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Retina Today

MAY/JUNE 2025 VOL. 20, NO. 4
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Advances in AMD

Navigating the maze of
clinical trial data and design.

EMERGING (DURABLE)
THERAPIES FOR WET AMD

FDA GUIDANCE: WHAT IT
MEANS FOR AMD TRIALS

GENE THERAPY FOR WET
AMD AND GA

SUBSCRIBE FOR FREE



SYFOVRE[®]

(pegcetacoplan injection)
15 mg/0.1 mL

Save more retinal tissue

Through Year 2, in OAKS and DERBY, SYFOVRE slowed GA lesion growth vs sham pooled.¹

SYFOVRE slowed GA lesion growth with **increasing effects over time up to 42%** in Year 3 (GALE) vs projected sham in patients without subfoveal lesions^{1,2}

- Through Year 2 (OAKS and DERBY), SYFOVRE slowed GA lesion growth (mm²) vs sham pooled by 22% (3.11 vs 3.98) and 18% (3.28 vs 4.00) monthly, and by 18% (3.26 vs 3.98) and 17% (3.31 vs 4.00) EOM^{1,2}
- Through Year 3 (GALE), SYFOVRE slowed GA lesion growth (mm²) vs sham pooled/projected sham by 25% (4.46 vs 5.94) monthly and 20% (4.74 vs 5.94) EOM. The greatest differences were observed in Year 3²
 - Reductions in patients without subfoveal lesions at baseline through Year 3: 32% (5.10 vs 7.54 (n=95)) monthly and 26% (5.60 vs 7.54 (n=104)) EOM. In this subset of patients, there was a 42% reduction with monthly SYFOVRE in Year 3 vs projected sham

SE in trials (monthly, EOM, sham pooled/projected sham): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17; GALE (total population): 0.16, 0.16, 0.19; GALE (without subfoveal): 0.26, 0.31, 0.41^{1,2}

EOM=every other month; GA=geographic atrophy; SE=standard error.

Discover more at
SyfovreECP.com

GALE Trial Limitations: GALE is an ongoing open-label, multi-center extension study, subject to patient dropouts over time. The analysis for the first year of GALE utilized a projected sham and may not reflect rate of change of all patients with GA. Projected sham assumes linear growth rate from Months 24–36 (GALE Year 1) based on the average of the mean rate of change of each 6-month period of sham treatment in OAKS and DERBY and natural history studies, which have shown there is a high correlation between prior 2-year growth rates of GA lesions and subsequent 2-year growth rates. This is a prespecified analysis but there is no statistical testing hierarchy, therefore the results on the individual components need cautious interpretation. Open-label studies can allow for selection bias.^{2,3}

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- SYFOVRE is contraindicated in patients with ocular or periocular infections, 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.
- **Retinal Vasculitis and/or Retinal Vascular Occlusion**
 - Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
- **Neovascular AMD**
 - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.

Intraocular Inflammation

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

Increased Intraocular Pressure

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

ADVERSE REACTIONS

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

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

OAKS and DERBY Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 2-year, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration) with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE every other month, sham monthly, or sham every other month, for 2 years. Change from baseline in the total area of GA lesions in the study eye (mm²) was measured by fundus autofluorescence (FAF).^{1,2}

GALE Trial Design: GALE (N=790) is a multi-center, 3-year, Phase 3, open-label extension study to evaluate the long-term safety and efficacy of pegcetacoplan in subjects with geographic atrophy secondary to age-related macular degeneration. Patients enrolled in GALE include those who completed OAKS or DERBY after 2 years and 10 patients from Phase 1b Study 103. Patients with GA (atrophic nonexudative age-related macular degeneration) with or without subfoveal involvement, secondary to AMD were assigned to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly or SYFOVRE EOM for 3 years. The first visit was required to be within 60 days of the final visit in OAKS and DERBY.²

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2024. 2. Data on file. Apellis Pharmaceuticals, Inc. 3. Sunness JS, Margalit E, Srikanth D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology*. 2007;114(2):271–277. doi:10.1016/j.ophtha.2006.09.016.



