figure. OCT biomarkers associated with the risk of progression to GA include drusen with hyporeflective cores (A), RPD (B), drusenoid PED (C), serous PED (D), calcified drusen (E), IRHF (F), nascent GA (G), and iRORA (H). The lesion of interest is indicated by a yellow arrow or dashed bracket. Of note, iRORA is also present in panel A, IRHFare present in panel C, and drusenoid PEDs are present in panel F.

(PEDs) can be quite large (hundreds of microns). Collapse of either lesion type is frequently followed by loss of outer retinal and retinal pigment epithelium (RPE) architecture, and for drusenoid PEDs, thinning of the underlying choroid.[11-13] Calcified drusen demonstrate either hyporeflective or heterogeneous internal reflectivity on OCT and appear refractile on examination.[14] Total drusen volume can be computed by automatic segmentation software. A greater than 0.03 mm^3 drusen volume constitutes a high drusen burden but only has a weak risk association with GA. Drusen undergo dynamic formation and regression with undulating total drusen volumes.[15] Progression to GA may be preceded by drusen regression, especially larger drusen.[16,17] While the total drusen volume trend may be more informative than any single absolute value, consideration of individual drusen attributes remains vastly more predictive.

INTRARETINAL HYPERREFLECTIVE FOCI (IRHF)

These foci are observed by OCT in the retina, often overlying drusen and drusenoid PEDs. They can be clustered or singular, and 87% are located below the junction between the outer plexiform layer and inner nuclear layer.[18] IRHF have a 66% correlation with pigment clumping on CFP.[18] These foci are hypothesized to be migrated RPE cells or infiltrating macrophages.[19,20] IRHF carry a significant risk for progression to advanced AMD with a risk association ranging between 5 and 15 and an estimated time to late AMD of 3.35 to 3.61 years.[6,21,22]

LOSS OF OUTER RETINAL INTEGRITY

The Classification of Atrophy Meeting group outlined the criteria and terminology for staging structural retinal deterioration preceding GA as well as defining GA. These stages are termed *incomplete RPE and outer retinal atrophy* (*iRORA*) and *complete RPE and outer retinal atrophy* (*cRORA*).[2] cRORA is defined by outer retinal and RPE loss with choroidal hypertransmission ≥ 250 µm in diameter. iRORA lesions include all three of these features but do not quite fulfill cRORA criteria.

A separate, somewhat intermediate imaging entity is nascent GA, which is defined by either subsidence of the outer plexiform layer and inner nuclear layer, or a hyporeflective wedge in Henle nerve fiber layer.[16] It may be accompanied by RPE attenuation and choroidal hypertransmission and often overlaps with iRORA lesions.[16] Objectively, iRORA and nascent GA lesions represent later stages of disease in which irreversible tissue loss has already occurred. Predictably, they are both highly associated with progression to GA. While this is useful for preparing patients for impending vision loss, these biomarkers are impractical for potential trials aiming to modify GA incidence. Imaging biomarkers that precede these substantive anatomic lesions would be more useful for any therapeutic attempts to forecast and modify GA incidence.

CHORIOCAPILLARIS PERFUSION AND THICKNESS

Focal thinning of the choriocapillaris has been associated with drusen, particularly drusen with hyporeflective cores. RPE loss correlates linearly with choriocapillaris loss, and focal flow impairments have been found in relation to drusen, as well as in areas of nascent GA.[23-25] In a meta-analysis, total choroidal thickness was inversely correlated with risk for GA (odds ratio = 0.476).

PIGMENTARY CHANGES

In a follow-up study to their meta-analysis, Trinh et al evaluated the accuracy of biomarker risk associations to predict advanced AMD.[22] The highest risk biomarkers from their prior analysis were compared with their prognostic accuracy against CFP in a real-world, longitudinal

study. Surprisingly, pigmentary abnormalities on CFP had the most impressive profile in terms of prevalence and prognostic performance (area under the curve = 77.7% [68.1, 87.3]) and sensitivity (92%). Pigmentary changes were previously independently identified as a risk factor for the presence of nascent GA (odds ratio = 16.84 [2.42-117.24]),[16] which is itself not distinguishable on examination or CFP. This study re-establishes that macular pigmentary changes should remain a reliable and highly predictive biomarker for progression to advanced dry AMD and may be especially useful in under-resourced clinics, remote screening programs, and AI algorithms.

IMPLEMENTING BIOMARKERS IN THE CLINIC

OCT is the cornerstone for dry AMD staging and risk stratification. Retina specialists should be aware of the range of possible structural changes in this heterogenous disease and their relative prognostic implication for progression to vision-threatening disease. Eventually, the integration of multivariable risk calculators may provide composite progression estimates for patients, clinicians, and researchers.

Progress toward this goal is underway, as our group and others have already developed deep-learning algorithms to predict progression to GA.[26,27] Automated prediction systems are already in use, as AI-based software (eg, RetInSight, Topcon) was approved in Europe, Australia, and New Zealand, and under investigational use in the United States.[28,29] Time will tell whether these systems will be integrated into the retina clinic, employed for patient screening, monitoring, and outcome quantitation in clinical research, or both. ■

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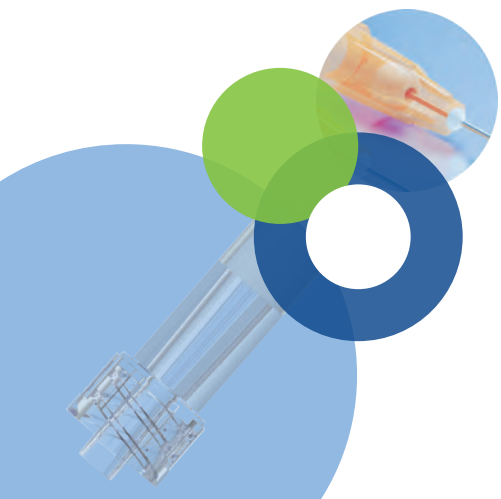
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PBM FOR AMD:

MECHANISMS, EVIDENCE, AND CLINICAL INTEGRATION

Photobiomodulation shows promise, but long-term data are needed.

By Luis Acabá-Berrocal, MD, and Anton Orlin, MD





The prevalence of AMD is projected to increase from approximately 200 million to more than 300 million individuals worldwide as global life expectancy rises.[1,2] Accordingly, the development of therapies that can prevent, slow, or treat AMD has become critical (Figure). The treatment landscape for AMD has evolved substantially, from AREDS supplementation to anti-VEGF therapies and complement inhibitors, and, most recently, photobiomodulation (PBM). Currently, PBM offers a noninvasive therapeutic option for patients with dry AMD.

In this article, we review its mechanisms of action, current clinical evidence, and practical considerations for real-world implementation.

WHAT IS PHOTOBIOMODULATION?

PBM involves the application of low-level light therapy using low-power lasers or light-emitting diodes at specific wavelengths, typically ranging from 590 nm to 850 nm. PBM is a nonthermal, noninvasive therapy that is thought to act primarily at the mitochondrial level, enhancing cytochrome c oxidase activity and promoting ATP production.[3] This aims to reduce oxidative stress and modulate inflammatory signaling pathways, ultimately promoting cellular survival and function.[3]

The biologic effects of PBM were first described in the 1960s, when researchers demonstrated its role in promoting wound healing.[4] Since then, PBM has been applied across many medical fields, including dermatology, neurology, and dentistry, where it has been shown to improve tissue repair, reduce neuropathic pain, and enhance bone remodeling.[3,5,6]

The retina represents an ideal target for PBM due to its high metabolic demand and high mitochondrial numbers within photoreceptors, retinal pigment epithelial (RPE) cells, and ganglion cells. By enhancing mitochondrial function and reducing inflammatory mediators, PBM may modify key pathogenic pathways implicated in AMD, including oxidative stress, mitochondrial dysfunction, and chronic inflammation.[7] Thus, PBM has emerged as a promising treatment to potentially alter the inflammatory and mitochondrial damage cycle of AMD and slow disease progression.

In the United States, the only FDA-approved PBM device for dry AMD is the Valeda Light Delivery System (Alcon). The system uses three wavelengths, yellow (590 nm), red (660 nm), and near-infrared (850 nm), to target multiple mitochondrial chromophores. In the European Union, both the Valeda system and the Eye-light (Espansione Group) have received CE marks for dry AMD. The Eye-light device,

KEY TAKEAWAYS

- Photobiomodulation (PBM) has been applied across many medical fields, including dermatology, neurology, and dentistry, where it has been shown to improve tissue repair, reduce neuropathic pain, and enhance bone remodeling.
- Ideal candidates for PBM include patients with intermediate dry AMD who are motivated to pursue a noninvasive treatment option.
- Patients typically undergo an initial series of nine treatment sessions over 3 to 5 weeks, followed by maintenance treatments every 4 to 6 months based on clinical response and patient preference.
- While PBM may improve visual function and slow disease progression, it is not curative. Outcomes may vary, and treatment benefits are generally more pronounced in earlier stages of disease.

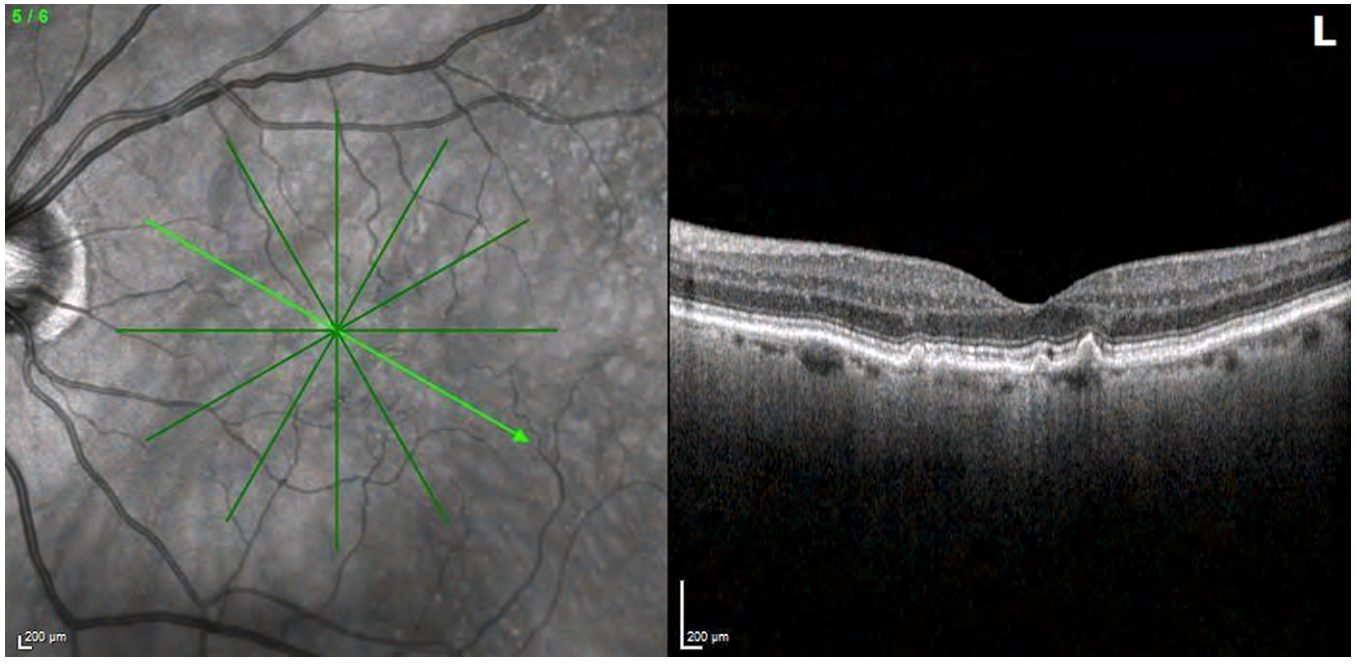


Figure. Patients such as this 68-year-old woman who has intermediate AMD, with the OCT of the left eye demonstrating drusen, may benefit from early treatment.

originally approved for dry eye disease and blepharitis, uses yellow (590 nm) and red (660 nm) wavelengths.

CLINICAL EVIDENCE

The LIGHTSITE I and II trials were randomized controlled studies evaluating the safety and efficacy of PBM using the Valeda system in patients with dry AMD. These studies demonstrated improvements in contrast sensitivity, BCVA, and stabilization of drusen volume compared with sham-treated controls. Treatment effects were more pronounced in patients with intermediate AMD compared with advanced disease.[8,9]

The LIGHTSITE III trial, a phase 3 multicenter, double-masked, prospective study, evaluated 100 patients with early to intermediate AMD over a 24-month period. Patients received nine treatment sessions (three times weekly) every 4 months.[10] The study demonstrated a statistically significant and sustained improvement in BCVA, with a mean gain of 5.9 letters at month 24 compared with sham ($P < .0001$). In addition, the treatment group showed stabilization of drusen volume, whereas the sham group exhibited a trend toward progression. A lower incidence of new-onset geographic atrophy (GA; 7% vs 24%) and improvements in vision-related quality of life were also observed. Importantly, no phototoxicity or major safety concerns were identified.[10]

LIGHTSITE IIIB, an extension study, followed a subset of patients for an additional 13 months.[11] There was a 20-month interruption period before the start of the extension study. During this interruption period, previously treated patients experienced a mean decline of 2.2 letters but regained approximately 5 letters after resuming therapy, with sustained benefit throughout the extension period.[11] In contrast, patients originally assigned to the sham group experienced greater visual decline and limited recovery after initiating treatment. At approximately 4.5 years of follow-up since the initiation of LIGHTSITE III, a 9.9-letter difference was observed between the original treatment and sham groups. Subgroup analysis suggested greater benefit in patients with worse baseline visual acuity (worse than 70 ETDRS letters). No significant safety signals were identified, although three patients developed wet AMD during follow-up.

A recent randomized multicenter European study evaluated the Eye-light device in 152 eyes with dry AMD.[7] Patients underwent two treatment sessions per week for 4 weeks. At the conclusion of treatment, a significantly higher proportion of treated eyes gained ≥ 5 letters compared with sham (20.3% vs 9%). Additionally, drusen volume remained stable in the treatment group compared with progression in the control group. The therapy was well tolerated, with no major adverse events reported.[7]

Limitations of Current Evidence

Despite promising results, limitations remain. The sample sizes in randomized controlled trials are relatively small, which may limit generalizability and increase susceptibility to confounding variables. Long-term data on progression to GA or wet AMD are limited. Furthermore, direct comparisons with established interventions such as AREDS supplementation and lifestyle modification have not been performed.

Similarly, optimal treatment protocols, including frequency, duration, and maintenance regimens, have not

WHILE PBM MAY IMPROVE VISUAL FUNCTION AND SLOW DISEASE PROGRESSION, IT IS NOT CURATIVE. OUTCOMES MAY VARY, AND TREATMENT BENEFITS ARE GENERALLY MORE PRONOUNCED IN EARLIER STAGES OF DISEASE.

been standardized. Sham controls in PBM studies are inherently imperfect, as they typically involve exposure to low-level light that may not be entirely biologically inert. Larger, long-term, comparative studies will be necessary to fully define the role of PBM in AMD management.

IMPLEMENTATION IN CLINICAL PRACTICE

Ideal candidates for PBM include patients with intermediate dry AMD who are motivated to pursue a noninvasive treatment option. Patients with nonfoveal GA may derive benefit, although outcomes are less predictable in advanced disease. We do not recommend PBM for patients with wet AMD or advanced fovea-involving GA.

Treatment Protocol and Workflow

In clinical practice, patients typically undergo an initial series of nine treatment sessions over 3 to 5 weeks (three sessions per week), followed by maintenance treatments every 4 to 6 months based on clinical response and patient preference. Each treatment session takes approximately 5 minutes per eye.

Patients do not require pharmacologic dilation and are scheduled specifically for treatment visits. They should be counseled regarding the time commitment associated with therapy and the importance of adherence to the treatment schedule. Transient visual afterimages may occur but typically resolve within seconds.

Counseling and Expectations

Setting realistic expectations is critical. While PBM may improve visual function and slow disease progression, it is not curative. Outcomes may vary, and treatment benefits are generally more pronounced in earlier stages of disease. Therefore, patient motivation and adherence play a key role in treatment success.

FUTURE DIRECTIONS

PBM is currently being investigated for a range of ocular conditions beyond AMD, including diabetic retinopathy, myopia, amblyopia, retinitis pigmentosa, retinopathy of prematurity, central serous chorioretinopathy, and Stargardt disease. Early studies suggest potential therapeutic benefits, although further research is needed to define efficacy across these indications.[12]

PBM potentially represents a promising, noninvasive adjunctive therapy for dry AMD, supported by a biologic rationale and a growing body of clinical evidence. Its benefits appear most pronounced in patients with early to intermediate disease. Broader adoption will depend on the availability of long-term efficacy data and standardization of treatment protocols. As evidence continues to evolve, PBM is likely to become an important component of a multimodal approach to AMD management. ■

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GAINING PATIENTS' BUY-IN WITH GEOGRAPHIC ATROPHY TREATMENT: THE JOURNEY FROM DIAGNOSIS TO LONG-TERM ADHERENCE

Setting realistic expectations for treatment with empathy, education, and reinforcement supports long-term adherence.

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By David S. Chin Yee, MD

When discussing geographic atrophy (GA) with patients, it is helpful to approach the conversation with three core communication principles: clarity, empathy, and hope. It is important to position GA as progressive but manageable, and not synonymous with complete loss of vision. However, it is also essential to educate patients on the realities of treatment.

Personalizing the Conversation

When I am delivering a diagnosis of GA to a patient, I try my best to simplify the disease process. I have found that using analogies—such as a worn carpet or patches of dead grass in a yard—helps improve patient understanding. I then tailor the conversation to the needs of the patient:

- For patients with early disease, I emphasize the importance of early detection and the opportunity to slow progression.
- For patients with advanced disease, I acknowledge the existing vision loss and reinforce that limiting further progression remains meaningful because preserving remaining vision and quality of life still matters.

Building Treatment Commitment and Support

After emphasizing the core goal of GA treatment—slowing disease progression rather than restoring vision—I review the main management options with my patients, depending on disease severity: monitoring or treatment with FDA-approved complement inhibitor therapies. I often share published data, but keep the message simple: With treatment, lesion growth can be slowed by about 20% to 30%, and with continued treatment the effect may increase over time, reaching up to about 42% to 45% in some longer-term or subgroup analyses.[1-4]

Because it can be painful to receive a diagnosis of GA, I also make sure patients receive support and reinforcement throughout the discussion. This includes:

- A **structured communication technique**, ask-tell-ask, to confirm understanding of the diagnosis and treatment goals.
- The patient's own **OCT and fundus autofluorescence** images to demonstrate progression over time.
- Supplementary **education**, such as videos and staff reinforcement.
- Inclusion of **care partners** to help with logistics, decision-making, and realistic treatment expectations.

Supporting Treatment Adherence and Addressing Barriers

In my experience, the most common reasons for nonadherence are treatment burden, transportation issues, cost concerns, and initial anxiety about injections. While we cannot address every reason for patient dropout, I use several proactive approaches to gauge patient comfort and commitment. In addition to setting expectations early about ongoing treatment requirements, I use commitment scaling, asking patients to rate their confidence with future compliance from 0 to 10, to assess readiness and to open the door to a discussion about barriers. I also normalize the injection process and explain that most patients find it easier than expected.

Life happens, and sometimes an appointment needs to be missed, so I reiterate that while reducing treatment lowers the overall benefit, it is not harmful. I make it a point to emphasize the long-term mindset: this is a marathon, not a sprint. If patients truly understand the benefit of treatment and feel that we are on this journey together, I have found that they are more likely to continue with treatment.

Leading With Empathy

My advice to fellow practitioners who are struggling with patient adherence is to lead treatment conversations with empathy and active listening. Make sure to understand what barriers exist for patients and what can be done to alleviate some of that stress. Validate why it is important to continue treatment. For patients to believe in it, practitioners must believe in the data. ■

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PEARLS AND PITFALLS OF TREATING GA AND WET AMD

Concurrent therapy can pose clinical challenges. Here's how you can manage these patients and maximize outcomes.

By Sean D. Adrean, MD, FAAO, and Wesley Han, BS





Treatments for geographic atrophy (GA) have been shown to delay the progression of the disease, offering hope to both patients and the retina community for this previously untreatable condition. While many patients present with either GA or wet AMD, an increasing percentage of patients have both active wet AMD and GA in the same eye (Figure 1). One study of Medicare patients found that between 25.6% and 28% of GA patients have coexisting wet AMD.[1]

While the benefits of treating wet AMD are apparent in improved biomarkers and vision, the slowing of GA progression is more opaque. Treating GA is like making deposits in the bank: Over time, the savings add up, providing patients with stabilized vision for longer. Combined treatment for GA and wet AMD has the potential to preserve patients' vision longer than treating wet AMD alone (Figure 2). However, with the advent of new and better treatment options for both conditions, clinicians must be aware of various treatment pitfalls to ensure the best outcomes for patients.