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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

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

Intraocular Inflammation

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

Increased Intraocular Pressure

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

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham. The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

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

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

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:

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

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

Punctate keratitis included: punctate keratitis, keratitis

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

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

Postmarketing Experience

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

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FEATURED ARTICLES

- 22 Emerging (Durable) Therapies for Wet AMD
By Jacob S. Heng, MD, PhD, and Adrienne W. Scott, MD
- 26 Gene Therapy for AMD: What You Need to Know
By Szilárd Kiss, MD, FASRS, and Peyman Razavi, MD
- 32 Beyond Complement: Emerging Therapeutics for Dry AMD
By Aumer Shughoury, MD, and Thomas A. Ciulla, MD, MBA
- 40 Imaging Biomarkers for GA Progression
By Maxwell S. Mayeda, MD, and Talisa E. de Carlo Forest, MD
- 46 FDA Guidance: What it Means for AMD Trials
By Nadia K. Waheed, MD, MPH; Ramiro Ribeiro, MD, PhD;
Victor Chong, MD, MBA, FARVO; Lanita C. Scott, MD;
and David J. Tanzer, MD

DEPARTMENTS

UP FRONT

- 9 Medical Editors' Page
- 10 Retina News

MEETING MINUTES

- 12 VBS 2025 Highlights: Surgical Scenarios
By Lauren Kiryakoza, MD; Prashant D. Tailor, MD;
and Hailey K. Robles-Holmes, MD

ONE TO WATCH

- 15 Sally S. Ong, MD
- 25 Claudia Gómez Hooten, MD

FELLOWS' FOCUS

- 16 Understanding—and Overcoming—Fellowship Challenges
By Vicente Lorenzo Cabahug, MD, DPBO,
and Andrew S.H. Tsai, MBBS, MCI, FRCOphth

GLOBAL PERSPECTIVES

- 19 AI Chatbots in Retina
By Matteo Mario Carlà, MD, and Stanislao Rizzo, MD

SPECIAL REPORT

- 50 Implantable Drug Delivery: A Look at Pharmacokinetics
By Charles C. Wykoff, MD, PhD, FASRS, FACS

SURGICAL PEARLS

- 53 A New Technique for Myopic Traction Maculopathy
By Nikoloz Labauri, MD; Tekla Mamageishvili, MD; Monika Zalinian, MD;
and Supriya Dabir, MD, PhD

RIISING STARS IN RETINA

- 56 Adrian Au, MD, PhD

CODING ADVISOR

- 57 Expanded Transfer of Care Policies in Retina
By Joy Woodke, COE, OCS, OCSR

MEDICAL RETINA

- 60 Posterior Placoid Changes Due to Nutritional Deficiency
By Eric W. Lai, MD; Brian K. Do, MD; and Sidney A. Schechet, MD

VISUALLY SPEAKING

- 64 Valsalva Retinopathy: The Silent Bleeder
By Inês Cerdeira Ludovico, MD; Patrícia Silva, MD; Joana Ferreira, MD;
Ana Luísa Basílio, MD; and Carlos Batalha, MD

IN THE BACK

- 65 Ad Index



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*Based on bench testing.

Reference: 1. Alcon data on file, 2024.

Alcon

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UNITY® VCS and CS Important Product Information

Caution: Federal (USA) law restricts this device to sale by, or on the order of, a physician.

Indications / Intended Use:

UNITY VCS:

The UNITY VCS console, when used with compatible devices, is indicated for use during anterior segment (i.e. phacoemulsification and removal of cataracts) and posterior segment (i.e. vitreoretinal) ophthalmic surgery.

In addition, with the optional laser this system is indicated for photocoagulation (i.e. vitreoretinal and macular pathologies), iridotomy and trabeculoplasty procedures.

UNITY CS:

The UNITY CS console, when used with compatible devices, is indicated for use during anterior segment (i.e. phacoemulsification and removal of cataracts) ophthalmic surgery.