CLINICAL AND RETROSPECTIVE TRIAL DATA

With the completion of the OAKS and DERBY trials for pegcetacoplan (Syfovre, Apellis) and the GATHER trials for avacincaptad pegol (Izervay, Astellas), the FDA approved these therapies in February and August 2023, respectively. While all three studies excluded patients with prior choroidal neovascularization (CNV) in the study eye, OAKS and DERBY continued patients who developed CNV in the study eye, beginning anti-VEGF treatment at the investigator's discretion. GATHER2 discontinued these patients.

The 2-year outcomes of OAKS and DERBY showed a reduction of GA progression of 19% and 22% in the every-month (EM) groups and 16% and 18% in the every-other-month (EOM) groups, respectively.[2] In the 3-year GALE extension study of pegcetacoplan, treated eyes experienced a 42% and 28% reduction when receiving EM and EOM injections, respectively, and GA progression was delayed by 1.5 years after 5 years of treatment.[3,4]

The 2-year GATHER2 results for avacincaptad pegol demonstrated 14% and 19% reductions in GA progression for EM and EOM injections, respectively.[5] The open-label GATHER2 extension demonstrated a 37% to 40.5% reduction after 3.5 years of treatment.[6]

KEY TAKEAWAYS

- Combined treatment for geographic atrophy (GA) and wet AMD can preserve patients' vision longer than treating wet AMD alone.
- The authors' research shows a 44% reduction in the rate of GA progression following GA treatment initiation in combination with anti-VEGF therapy compared with the prior year of patients only receiving anti-VEGF treatments.
- When treating concurrent GA and wet AMD, clinicians can schedule follow-up treatments based on the treatment the patient received that day.
- To avoid increased injection volume after two injections within a short time, consider treating wet AMD and GA on different days.

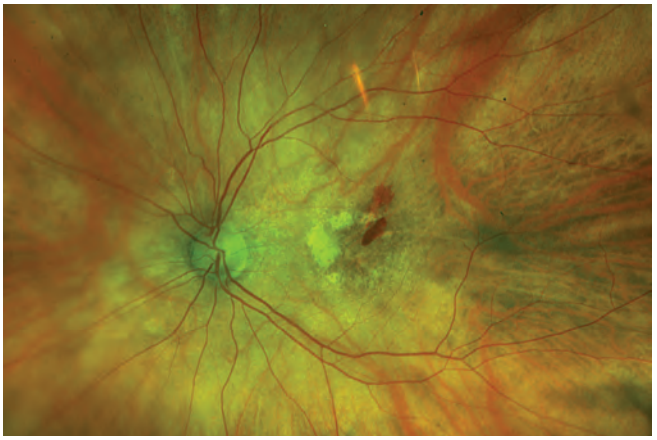


Figure 1. This patient with both CNV due to wet AMD and GA may benefit from combined treatment of both conditions.

OAKS and DERBY reported that 12.2% and 6.7% of GA patients developed CNV when receiving EM and EOM treatments (sham was 3.1%), while at 2 years, GATHER2 reported 11.6% CNV occurrence (sham was 9.0%).[2,5]

In GALE, patients who developed wet AMD lost an average of 2.8 letters at wet AMD diagnosis compared with the prior visit and lost 4.3 letters by month 12 compared with their visit when wet AMD was diagnosed.[3]

Yet there remains sparse research on patients with pre-existing wet AMD with coexisting GA. Thus, we recently identified and examined 31 patients with pre-existing wet AMD who also had nonfoveal GA develop during their wet AMD treatment. We retrospectively analyzed the data of patients who were previously treated for wet AMD for at least 1 year before beginning pegcetacoplan treatment and continuing both pegcetacoplan and anti-VEGF treatments for another year. We excluded wet AMD patients with subfoveal GA and/or macular atrophy, as that constitutes a distinct disease state with poor visual prognosis with anti-VEGF treatment.[7,8]

The 1-year outcomes showed a 44% reduction in the rate of GA progression following pegcetacoplan treatment initiation in combination with anti-VEGF therapy compared with the prior year when patients were only receiving anti-VEGF treatments.[9] The average vision changed from 68.3 ETDRS letters to 67.9, which was nonsignificant, and 22 patients remained dry while nine had persistent but non-worsening retinal fluid.[9]

Patients were previously treated for wet AMD on average for 6.5 years, using a treat-extend-stop protocol.[9] After 1 year of receiving both treatments, the average anti-VEGF injection interval was 12 weeks while pegcetacoplan treatments averaged every 8.1 weeks.[9,10]

Pearls for Treating GA and CNV

- Treat both GA and wet AMD (should have one visit per disease process)
- Monitor wet AMD between injections
- Schedule follow-up based on the eye treated and disease state
- Prioritize wet AMD in treatment

Pitfalls of Concurrent Treatment

- More complex workflow, charting, and scheduling
- Injection fatigue
- Missed visits or worsening of CNV during GA treatment visits
- Billing issues

CONSIDERATIONS FOR MANAGING GA AND CNV

With treatment options for both GA and wet AMD, we can reduce exudation from CNV to restore lost vision, and slow GA lesion growth to preserve vision longer. Despite these treatments, some clinicians hesitate to treat both diseases when they present concurrently, mainly due to a dearth of research regarding these coexisting disease states.

Clinical Practice Pearls

From personal clinical experience, we learned that for patients with bilateral GA, it helps to treat both eyes on the same day and keep the same time interval between treatments. We currently treat most GA patients at a 5- to 6-week time interval. Yet, unlike patients in the OAKS/DERBY/GALE trials, we do not treat both wet AMD and GA on the same day in the same eye. This helps avoid increased injection volume after two injections within a short time. In the trials, clinicians waited 30 minutes between treatments, which is not practical for real-world clinics because it increases visit time and inhibits clinic flow.

In our clinic, we schedule follow-up based on the treatment the patient received that day. If a patient presents for GA treatment in the left eye, we schedule the follow-up visit only for the GA treatment. We still review the chart to make sure the wet AMD treatments have been scheduled, and all staff involved carefully review the chart and confirm with the patient the correct treatment for the correct eye. This treatment approach can be particularly challenging when a patient is receiving four shots total (two per eye) at varying treatment intervals. While injections for CNV vary based on disease activity, patients typically have fixed intervals for GA therapy.

Overcoming Injection Fatigue

Another important pitfall to avoid is injection fatigue. At the onset, we iterate that GA therapy requires a lifelong commitment to experience the benefits, and we often act as cheerleaders, advocating for the patient to continue treatment. During visits for GA, we discuss how the treatment is slowing the disease process, educate patients on the characteristics of progression using autofluorescence,

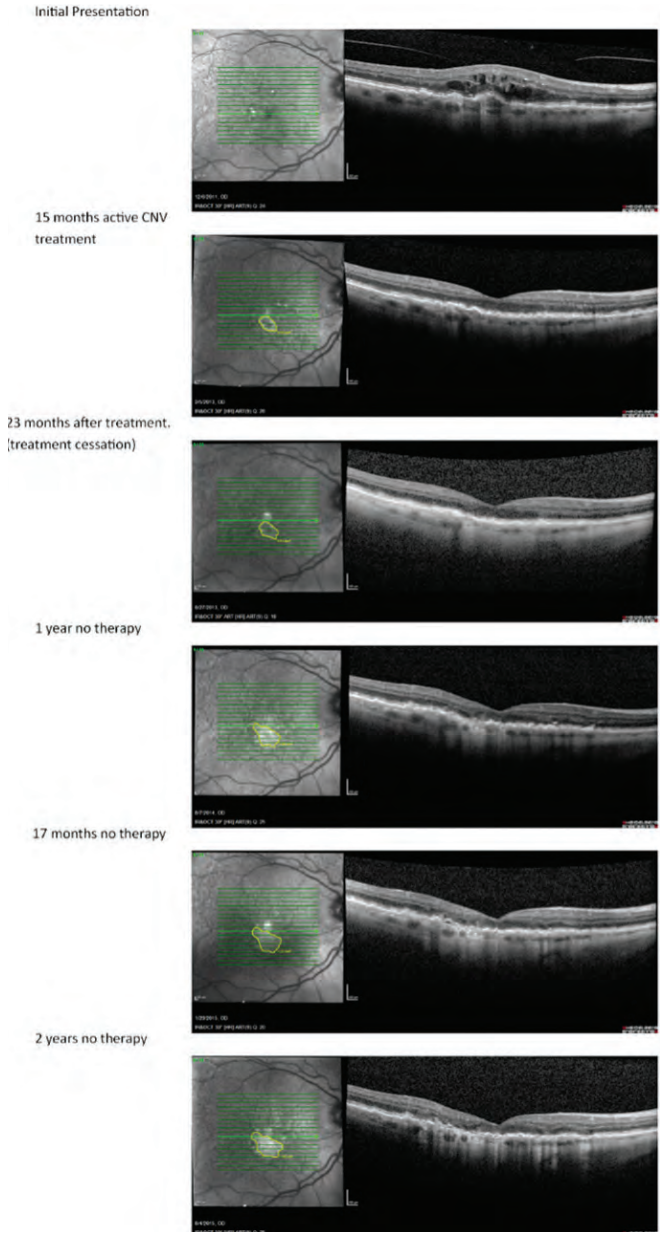


Image courtesy: This figure has been submitted to Retina but has yet to be accepted for publication

Figure 2. This patient with CNV reached treatment cessation but developed GA.

and describe how GA encroaches on central vision. During visits for wet AMD, we spend more time reviewing the OCT images with the patient and (hopefully) highlighting the regression in exudation and improved vision.

Given the number of injections required, patients may also miss their appointments for various reasons. Because it becomes harder to track wet AMD visits when patients are also receiving GA treatments (ie, with more visits, patients are more likely to forget a visit or be confused), patients may fall through the cracks. When assessing risk to vision, we must be preferential toward wet AMD treatments and be ready to postpone the GA treatment if the wet AMD worsens. It is much more difficult to recover vision after multiple fluid recurrences from CNV. Slowing GA is important, but anticomplement therapy does not restore vision.

Patients with GA may at times complain of vision loss, which is typical. When this occurs, we mention that patients with GA often have fluctuating vision depending on the day or week. We review their chart and highlight their current vision and range of vision over several visits to encourage them to continue with the treatment regimen.

BALANCING A BUSY SCHEDULE

Patients with wet AMD and GA may be successfully treated for both conditions, and our study found an associated reduction in GA with maintained vision.[9] However, complex workflows, the management of multiple treatments (sometimes in both eyes), and patient charting require greater vigilance from clinicians and staff. To ensure successful outcomes, treatment of both diseases requires proactive scheduling, close monitoring of both diseases, and efficient communication to ensure patients do not fall through the cracks. Our ability to further protect the vision of patients with coexisting wet AMD and GA represents an important paradigm shift for this subset of patients. ■

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ONE TO WATCH

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Hong-Uyen Hua, MD



Dr. Hua's advice: Think critically about what your life priorities are and what truly brings you joy. This is the first time in many years that you finally dictate your life trajectory, so keeping your priorities in mind will help with difficult decisions!

WHERE IT ALL BEGAN

I'm a second-generation Vietnamese-American who grew up in South Florida. I always dreamed of becoming a surgeon. To chase that dream, I was the first in my family to go to medical school. A proud triple 'Cane, I went to the University of Miami for undergraduate and medical school, where I have returned as faculty. My training journey took me coast-to-coast: Boston for an internship, Los Angeles for residency at the University of Southern California (USC) Roski Eye Institute, and Cleveland for retina fellowship at the Cleveland Clinic Cole Eye Institute.

MY PATH TO RETINA

I first encountered the field of retina as a medical student when I met Audina M. Berrocal, MD—the queen of mentorship in ophthalmology. At the time, I knew little about retina, but she knew I would become a retina specialist. By the end of my rotation with her, I also knew I wanted to pursue retina, with a focus on pediatric retina. From the rewarding lifelong relationships and decades of saved vision, to the fascinating and complex medical and surgical pathology, pediatric retina captured my heart. Residency at USC with Aaron Nagiel, MD, PhD, and Thomas Lee, MD, and fellowship at Cole Eye with Jonathan Sears, MD, only reaffirmed my career aspirations.

SUPPORT ALONG THE WAY

Dr. Berrocal was a formative mentor early in my medical career. She is an exemplary model of an inclusive team builder who challenges all her mentees to be the best they can be. My dream was to one day return to Bascom Palmer Eye Institute and work as her partner in pediatric retina and, with hard work and some luck, that dream came true!

AN EXPERIENCE TO REMEMBER

I remember a challenging case of an aggressive Coats funnel detachment in a young boy. His parents were, understandably, extremely worried about his prognosis and very involved in his care. It took several trips to the OR and many consultations with trusted colleagues, but we were finally able to flatten his retina with external drainage and laser. I will never forget the feeling of how grateful his parents were for his care. ■

Hong-Uyen Hua, MD, is an assistant professor of Clinical Ophthalmology, Adult and Pediatric Retina, at Bascom Palmer Eye Institute, University of Miami Miller School of Medicine. She is on the advisory board for Abbvie, Alcon, ANI, Apellis, and Eyepoint, and has received honoraria from AmGen. She can be reached at honguyenhua@gmail.com.

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INFLUENCE OF MEDITERRANEAN-STYLE DIET ON AMD

Our findings suggest certain dietary and lifestyle habits may confer long-term protective benefits.

By Christopher Phung, BA; Beryl Zhou, BS*; Robert Luca, BA*; and Dimitra Skondra, MD, PhD



AMD is a progressive, multifactorial cause of vision loss, especially in Western countries. While early stages may be only mildly symptomatic, advanced AMD, whether geographic atrophy or neovascular disease, can significantly affect a patient's independence and quality of life. Among the identified risk factors—age, genetics, smoking, race, hypertension, diet—few are readily modifiable, which, given the noncurative nature of currently available therapies, places great emphasis on those that are adjustable.

Epidemiological research has demonstrated an association between diet and the risk of AMD development or progression. Diets rich in saturated fats, refined grains, and red meats, reflective of a typical Western diet, are linked to increased AMD risk.[1] In contrast, a Mediterranean diet, characterized by high levels of fruits, vegetables, whole grains, and fish, is associated with slower disease progression.[2] Despite these findings, a definitive causal link has not been established, and the biological mechanisms underlying this apparent gut-eye connection remain poorly understood.

Thus, gut microbiome has gained attention as a promising area of investigation with significant mechanistic and therapeutic implications. The gut microbiome is a complex ecosystem of microbes within the gastrointestinal tract that is heavily influenced by host intake and exerts systemic effects on host immune function and metabolism. Beyond its immediate effect on the gut, alterations in the gut microbiome have been implicated in a wide array of systemic diseases, ranging from Alzheimer disease to diabetes.[3] Gut dysbiosis, or an imbalance in the composition of the gut microbiome, has been identified in patients with AMD, pointing toward a potential role of the microbiome in disease progression.[1]

Using a laser-induced choroidal neovascularization (CNV) mouse model of wet AMD, our team demonstrated that dietary changes may induce gut dysbiosis and modify susceptibility to neovascularization.

THE MEDITERRANEAN DIET PROTECTS AGAINST CNV

In our study, mice were fed one of three diets: a Mediterranean-style diet (MED) rich in olive oil, fish protein, and egg whites to replicate a human Mediterranean diet; a Western style diet (WD) with predominantly simple sugars

KEY TAKEAWAYS

- Gut dysbiosis, or an imbalance in the composition of the gut microbiome, has been identified in patients with AMD, pointing toward a potential role of the microbiome in disease progression.
- In our study, mice were fed three diets: a Mediterranean diet, a Western diet, and a low fat, high fiber mouse diet rich in wheat and corn that is standard for laboratory mice.
- Compared with the Western diet, the Mediterranean diet was protective against wet AMD and was associated with a decrease in proinflammatory gut bacteria.

DIETS RICH IN SATURATED FATS, REFINED GRAINS, AND RED MEATS, REFLECTIVE OF A TYPICAL WESTERN DIET, ARE LINKED TO INCREASED AMD RISK.

and butter-based fats to mimic a typical human Western diet; and a low fat, high fiber mouse diet (LFHFb) rich in wheat and corn that is standard for laboratory mice. The MED and WD contained similar amounts of carbohydrates, proteins, and fats but differed in the sources of these macronutrients. The mice were fed their assigned diets for 6 months, a duration considered to represent long-term dietary exposure in murine models.

Afterward, all mice underwent laser-induced CNV, and 1 week later, the eyes were assessed for lesion size and subretinal microglia/macrophage infiltration. We found that the WD mice had significantly increased angiogenic and local inflammatory response, while the MED mice had suppressed lesion size and microglia/macrophage recruitment, reinforcing our current understanding of diet as an AMD risk factor in humans.

MICROBIAL DYSBIOSIS MEDIATES INFLAMMATORY SUSCEPTIBILITY

To investigate the role of the gut microbiome in driving these findings, we investigated the makeup of the gut microbiome from each group using 16s sequencing of the bacterial DNA from their stool. This revealed distinct microbial signatures between the MED-, LFHFb-, and WD-fed mice. Although each group displayed a dominance of Firmicutes at the phylum level, clear compositional divergence emerged when comparing MED mice with WD mice. Proinflammatory bacteria such as *Lactococcus*, *Eubacterium*, and *Romboutsia* were higher in WD mice, yet were almost absent with the MED and LFHFb mice.

When the gut microbiome is altered as such, the integrity of the intestinal wall can be compromised, allowing absorption of bacterial toxins into the blood and promotion of a low-grade systemic inflammation.[4] Downstream signaling pathways can subsequently activate choroidal angiogenesis via increased production of interleukin-1-beta and VEGF.[5] Mamun et al showed increased *Lactococcus* abundance in high-fat or metabolic disease states in mice and humans.[6] *Eubacterium ventriosum* has also been found to be enriched in patients with AMD compared with controls, which has been associated with elevated levels of proinflammatory cytokines.[7,8] These taxa have been linked to gut barrier dysfunction, increased endotoxin release, and systemic inflammatory priming, processes known to propagate complement factor H activation and angiogenic signaling in the retina.[1] Therefore, these diet-induced alterations could contribute to susceptibility to AMD and neovascularization.

After identifying these compositional differences, we performed mass spectrometry to assess levels of bacterially produced metabolites. This revealed increased levels of antiinflammatory metabolites, including isobutyrate, propionate, and valerate, in MED mice compared with WD mice. Isobutyrate is a branched chain fatty acid derived from dietary protein, while propionate and valerate are short chain fatty acids derived from fiber. They play active roles both locally in the gut and systemically. At the gut wall, they promote integrity of the intestinal wall barrier, preventing absorption of bacterial toxins and associated low-grade inflammation. Impairments in this process have been previously associated with ocular diseases, such as diabetic retinopathy and uveitis, in addition to AMD.[4] Short chain fatty acids can also be absorbed and delivered to the eye, where they mitigate the proinflammatory response by reducing cytokine production and limiting immune cell migration, which could explain our observed microglia results.[9]

THE GUT MICROBIOME DRIVES THE CONNECTION

To determine whether the observed dietary effects on wet AMD features were truly driven by the microbiome changes, we conducted fecal transplants from MED and WD mice to germ-free mice, which lack their own innate gut microbiome. The germ-free mice were kept on the standard LFHFb diet and underwent the same laser-induced CNV. The fecal transplants replicated the original diet-induced phenotypes seen in the donors. Fecal transplants from MED mice led to decreased CNV and immune cell infiltration, while transplants from WD mice were associated with greater angiogenic response. This finding suggests diet-driven microbial communities can shape host susceptibility to CNV, even in the absence of direct dietary exposure. Moreover, reduced microglial and macrophage infiltration in MED transplant recipients further supports the notion that gut-derived signals influence retinal immune tone, possibly by limiting proinflammatory or proangiogenic pathways that exacerbate lesion expansion and severity.

These results reinforce the emerging concept of a gut-retina axis and indicate that MED-associated microbiota may confer resilience against CNV by attenuating both angiogenic and inflammatory responses. As such, our study raises the possibility that targeting the gut microbial composition—either through dietary interventions, probiotic/prebiotic

(Continued on page 50)

A PRIMER ON FAF




Even with the advances in imaging technology, fundus autofluorescence remains integral to our imaging protocols. Here's why.

BY THOMAS ACH, MD, MSC, FEBO, AND ANDREAS POLLREISZ, MD

Fundus autofluorescence (FAF) is a noninvasive imaging technique that visualizes the naturally occurring fluorescence of structures in the outer retina and beyond. Autofluorescence occurs when endogenous fluorophores are excited by light of a suitable wavelength and then re-emitted with lower energy.[1] This article offers a brief guideline for understanding how FAF works and its use in diagnosing and managing various retinal diseases.