Warnings:

Appropriate use of UNITY VCS and CS parameters and accessories is important for successful procedures. The console supports various accessories to perform various surgical procedures. Accessories include handpieces and probes, as well as tips and sleeves when necessary. Different accessories are required for different procedures and operating modes.

Test for adequate irrigation and aspiration flow, reflux, and operation of each accessory prior to entering the eye.

The consumables used in conjunction with ALCON® instrument products constitute a complete surgical system. To avoid the risk of a patient hazard, do not mismatch consumable components or use settings not specifically adjusted for particular consumable component combinations.

AEs/Complications:

Inadvertent activation of functions that are intended for priming or tuning accessories while the accessory is in the eye can create a hazardous situation that could result in patient injury. During any ultrasonic procedure, metal particles may result from inadvertent touching of the ultrasonic tip with a second instrument. Another potential source of metal particles resulting from any ultrasonic handpiece may be the result of ultrasonic energy causing micro abrasion of the ultrasonic tip.

ATTENTION:

Refer to the Directions for Use for the accessories/consumables and User Manual for a complete listing of indications, warnings, cautions and notes.

Alcon

RETINA MEETINGS: 2025 – 2026

Looking to present an interesting case, boost your continuing education, or find networking opportunities? These conferences are the place to be!

2025

JULY 2025

15th Annual Mass Eye and Ear Vitrectomy Course
July 11 – 12
Boston, MA

ASRS

July 30 – August 2
Long Beach Convention & Entertainment Center
Long Beach, CA

AUGUST 2025

26th Annual Advanced Vitreoretinal Techniques & Technology Symposium and Fellows' Course
August 22 – 24
Chicago, IL

SEPTEMBER 2025

Euretina
September 4 – 7
Le Palais des Congres
Paris, France

The Retina Society
September 10 – 13
The Ritz-Carlton Chicago
Chicago, IL

Advances in Pediatric Retina
September 18 – 20
Durham, NC

OCTOBER 2025

AAO
October 17 – 20
Orange County Convention Center
Orlando, FL

NOVEMBER 2025

22nd European VitreoRetinal Society Meeting
November 13 – 16
Cancun, Mexico

DECEMBER 2025

FloRetina
December 4 – 7
Fortezza da Basso
Florence, Italy

To find links to each of these meetings, visit our online conference calendar at retinatoday.com/calendar.



The American Society of Retina Specialists will convene at the Long Beach Convention & Entertainment Center, July 30 – August 2.

2026

JANUARY 2026

Atlantic Coast Retina Club & Macula
January 8 – 10
Philadelphia, PA

29th Annual American Uveitis Society Meeting
January 17 – 19
Park City, UT

26th Annual Fellows Forum
January 30 – 31
Westin Chicago North
Chicago, IL

FEBRUARY 2026

Telluride Retina Film Festival
February 4 – 7
Telluride Conference Center
Telluride, CO

49th Annual Macula Society Meeting
February 25 – 28
Del Coronado
San Diego, CA

54th Annual Aspen Retinal Detachment Society Meeting
February 28 – March 4
The Viceroy
Snowmass, CO

APRIL 2026

14th Annual Vit-Buckle Society Meeting
April 9 – 11
Las Vegas, NV

MAY 2026

ARVO
May 3 – 7
Denver, CO

12th Annual Pacific Retina Club & 13th Annual International Retinal Imaging Symposium
May 14 – 16
Los Angeles, CA

2026 SAVE THE DATES

ASRS: Montreal, Canada, July 15 – 18
AAO: New Orleans, October 9 – 12

RETINA BY THE NUMBERS



One of the most fascinating (and frustrating) aspects of the retina space is the sheer volume of patients we

care for with just over 3,000 retina specialists in the United States.¹ There are an estimated 19.8 million Americans with AMD (1.49 million of whom have vision-threatening disease) and another 9.6 million with diabetic retinopathy (DR; 1.84 million cases are vision-threatening).^{2,3} That's approximately 1.1 million AMD/DR patients with vision-threatening disease per retina specialist in the United States! While there are myriad other retinal conditions that require our care, these two are often chronic with ongoing, even monthly, therapy.