HOW IT WORKS

The main anatomical sources of autofluorescence are the photoreceptors and the retinal pigment epithelium (RPE). In particular, the RPE is the main contributor to short-wavelength FAF through lipofuscin and melanolipofuscin organelles, and to near-infrared (NIR) FAF through melanin-containing organelles, such as melanosomes.

Under normal physiological conditions, bisretinoids are formed as byproducts of the visual cycle and gradually accumulate, together with lipids, within RPE lysosomes, forming lipofuscin and melanolipofuscin granules. These granules represent the dominant source of the FAF signal. The number, size, and spatial distribution of these granules within the RPE cells largely determine the FAF pattern observed with short-wavelength excitation (Figure 1).

Granule density increases with age, leading to a progressive rise in FAF intensity, particularly in the perifoveal region and adjacent retinal periphery, often with the highest intensity in the temporal to superotemporal retina.[2] This age-related increase has been confirmed by quantitative measurements using spectrophotometry and confocal scanning laser ophthalmoscopy.[3] In advanced age, FAF intensity tends to decline, corresponding histologically to a reduction in autofluorescent granules and degenerative RPE changes.

FAF commonly uses short-wavelength excitation around 488 nm with detection above approximately 510 nm, although alternative excitation wavelengths are available. Quantitative FAF (QAF) enables standardized measurement of autofluorescence intensity, allowing comparisons across retinal regions, patients, and longitudinally. Additional techniques, such as fluorescence lifetime imaging ophthalmoscopy and spectral analysis, provide complementary information on the temporal and spectral properties of the signal. Longer-wavelength excitation (green and red/NIR) reduces the influence of the lens and macular pigment.

FAF IN THE OFFICE

In clinical practice, FAF findings are commonly described using three terms. *Isoautofluorescence* denotes a uniform signal regarded as normal. *Hypoautofluorescence* indicates reduced signal intensity, which may result from the loss or depletion of fluorophores, masking by pigment or blood, or tissue loss. *Hyperautofluorescence* describes increased signal intensity caused by higher fluorophore concentrations, altered fluorophore composition, or structural changes with accumulation of (auto)fluorescent material.

This terminology forms the basis for pattern recognition and interpretation in daily practice for many conditions, particularly macular degeneration, inherited retinal conditions, inflammatory disease, and tumors.

Macular Degeneration

AMD illustrates the clinical relevance of FAF impressively (Figure 2). QAF analyses show that FAF is often reduced overall in AMD, reflecting RPE degeneration and cell loss.[4,5] At the same time, a rim or patches of increased autofluorescence are often found at the edges of atrophic areas. Histological-imaging correlations have shown that this hyperautofluorescent signal is due to vertically superimposed or extruded RPE cells, migrating RPE cell populations, and accumulated cell material at the border between intact and atrophic retina.[6] In the transition zone between non-atrophic and atrophic areas, a complex mosaic structure of hypo- and hyperautofluorescent areas emerges, reflecting basement membrane deposits, cell migration, and varying stages of RPE loss.[6] In completely atrophic regions with complete RPE loss, the FAF signal is almost extinguished. In geographic atrophy (GA) due to AMD, atrophic area as determined by short-wavelength FAF is an accepted clinic endpoint in disease and therapy monitoring. FAF is recommended within a multimodal imaging approach for longitudinal assessment of GA progression.



Figure 1. In this this short-wavelength FAF of a healthy eye, the optic disc and retinal vessels are mostly hypoautofluorescent. At the fovea and perifovea, there is hypoautofluorescence due to the macular pigment absorbing blue light. The highest intensity of FAF is normally in the superotemporal edge of the macula.

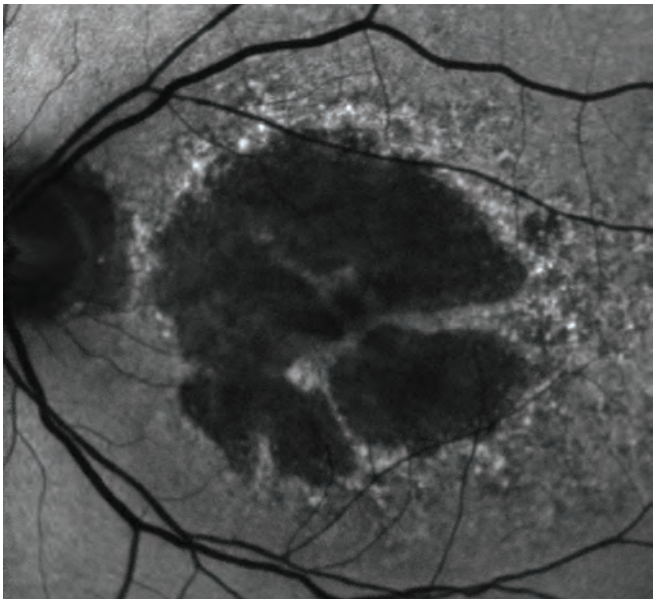


Figure 2. In the short-wavelength FAF of an eye with late-stage GA due to AMD, the area of GA appears hypoautofluorescent due to RPE cell loss. The transitional zone adjacent to the GA lesion is hyperautofluorescent and hypoautofluorescent. Hyperautofluorescence results from stacked RPE cells.

Rare Disease

FAF imaging is particularly useful for inherited retinal diseases, as it reflects dysfunction of the RPE and abnormal accumulation of autofluorescent material. FAF is an important part of multimodal imaging for the diagnosis and long-term monitoring in these conditions, as it helps characterize disease patterns and supports the differential diagnosis.

In Stargardt disease, FAF typically shows areas of increased autofluorescence caused by excess subretinal accumulation of bisretinoids, often with characteristic fleck-like lesions, alongside expanding regions of reduced autofluorescence that indicate progressive RPE atrophy.[7]

In Best vitelliform macular dystrophy, marked central hyperautofluorescence is seen in the vitelliform stage. As the disease progresses, FAF becomes heterogeneous, with mixed areas of increased and decreased signal, and advanced stages are characterized by pronounced hypoautofluorescence, indicating RPE loss.[8]

Pattern dystrophies display distinctive, often symmetrical patterns of increased autofluorescence related to abnormal autofluorescence material distribution within the RPE.

In retinitis pigmentosa, FAF commonly reveals a parafoveal ring of increased autofluorescence that constricts over time, highlighting the border between relatively preserved and degenerating retina, while peripheral hypoautofluorescence reflects widespread RPE degeneration.[7]

Choroideremia typically shows large, well-defined areas of reduced autofluorescence corresponding to chorioretinal atrophy, with residual islands of preserved signal in earlier stages.[7]

Other Retinal Conditions

FAF imaging is also useful for identifying drug-induced retinal toxicity. In hydroxychloroquine retinopathy, FAF commonly shows a parafoveal or pericentral ring of increased autofluorescence, indicating early stress of the RPE. With progression, central areas of reduced autofluorescence emerge, reflecting irreversible RPE damage. Notably, FAF changes can be detected before visible fundus abnormalities become apparent on clinical examination. FAF imaging should be performed early after initiating hydroxychloroquine to exclude pre-existing abnormalities and provide a reference for follow-up. During treatment, annual FAF is advised, although screening may be postponed within the first 5 years in the absence of major risk factors such as high dosage, prolonged use, renal impairment, or tamoxifen therapy.[9] Interestingly, QAF studies in patients on hydroxychloroquine therapy revealed a general increased autofluorescent signal at the posterior pole, independent of pathological changes.[10]

FAF is also useful for evaluating the activity and distribution of inflammatory retinal diseases and is recommended both in the initial differential diagnostic assessment and for follow-up after diagnosis is established. In multiple evanescent white-dot syndrome, FAF shows multiple small hyperautofluorescent spots that often fade as the patient recovers. In acute zonal occult outer retinopathy, sharply defined areas of hypoautofluorescence correspond to outer retinal and RPE dysfunction. In multifocal choroiditis and serpiginous choroiditis, active lesions often have hyperautofluorescent borders, while older, inactive scars appear

hypoautofluorescent due to permanent tissue loss.[11]

Tumors such as choroidal melanomas or other intraocular space-occupying lesions alter the FAF signal due to melanin content, the reactive RPE changes, and accompanying fluid or exudates, the latter often leading to hyperautofluorescence. In these situations, FAF helps to detect the extent and activity of lesions, assess disease progression, and document the effects of therapy.[12]

A TOOL THAT'S TRIED-AND-TRUE

FAF provides a window into the metabolic and structural status of the RPE-photoreceptor complex. Areas of increased or decreased autofluorescence reflect local changes in fluorophore levels, cell health, and overlying tissue, making FAF a valuable tool for monitoring disease activity and progression. Once primarily descriptive, FAF is now widely used for diagnosis, prognostic assessment, and guiding treatment strategies in diverse retinal diseases—with even better and more detailed analysis thanks to future autofluorescence techniques such as spectral analysis or fluorescence lifetime analysis.[13] ■

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(Continued from page 47)

supplements, or human fecal transplants from healthy donors—could offer a novel tregy to either directly mitigate CNV in wet AMD or to be used as an adjunctive therapy with current treatment standards.

NEW TREATMENT POSSIBILITIES

Although additional studies are warranted to further delineate the underlying pathways and mechanisms involved, the gut microbiome may represent a promising new avenue for approaching AMD treatment. ■

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**contributed equally*

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REGENXBIO

Retina Today (RT): **When did you first know that you wanted to become a retina specialist?**

My father's stories about his work as a retina surgeon are a cherished part of my childhood. After his fellowship in Montreal, he returned to Syria in the 1970s to carry out the country's first modern retinal detachment repairs. It's no surprise that I went to medical school already wanting to pursue retina. Residency confirmed that retina was the perfect fit because it involved everything I enjoy: surgery, medicine, and technology.

***RT*: Who do you look up to as mentors in the field?**

Mentorship has come to me in many forms, and from more people than I could fairly name here. A few stand out because they opened doors and helped shape the path I'm on today. In Montreal, Renaud Duval, MD, introduced me to AI in medicine, and he also supervised my first vitrectomy as a resident. Pearse A. Keane, MD, mentored me during my medical AI fellowship at Moorfields Eye Hospital in London, and he helped me grow as a clinician-scientist in that space. I have learned so much about leadership just by watching him.

Sunil Srivastava, MD, recruited me to the Cleveland Clinic's Cole Eye Institute for fellowship and immediately made me feel welcome. He treats his trainees like family, and that sense of support made a huge difference in my training. He is a patient and generous educator to whom I owe much of my surgical foundation.

Finally, Salim Lahoud, MD; Karim Hammamji, MD; and Mona Harissi-Dagher, MD, were instrumental in bringing me back to Montreal and recruiting me to the Centre Hospitalier de l'Université de Montréal. I am grateful for their trust and support and thrilled to join a team of colleagues who share the same commitment to thoughtful, patient-centered care.

RT: **What has been one of the most memorable experiences of your fellowship thus far?**

My most memorable experience has been operating alongside Jonathan E. Sears, MD, and his nurse, Christine Sonnie, BSN, CRNO, RN. Caring for complex pediatric retina cases with them has been very inspiring. Retina surgery in children carries a unique responsibility, and Dr. Sears showed me what "first, do no harm" truly looks like in practice: restraint, humility, and empathy. Learning beside them was a privilege I will not forget.

FIRST CAREER MILESTONE

Dr. Antaki is joining his alma mater, Centre Hospitalier de l'Université de Montréal, as a vitreoretinal surgeon.

RT: **What advice can you offer to residents who are considering retina?**

Stay humble and keep learning. In surgery, approach each case from basic principles; break it down step by step and understand the reasoning behind every move. When possible, record your cases and review them to see where you can improve. That steady habit of reflection and refinement is what makes great retina surgeons. ■

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CHOROIDAL NEVUS GROWTH INTO MELANOMA IN A YOUNG PATIENT



Know the clinical risk factors for the development of malignancy.

BY HENRY M. NGUYEN, BS; ARUBA ZAFAR, MD; ROBERT J. MEDINA, BA; AND CAROL L. SHIELDS, MD

Uveal melanoma (UM) is the most common primary intraocular cancer in adults, with an annual incidence of 5.1 cases per 1 million individuals in the United States and a propensity to affect individuals with more lightly pigmented skin.[1,2] UM mainly presents in the choroid (90%), with fewer tumors arising in the ciliary body (6%) and iris (4%).[3,4] Prognosis worsens when the ciliary body is involved, owing to the greater tumor thickness, greater risk for cytogenetic abnormalities, and higher metastatic potential.[5] In one series of 1,059 patients tested for genetic abnormalities, ciliary body tumors demonstrated the highest odds ratio (OR) for chromosome 3 monosomy (OR = 8.17, $P < .001$) and chromosome 8q gain (OR = 102.87, $P = .001$), two alterations that are strongly predictive of metastasis.[5]

Despite advances in local control of UM, approximately 50% of patients develop metastasis, mainly to the liver via hematogenous spread.[4,6,7] This persistent risk for systemic spread underscores the need for early detection and structured, risk-based monitoring to improve long-term outcomes. While risk-assessment tools have been published and apply across all ages, nevus transformation into melanoma remains rare in patients under 30 years of age.[8-10]

In this article, we describe a case of melanocytic growth of a choroidal nevus in a 28-year-old patient, our treatment approach, and the importance of balancing vigilance with measured follow-up in patients of all ages.

RISK FACTORS FOR CHOROIDAL NEVUS TRANSFORMATION INTO MELANOMA

Careful monitoring must be guided by objective criteria rather than age alone. One widely used framework to standardize the criteria for nevus transformation to melanoma is the mnemonic "To Find Small Ocular Melanoma Doing Imaging" (ie, TFSOM-DIM):[11]

- **T**hickness > 2 mm (by ultrasonography)
- **F**luid, subretinal (by OCT)
- **S**ymptoms of VA loss to ≤ 20/50 (by Snellen acuity)
- **O**range pigment (by fundus autofluorescence [FAF])
- **M**elanoma showing acoustic hollowness (by ultrasonography)
- **DIaM**eter > 5 mm (by fundus photography)

Previous analyses of 1,329 and 1,287 patients with small melanocytic choroidal tumors first highlighted these important features as key predictors of growth and occasional metastasis, with risks compounding when several of these factors were present.[12,13] A larger subsequent series of 3,806 patients with choroidal nevus showed that the probability of transformation into melanoma increased when more risk factors were present at the time of diagnosis and over time.[11] The 5-year Kaplan-Meier transformation rates were 1% with no factors, 11% with any one factor, 22% with two factors, 34% with three factors, and > 50% with at least four factors.[11] The three strongest predictors of transformation of nevus into melanoma included tumor thickness > 2 mm on ultrasonography, subretinal fluid on OCT, and orange pigment on FAF. A smaller effect was noted for symptoms of visual acuity loss on Snellen acuity, melanoma acoustic hollowness on ultrasonography, and tumor diameter > 5 mm on fundus photography.[11]

In addition to TFSOM-DIM, the MOLES scoring system—Mushroom shape on ultrasonography, Orange pigment on fundus photography and FAF, Large size (≥ 3 disc diameters in base or thickness ≥ 1 mm), Enlarging tumor with growth, and Subretinal fluid on OCT—has been proposed for use by nonspecialists and communities with limited

access to advanced imaging techniques in an effort to guide monitoring and referral.[14] Despite its good specificity and sensitivity, the accuracy of the MOLES system diminishes for very small tumors.[14] These predictive algorithms can help clinicians implement targeted surveillance and timely intervention for patients with one or more high-risk features.

CASE REPORT

A 28-year-old White man with no ocular melanocytosis was observed with a choroidal nevus in his right eye for 6 years. Initial fundoscopic imaging elsewhere showed a flat pigmented lesion measuring 4 mm x 4 mm in diameter (Figure 1A, arrow) and demonstrated hypoautofluorescence (Figure 1B, arrow). He was referred to our team with a possible tumor growth of a nevus into melanoma. His BCVA was 20/25 OU. Fundus examination of the right eye confirmed a dome-shaped pigmented mass in the nasal juxtapapillary region (Figure 2A) with overlying orange pigment on FAF (Figure 2B) and ultrasonographic acoustic hollowness (Figure 2C). OCT showed overlying subretinal fluid and a pocket of subretinal fluid inferonasally (Figure 2D, arrow). The lesion measured 9 mm in largest basal diameter and 2.6 mm in thickness. The fellow eye was unremarkable. By TFSOM-DIM criteria, the tumor met four of six risk factors, and the patient was subsequently diagnosed with a small, growing choroidal melanoma. Plaque radiotherapy with apex dose of 7,000 cGy was subsequently provided.

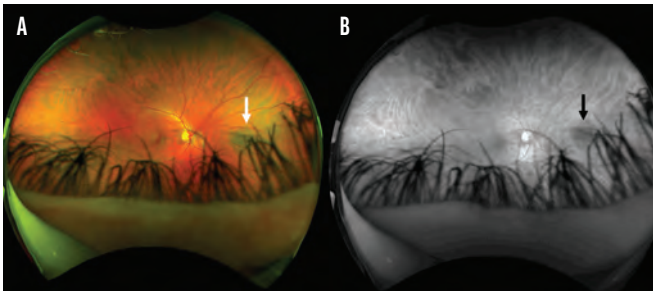


Figure 1. Fundus photography (A) and FAF (B) showed a flat pigmented choroidal nevus with hypoautofluorescence (arrows) and no orange pigment.

AGE-STRATIFIED TRANSFORMATION RISK

The likelihood of nevus transformation increases with advancing age based on a reliable study by Singh et al.[8,11,15] This study evaluated a population-based model of the US White population and found that the risk is negligible in teenagers (one in 270,000) but increases sharply with age, becoming nearly 75-times more likely by the eighth decade of life (one in 3,600).[8] Age also influences the anatomic distribution of tumors, as shown in our series of 8,033 patients, with the proportion of iris and ciliary body involvement more predominant in younger patients (29%, $P < .05$) compared with older adults (9%, $P < .05$), although the choroid remained the most common site for UM for all age brackets.[4]

Long-term metastasis rates in this same group were

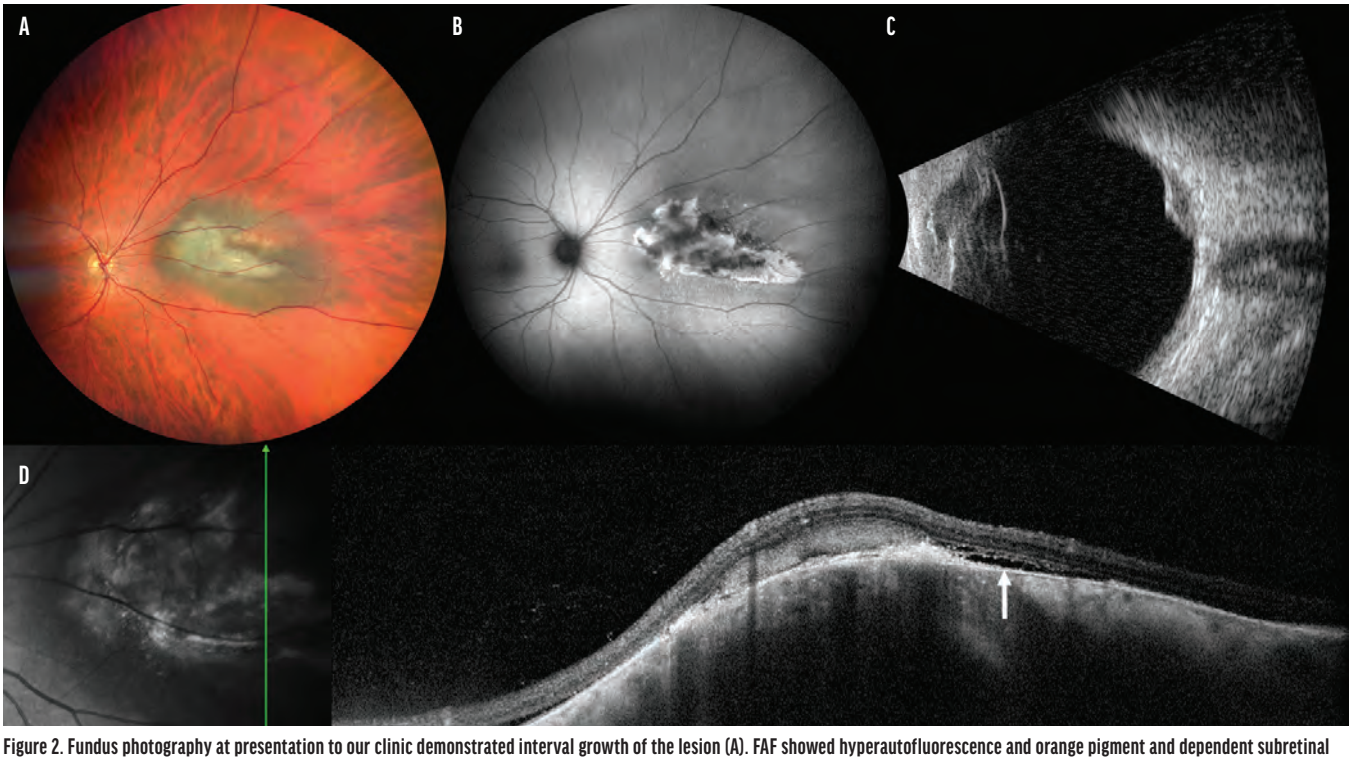


Figure 2. Fundus photography at presentation to our clinic demonstrated interval growth of the lesion (A). FAF showed hyperautofluorescence and orange pigment and dependent subretinal fluid (B). B-scan ultrasonography showed an echolucent choroidal mass of 9 mm in largest basal diameter and 2.6 mm in thickness (C). OCT vertical cut through the lesion showed shallow subretinal fluid, including a pocket of fluid superiorly and tracking down inferiorly (D).