So, it's no wonder our clinical trial pipeline is packed with efforts to extend the duration of treatment effect to help ease the burden on our patients and our clinics. For example, more than 20 therapies are under investigation for AMD—approximately half of which (11, to be exact) are potentially one-and-done gene therapies (Table). That's a wild statistic. With so many shots on goal, we are reaching a tipping point; a few of these investigational drugs will likely cross the finish line in the next few years, completely disrupting our current treatment approach for wet AMD. But for now, we must watch and wait as the trials collect data and churn out interim findings every few months.

In this issue, we take a deep dive into AMD care, with articles on the therapies shaping our current treatment paradigm for AMD and those poised to completely upend our workflow with increased treatment durability.

Of particular interest is an article detailing those 11 gene therapies for AMD, authored by Szilárd Kiss, MD, FASRS, and Peyman Razavi, MD. Three are already in phase 3: ABBV-RGX-314 (Regenxbio/Abbvie), 4D-150 (4D Molecular Therapeutics), and ixo-vec (Adverum Biotechnologies).

In addition, Jacob S. Heng, MD, PhD, and Adrienne W. Scott, MD, discuss ways to incorporate our current second-generation AMD therapies into practice, and they provide their own treatment decision tree when switching AMD patients to faricimab (Vabysmo, Genentech/Roche), 8 mg aflibercept (Eylea HD, Regeneron), or the port delivery system (Susvimo, Genentech/Roche).

Aumer Shughoury, MD, and Thomas Ciulla, MD, provide a review of the dry AMD pipeline, giving us an excellent overview of the ways in which these new drugs are targeting inflammation, mitochondrial health, and neuroprotection. In addition, Maxwell S. Mayeda, MD,

TABLE. GENE THERAPIES IN THE PIPELINE FOR AMD

Company	Agent	Disease Target	NCT	Phase
Regenxbio/Abbvie	ABBV-RGX-314	Wet AMD	NCT05407636	Phase 3
4D Molecular Therapeutics	4D-150	Wet AMD	NCT06864988	Phase 3
Adverum Biotechnologies	Ixo-vec	Wet AMD	NCT06856577	Phase 3
Chengdu Origen Biotechnology	KH631 KH658	Wet AMD	NCT05672121 NCT06825858	Phase 1/2 Phase 1
Frontera Therapeutics	FT-003	Wet AMD	NCT06492863	Phase 1/2
HuidaGene Therapeutics	HG202	Wet AMD	NCT06623279 NCT06031727	Phase 1
ExeGenesis Bio	EXG102-031 EXG202	Wet AMD	NCT05903794 NCT06888492	Phase 1
Janssen	JNJ-1887	Geographic atrophy	NCT05811351	Phase 2
Ocugen	OCU410	Geographic atrophy	NCT06018558	Phase 1/2

and Talisa E. de Carlo Forest, MD, share their research on imaging biomarkers in geographic atrophy to help us identify high-risk patients who might be candidates for complement inhibition.

Lastly, we stepped away from the clinic to look at the changing landscape of clinical trial designs, given the 2023 FDA draft guidance. Several biotech chief medical officers share how the document and their conversations with the FDA shaped their phase 3 clinical trial designs and what those decisions might mean for future therapeutics.

Retina seems to be a numbers game these days, as we do our best to balance the patient volume with the data volume. But if we stay the course and follow the numbers, we will, one day, have more durable treatment options to help our patients with AMD. ■

ALLEN C. HO, MD
CHIEF MEDICAL EDITOR

ROBERT L. AVERY, MD
ASSOCIATE MEDICAL EDITOR

1. About us. American Society of Retina Specialists. Accessed May 6, 2025. www.asrs.org/about

2. VEHSS modeled estimates for age-related macular degeneration (AMD). Centers for Disease Control and Prevention Vision and Eye Health Surveillance System. May 15, 2024. Accessed May 6, 2025. bit.ly/4mcDpyp

3. VEHSS modeled estimates: Prevalence of diabetic retinopathy. Centers for Disease Control and Prevention Vision and Eye Health Surveillance System. May 15, 2024. Accessed May 6, 2025. www.cdc.gov/vision-health-data/prevalence-estimates/dr-prevalence.html

SYMMETRICAL PERIPHERAL RETINAL VASCULAR LOSS FOUND IN RP

A study published in *Ophthalmology* evaluated retinitis pigmentosa (RP), the most common inherited retinal disease, and found compelling evidence of substantial symmetrical peripheral retinal vascular loss. This finding may aid in clinical diagnosis of the disease and have significant therapeutic implications, according to the authors.¹

The study included 181 eyes of 107 patients with RP and 130 eyes of 84 patients without RP as controls. The researchers divided ultra-widefield fundus images into three zones: posterior, midperiphery, and far periphery. To evaluate retinal vascularity, the vessels were counted at the border of the posterior and midperipheral zones (Z1/2) and the border of the midperipheral and far peripheral zones (Z2/3).¹

In the RP group, the median vessel counts at Z1/2 and

Z2/3 were eight and three, respectively. These numbers were significantly lower than the control group, with median vessel counts of 42 and 43.5 at Z1/2 and Z2/3, respectively. Of the RP eyes, 22% were avascular in the far periphery, and 7% were avascular in both the midperiphery and far periphery. Only 5% of RP eyes had more than 25 vessels at Z2/3. There were significantly fewer vessels in the temporal retina at both Z1/2 and Z2/3 in RP eyes. Furthermore, eyes with a VA of 20/200 or worse had significantly fewer vessels at Z1/2 and Z2/3. There were no significant differences in the number of vessels at Z1/2 and Z2/3 between the right and left eyes of RP patients with both eyes included in the study.¹

1. Ameri H, Hong AT, Chwa J. Loss of peripheral retinal vessels in retinitis pigmentosa. *Ophthalmology*. 2025;5(4):100767.

ERG INCLUDED IN UPDATED AAO PPP GUIDELINES FOR DR

LKC Technologies recently announced that electroretinography (ERG) was included in the 2024 update of the AAO's Preferred Practice Pattern Guidelines for diabetic retinopathy (DR).^{1,2} This inclusion reflects the notion that objective functional testing, combined with structural imaging, is critical for comprehensive DR assessment.² ERG has been used in research and academic settings for decades, but its use in clinical practice remains limited. FDA-cleared RETeval (LKC Technologies) is a portable device that allows for objective assessment of retinal function without the need for dilation.²

"As diagnosticians and treating physicians, we need an objective functional complement to structural imaging," Sruthi Arepalli, MD, a retina specialist and assistant professor at Emory University School of Medicine, said in a release. "ERG provides this, helping us detect early retinal dysfunction that may precede visible structural changes. This allows for earlier intervention and more personalized patient care."^{2,3}

1. Lim JJ, Kim SJ, Bailey ST, et al. Diabetic Retinopathy Preferred Practice Pattern. *Ophthalmology*. 2025;132(4):P75-P162.

2. Electroretinography added to AAO's Diabetic Retinopathy Preferred Practice Pattern Guidelines. LKC Technologies. March 24, 2025. Accessed April 29, 2025. lkc.com/new/erg-added-to-preferred-practice-pattern-guidelines

3. Ratra D, Nagarajan R, Dalan D, et al. Early structural and functional neurovascular changes in the retina in the prediabetic stage. *Eye (Lond)*. 2021;35(3):858-867.