markedly age dependent as well, with patients older than 60 years of age experiencing a higher proportion of metastasis and death compared with younger groups.[4] The prognostic effect of age is even more pronounced with multiple TFSOM-DIM features.[11] These findings should prompt more frequent imaging and longer-term follow-up in older patients with high-risk features. While transformation is exceedingly uncommon in teenagers and children, the small subset who develop melanoma may still carry a risk of metastasis and mortality.[9,10,15,16]

PEDIATRIC UVEAL MELANOMA

Pediatric UM, although uncommon, presents unique physiological and clinical challenges distinct from adult UM. A pooled study sample of 5,533 children with 48 choroidal nevi demonstrated that the prevalence of choroidal nevi increased steadily with age.[15] Longitudinal data was available for 23 of these nevi and showed that 78% remained stable, a minority (22%) demonstrated subtle growth, and none transformed into melanoma.[15] While this study underscores the rarity of choroidal nevus transformation to melanoma in pediatric populations, the occurrence of pediatric UM is well documented.[10] In a multicenter series of 133 pediatric patients ≤ 12 years of age, pediatric UM most often arose in the choroid or ciliary body and less commonly in the iris, with ocular melanocytosis (a predisposing factor for the development of UM) present in 15% of choroidal/ciliary body tumors and 11% of iris tumors, compared with 0.04% in the general population.[10] These findings align with our own observation in children and teenagers, where most tumors have originated in the choroid, with lower rates in the iris and ciliary body.[9]

In our series, metastasis rates increased over decades of follow-up, and treatment for pediatric UM most often included radiotherapy or enucleation.[9] At the more severe end of the spectrum, a small series of 13 infants under 2 years of age found that all eyes were surgically removed (85% through enucleation and 15% through exenteration), with around 15% of patients developing metastasis and 8% dying within 6 months.[16] Although rare, pediatric UM can follow an aggressive course; outcomes may be severe, emphasizing the need for clinical vigilance.

RARE, BUT POSSIBLE

Rare transformation of choroidal nevus into melanoma can occur, such as in the young adult discussed here. Use of the structured evaluation with TFSOM-DIM, combined with careful documentation of growth and risk features, remains a cornerstone of early melanoma detection. ■

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UNDERSTANDING FAST PROGRESSION IN GEOGRAPHIC ATROPHY

Risk stratification, imaging, and patient counseling all support earlier recognition and management of GA.

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Carl J. Danzig, MD, FASRS

In my experience, the commonly used term "fast progressor" in the context of geographic atrophy (GA) lacks precision in clinical practice. We should instead think in terms of patients at higher risk for disease progression, not definitively measurable rates. Decision-making is based on risk stratification, not exact progression metrics, and that distinction helps guide treatment conversations.

Identifying Patients at a Higher Risk for Progression

While we cannot quantify progression rate with current tools, clinicians often rely on recognizable imaging findings and clinical features to identify patients at a higher risk of progression, including

- bilateral disease;
- extrafoveal involvement;
- multifocal lesions; and
- hyperautofluorescence on fundus autofluorescence (FAF) surrounding GA lesions.

These features increase concern for more rapid lesion growth and potential functional decline, which may guide earlier treatment discussions, even though they do not define a fixed trajectory for an individual patient.

Treatment Framing and Clinical Urgency

When speaking to patients about treatment, I reiterate that the goal is to protect their healthy retina tissue longer, potentially preserve their vision longer, and give them hope that they can continue their life independently with the vision they have for as long as possible. I remind patients that treatment will not improve their vision; it's not going to turn back the clock. I let them know this is an ongoing treatment and, while it is a commitment, this is a worthwhile and potentially beneficial endeavor. Although it is not always imperative to begin treatment immediately, I encourage patients not to delay treatment by 6 to 12 months. Keeping patients motivated requires clear, repeated discussion about what treatment can realistically accomplish.

Management Strategy

Following a diagnosis of GA, I explain to patients that treatment requires ongoing injections and frequent visits, and we discuss any barriers that may prevent or challenge their access to treatment. Patients often need time to process their diagnosis before beginning treatment. My follow-up approach is a 3-month revisit for undecided patients and approximately 6-month follow-ups for those outright declining treatment.

I collect OCT images at every visit and FAF photos every 6 months. This imaging strategy helps identify high-risk features of disease, track structural progression, and monitor for conversion to wet AMD, particularly in treated patients. Additional management considerations I suggest to high-risk patients include the continued use of AREDS vitamins and a discussion of clinical trial options when appropriate.

Expectations and Visualization of Risk

The expectation versus the reality of GA treatment can remain challenging for some patients to accept. When identifying higher-risk patients, I find it helpful to revisit treatment goals at follow-up visits every 3 to 6 months. I reinforce that visual stability and an absence of adverse events equals success. Use of patients' FAF images is my preferred communication tool because it helps visually demonstrate atrophy and disease extent. Not only does this method improve understanding for patients and family members, but it also makes the risk of progression more tangible than an abstract discussion.

Final Clinical Pearls

In my experience, a core issue surrounding GA is that so much is missed. Often, GA is misdiagnosed or labeled as early AMD. Recently, a patient referred to me was diagnosed as having early AMD when they really had wet AMD OU and GA in both eyes. My diagnostic recommendations for identifying GA are to use OCT to evaluate the full macula, including above and below the foveal avascular zone; identify complete retinal pigment epithelium and outer retina atrophy (cRORA) and atrophic changes; and incorporate FAF photos frequently.

I encourage clinicians to avoid relying on one method of examination. Conduct a careful evaluation, spend time studying patient imaging, and ask patients questions about their vision. Find out if they have symptoms even if they have good vision, including difficulty with dim lighting, reading, and driving. A color photo is not adequate on its own. My biggest pearl is that active detection is essential; clinicians can miss GA if they are not specifically looking for it. ■

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FIGURE 1

PERIPHERAL FIRESTORM: THE ISCHEMIC RETINA





Proliferative disease may still be progressing despite good vision.

BY APOORVA JADHAV, MBBS, DNB; UNNIKRISHNAN NAIR, MS, FRCS, FMRF; AND MANOJ SOMAN, DNB, FICO, FRCS

A 62-year-old man with a history of diabetes for the past 10 years presented with complaints of bilateral blurred vision for 2 months with a BCVA of 20/30 OU. Findings on color fundus photography were suggestive of proliferative diabetic retinopathy with fibrovascular proliferation around the optic disc and along the vascular arcades (Figure 1). Widefield OCT demonstrated mild alteration of the foveal contour with minimal parafoveal cystic spaces (Figure 2). The left eye also showed internal limiting membrane folds with vitreomacular adhesion. No significant macular edema was noted.

Widefield OCT angiography (OCTA) demonstrated extensive peripheral microvascular alterations consistent with a severe ischemic retinopathy (Figure 3). The most striking feature was the presence of large areas of capillary nonperfusion involving the mid- and far-peripheral retina bilaterally. These regions appeared as well-demarcated flow voids on widefield OCTA, indicating significant capillary dropout and retinal ischemia. At the junction of perfusion and nonperfusion, there were multiple abnormal vascular proliferations visualized as bright, irregular, high-flow networks. These frond-like vascular complexes exhibited disorganized branching and looping patterns, characteristic of neovascularization elsewhere.

The bilateral and relatively symmetrical involvement, in conjunction with extensive peripheral capillary nonperfusion and widespread neovascularization, was highly suggestive of proliferative diabetic retinopathy. Given the extent

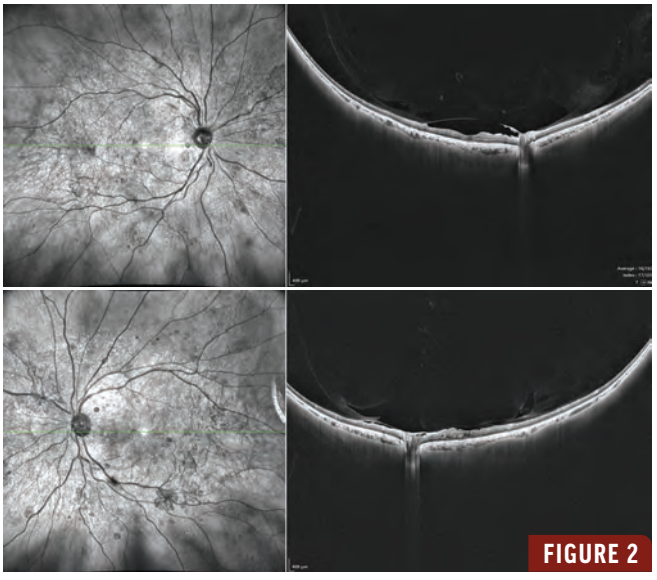


FIGURE 2

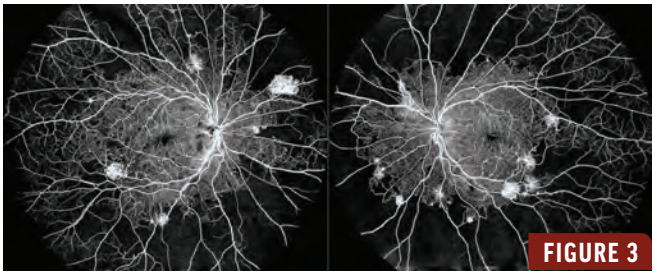


FIGURE 3

of nonperfusion and the presence of active neovascular complexes, this patient was deemed to be at increased risk for vision-threatening complications, such as vitreous hemorrhage and tractional retinal detachment. Panretinal photocoagulation was performed in each eye with close follow-up.