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- **Your Money:** Success Factors for Employed Ophthalmologists, by David Mandell, JD, MBA
- **Practice Management:** How to Train Your Scribes, by Nikisha Kothari, MD

AFLIBERCEPT BIOSIMILAR YESAFILI APPROVED TO LAUNCH IN UNITED STATES

Biocon Biologics announced an agreement with Regeneron that clears the way to commercialize aflibercept-jbvf (Yesafili, Biocon Biologics), an interchangeable aflibercept biosimilar, in the United States.¹

The drug was first approved by the FDA in May 2024 based on analytical, nonclinical, and clinical data, including findings from the phase 3 INSIGHT study, which compared Yesafili with 2 mg aflibercept (Eylea, Regeneron) in patients with diabetic macular edema.²

The announcement comes after Biocon and Regeneron reached a settlement in the suit Regeneron filed under the Biologics Price Competition and Innovation Act against several companies with aflibercept biosimilars.³ The agreement enables Biocon to launch in the United States in the second half of 2026, or earlier in certain circumstances.¹

1. Biocon Biologics secures market entry date for Yesafili, interchangeable biosimilar to Eylea in the US [press release]. Eyewire+. April 15, 2025. Accessed April 29, 2025. eyewire.news/news/biocon-biologics-secures-market-entry-date-for-yesafili-interchangeable-biosimilar-to-eylea-in-the-us

2. Biocon Biologics obtains U.S. FDA approval for biosimilar aflibercept for Yesafili. Enters U.S. ophthalmology market [press release]. Biocon Biologics. May 21, 2024. Accessed April 29, 2025. www.bioconbiologics.com/biocon-biologics-obtains-u-s-fda-approval-for-biosimilar-aflibercept-for-yesafili-enters-u-s-ophthalmology-market

3. Padula A. Regeneron, Mylan, and Biocon settle in aflibercept BPCIA litigation. Big Molecule Watch. April 28, 2025. Accessed April 29, 2025. www.bigmoleculewatch.com/2025/04/28/regeneron-mylan-and-biocon-settle-in-aflibercept-bpcia-litigation

PREVENT BLINDNESS CALLS ON WV TO REJECT BILL THREATENING KIDS' VISION

Prevent Blindness recently published a letter calling on the West Virginia State House to reject HB 3444. The vision advocacy group said that, if enacted, the legislation would remove the mandate that all newborns in the state receive erythromycin ointment applied to their eyes after birth, which can help avoid ophthalmia neonatorum, a potentially blinding eye infection that is easily preventable.¹

In removing the mandate, legislators are relying instead on parental notification and choice, according to the letter. "The legislation does not, however, provide a clear method to define or ensure that informed parental consent has occurred. While providers will still move forward with clinical practice standards set by the American Academy of Pediatrics in application of a topical prophylaxis, the removal of a mandate creates a pathway for parental confusion and misinformation to the science that has driven this proven public health intervention," the letter states.¹

As it stands, the West Virginia Legislature is expected to take a final vote on the measure before referring it to Governor Patrick Morrisey for signature.¹

1. Prevent Blindness days West Virginia State House bill would imperil children's vision [press release]. Eyewire+. April 15, 2025. Accessed April 29, 2025. bit.ly/4d5dHY0

ALCON OFFICIALLY LAUNCHES UNITY VCS/CS

Alcon has introduced its new surgical consoles, the UNITY Vitreoretinal Cataract System (VCS) and UNITY Cataract System (CS).¹ According to the company, the two consoles feature many first-to-market and advanced technologies, including the following¹:

- UNITY 4D Phaco
- HYPERVIT 30K
- UNITY Intelligent Fluidics
- Advanced instrumentation, such as the UNITY 27 gauge portfolio, the UNITY TetraSpot, and UNITY Illumination
- UNITY Intelligent Sentry
- UNITY Thermal Sentry

The UNITY VCS received CE Mark and regulatory approval in Australia, Japan, and the United States, and it became available in May. The company plans to enter other markets in the third quarter of 2025, pending regulatory approvals.¹ ■

1. Alcon launches UNITY VCS and UNITY CS for vitreoretinal and cataract surgery [press release]. Eyewire+. April 29, 2025. Accessed April 30, 2025. eyewire.news/news/alcon-launches-unity-vcs-and-unity-cs-for-vitreoretinal-and-cataract-surgery