MIND THE PERIPHERAL RETINA

This case demonstrates that even with relatively preserved visual acuity, advanced peripheral ischemic changes can be present, emphasizing the critical role of widefield imaging in comprehensive retinal evaluation. ■

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

This Brief Summary does not include all of the information needed to use ENCELTO™ safely and effectively.

See full Prescribing Information for ENCELTO.

ENCELTO (revakinagene taroretcel-lwey) implant, for intravitreal use

Initial U.S. Approval: 2025

INDICATIONS AND USAGE

ENCELTO is indicated for the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel).

DOSAGE AND ADMINISTRATION

Recommended Dose

For intravitreal implantation only

- ENCELTO is administered by a single surgical intravitreal procedure performed by a qualified ophthalmologist.
- The recommended dose is one ENCELTO implant per affected eye. Each ENCELTO implant contains 200,000 to 440,000 allogeneic retinal pigment epithelial cells expressing recombinant human ciliary neurotrophic factor (rhCNTF) (NTC-201-6A cell line), a neurotrophic factor.

CONTRAINDICATIONS

ENCELTO is contraindicated in patients with:

- Active or suspected ocular or periocular infections.
- Known hypersensitivity to Endothelial Serum Free Media (Endo-SFM)

WARNINGS AND PRECAUTIONS

Severe Vision Loss

Severe vision loss defined as three or more lines of visual acuity loss [≥15 Early Treatment Diabetic Retinopathy Study (ETDRS) letters] has occurred following ENCELTO implantation. Monitor patients for signs and symptoms of vision loss and manage as clinically indicated.

Infectious Endophthalmitis

Infectious endophthalmitis may occur following ENCELTO implantation. Signs and symptoms of infectious endophthalmitis include progressively worsening eye pain, vision loss, or scleral and conjunctival injection. To mitigate the risk of endophthalmitis, use proper aseptic surgical technique for ENCELTO implantation. Monitor patients for signs or symptoms of infectious endophthalmitis. Remove ENCELTO implant if infectious endophthalmitis occurs and manage symptoms according to clinical practice.

Retinal Tear and Detachment

Retinal tears and retinal detachment may occur following ENCELTO implantation. Signs and symptoms of retinal tears include acute onset of flashing lights, floaters, and/or loss of visual acuity. Signs and symptoms of retinal detachment may include progressive visual field loss and/or loss of visual acuity. Use standard vitreoretinal surgical techniques during ENCELTO implantation to minimize the risk of retinal tears and retinal detachment. Monitor for any signs or symptoms of retinal tear and/or retinal detachment. Treat rhegmatogenous retinal detachment and retinal tears promptly. Remove ENCELTO implant, if vitrectomy with a complete gas fill or silicone oil fill is required.

Vitreous Hemorrhage

Vitreous hemorrhage, which may result in temporary vision loss, has occurred following ENCELTO implantation. Patients receiving antithrombotic medication (e.g., oral anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs) may be at increased risk of vitreous hemorrhage. To reduce the risk of vitreous hemorrhage, interrupt antithrombotic medications prior to the ENCELTO implantation. Vitrectomy surgery may be necessary to clear severe, recurrent, or non-clearing vitreous hemorrhage. If the patient has a late onset vitreous hemorrhage (greater than one year following ENCELTO implantation surgery), examine the ENCELTO implantation site for possible implant extrusion. If implant extrusion has occurred, surgically reposition ENCELTO.

Implant Extrusion

Implant extrusion through the initial scleral wound has occurred following ENCELTO implantation. Signs and symptoms of implant extrusion include recurrent uveitis, vitreous hemorrhage, eye pain more than one year after implantation, or visibility of titanium fixation loop under the conjunctiva. To reduce the risk of implant extrusion, carefully follow the specific surgical steps for ENCELTO implantation.

Evaluate patients after 6 months to confirm proper positioning of ENCELTO and then annually. If ENCELTO begins to extrude, surgically reposition ENCELTO to a proper scleral wound depth either in the same site or in the opposing inferior quadrant of the vitreous cavity.

Cataract Formation

Cataract formation, including cataract cortical, cataract nuclear, cataract subcapsular, cataract traumatic, and lenticular opacities, has occurred following ENCELTO implantation. To reduce the risk of ENCELTO-related cataract formation or progression, carefully follow the specific surgical steps for ENCELTO implantation.

Suture Related Complications

Suture related complications, including conjunctival erosions due to suture tips and suture knots, have occurred following ENCELTO implantation.

To mitigate the risk of suture related complications, carefully follow the specific surgical steps for ENCELTO implantation and manage suture-related complications as clinically indicated.

Delayed Dark Adaptation

Delayed Dark Adaptation, a delay in the ability to adjust vision from a bright lighting condition to a dim lighting, has occurred following ENCELTO administration which remained unchanged for the duration of study follow up. Advise patients to take caution while driving and navigating in the dark.

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.

ADVERSE REACTIONS (cont'd)

Clinical Trials Experience (cont'd)

The safety data described in this section reflects exposure to ENCELTO in two clinical trials, Study 1 (NTMT-03-A) and Study 2 (NTMT-03-B) and are pooled for analysis. A total of 117 patients received ENCELTO, and 111 patients underwent a sham procedure and were followed for a duration of 24 months.

Serious adverse reactions occurred in six patients (5%) including suture related complications (n=5) and implant extrusion (n=1).

Table 1 lists the most common adverse reactions that occurred in ≥2% patients and with higher frequency in ENCELTO group compared to Sham group in Study 1 and Study 2.

Table 1. Adverse Reactions occurring in ≥2% of Patients and with higher frequency in ENCELTO group compared to Sham group in ENCELTO studies*

Adverse Reactions	ENCELTO (N=117) n (%)	Sham (N=111) n (%)
Conjunctival hemorrhage	36 (31)	29 (26)
Delayed dark adaptation	27 (23.1)	1 (1)
Foreign body sensation in eyes	18 (15)	15 (13.5)
Eye pain	18 (15)	10 (9)
Suture related complication**	18 (15.4)	3 (2.7)
Miosis	18 (15.4)	0 (0.0)
Conjunctival hyperemia	13 (11)	9 (8)
Eye pruritus	10 (9)	4 (3.6)
Ocular discomfort	10 (9)	1 (1)
Vitreous hemorrhage	10 (8.5)	0 (0.0)
Vision blurred	8 (7)	4 (4)
Headache	8 (7)	1 (1)
Dry eye	7 (6)	2 (2)
Eye irritation	6 (5.1)	2 (2)
Cumulative cataract incidence	6 (5)	0 (0)
Vitreous floaters	6 (5)	0 (0.0)
Severe visual loss>15 letters***	4 (3)	0 (0)
Eye discharge	4 (3.4)	1 (0.9)
Anterior chamber cell	4 (3.4)	0 (0.0)
Iridocyclitis	3 (2.6)	0 (0)

*Pooled data from Study 1 and Study 2; Adverse reaction rates were comparable between the two studies

**Suture related complications include exposed suture, foreign body sensation, conjunctival wound dehiscence, painful sutures, suture irritation, suture granuloma, scleral wound opening, and itchy suture

***Includes one case of visual loss due to cataract formation which remained unresolved at the end of the study

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no data on the use of ENCELTO in pregnant women. Endogenous CNTF is naturally found in maternal plasma, placental cells, and umbilical cord blood. It is not known if the use of ENCELTO increases CNTF above naturally occurring levels in these tissues.

In animal reproduction studies, subcutaneous administration of rhCNTF to pregnant rats and rabbits demonstrated no evidence of teratogenic effects on the fetus. However, when administered to rabbits at a dose level of 10ug/kg/day, a decrease in implantations and live fetuses was observed. When administered to rats at a dose level of 100ug/kg/day a decrease in corpora lutea was observed.

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

Data

Animal Data

See *Risk Summary* for details on data.

Lactation

Risk Summary

There is no data on the presence of ENCELTO in human milk, its effects on the breastfed infant, or its impact on milk production.

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

Pediatric Use

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

Geriatric Use

There were 38 patients (32%) 65 years of age and older and two patients (1%) 75 years of age and older in Study 1 and Study 2 who received ENCELTO. Clinical studies of ENCELTO did not include sufficient numbers of patients aged 65 and over to determine whether they respond differently than younger patients.

Manufactured for:
Neurotech Pharmaceuticals, Inc.
Cumberland, RI 02864

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ENCELTO™
(revakinagene taroretcel-lwey)
implant, for intravitreal use

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The **first and only** FDA-approved treatment for adults with idiopathic macular telangiectasia type 2 (MacTel)[1]

ENCELTO™
(revakinagene taroretcel-lwey)
implant, for intravitreal use



Proven to **slow disease progression** in two phase 3 studies[1,2]*

*Based on two phase 3, randomized, multicenter, sham-controlled studies (Study A and Study B). Both studies evaluated the rate of ellipsoid zone (EZ) area loss (macular photoreceptor loss) in 228 adults with MacTel type 2 over 24 months. Results for ENCELTO: 54.8% reduction in retinal degeneration in Study A ($P<0.0001$); 30.6% reduction in Study B ($P=0.0186$).[1,2]

The permanent J-code for ENCELTO is now available: **J3403**

Scan the QR code for more information about accessing ENCELTO

INDICATIONS AND USAGE

ENCELTO is an allogeneic encapsulated cell-based gene therapy indicated for the treatment of adults with idiopathic macular telangiectasia type 2 (MacTel).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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WARNINGS AND PRECAUTIONS

ENCELTO implantation surgery and/or implantation related procedures have been associated with the following:

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ADVERSE REACTIONS

The most common adverse reactions (≥2%) reported with ENCELTO were conjunctival hemorrhage, delayed dark adaptation, foreign body sensation, eye pain, suture related complications, miosis, conjunctival hyperemia, eye pruritus, ocular discomfort, vitreous hemorrhage, blurred vision, headache, dry eye, eye irritation, cataract progression or formation, vitreous floaters, severe vision loss, eye discharge, anterior chamber cell, iridocyclitis.

Please see Brief Summary of full Prescribing Information on adjacent pages.

References: 1. ENCELTO [prescribing information]. Cumberland, RI. Neurotech Pharmaceuticals, Inc. **2.** Data on file. Neurotech Pharmaceuticals, Inc. Cumberland, RI.

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