Eyewire+ Pharma Update

- **Atsena Therapeutics** received Regenerative Medicine Advanced Therapy designation from the FDA for ATSN-201, its gene therapy candidate for the treatment of X-linked retinoschisis.
- **Oculus** completed enrollment for its phase 3 DIAMOND-1 and DIAMOND-2 trials evaluating OCS-01 for the treatment of diabetic macular edema.
- **Opthea** discontinued development of its investigational combination drug for the treatment of wet AMD, 2 mg sozinibercept combined with 2 mg aflibercept (Eylea, Regeneron), after its two phase 3 trials did not meet their primary endpoints.
- **Outlook Therapeutics** resubmitted its biologic license application (BLA) for bevacizumab-vikg (ONS-5010), an investigational ophthalmic formulation of bevacizumab for the treatment of wet AMD. The company received regulatory approval in the European Union and the United Kingdom last year.
- **Regeneron** was granted Priority Review for its supplemental BLA (sBLA) for 8 mg aflibercept (Eylea HD). The sBLA is for the use of 8 mg aflibercept in the treatment of macular edema following retinal vein occlusion and a dosing schedule of every 4 weeks across approved indications. The FDA recently rejected Regeneron's BLA for extended dosing intervals of up to 24 weeks for 8 mg aflibercept.

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VBS 2025 HIGHLIGHTS: SURGICAL SCENARIOS



Experts shared their preferred surgical management approach for bilateral retinal detachments.

BY LAUREN KIRYAKOZA, MD; PRASHANT D. TAILOR, MD; AND HAILEY K. ROBLES-HOLMES, MD

The 13th annual Vit-Buckle Society meeting, held March 20 – 22, 2025, in Austin, Texas, was another feat of clinical and surgical education, professional growth, and networking. With a wild west theme, speakers and attendees swaggered on stage to discuss challenging surgical cases, hurdles to patient care, wellness, and more.

A highlight of the meeting was a unique panel discussion that focused on complex bilateral retinal detachment (RD) cases. Moderators Tavish Nanda, MD, and Carl D. Regillo, MD, introduced several cases that mirrored real-life challenges, including patients walking in late on a Friday afternoon with retinal pathology in both eyes simultaneously. The goal of the panel was to explore each panelist's clinical reasoning and the variation in surgical approaches among experts across different practice settings. Each case included a survey of the audience to compare general consensus against the panelists. Here is what María H. Berrocal, MD; Steve Charles, MD; Peter J. Kertes, MD; and Ashleigh L. Levison, MD, had to say (Figure 1).

CASE NO. 1: GIANT RETINAL TEAR

A 60-year-old phakic woman presented with a 1-week shadow in her left eye. Her VA was 20/30 OU. Dilated fundus examination reveal a nasal detachment with a giant retinal tear (GRT) in the left eye and an unexpected superotemporal RD in the right eye with multiple breaks (Figure 2). Each eye was still macula-on.

The audience was asked which eye should be treated first. The majority selected the left eye due to the presence of a GRT, although 14% supported simultaneous bilateral repair. Dr. Berrocal recommended treating the left eye first with a vitrectomy, scleral buckle, and silicone oil. She preferred to wait to perform a straight buckle (sponge, no drainage) on



Figure 1. During the surgical scenarios panel (from left to right), Drs. Nanda, Charles, Kertes, Berrocal, Levison (inset left), and Regillo (inset right) discussed their various approaches to the surgical management of bilateral RDs.

the right eye until 2 days later. Dr. Regillo rarely performs bilateral surgery but supported operating 1 to 2 weeks apart.

Dr. Charles opposed buckling altogether, calling himself “Mr. Anti-Buckle” and highlighting the possible buckle-related complications of refractive error, diplopia, discomfort, and longer operating time. He advocated for vitrectomy with silicone oil in the left eye and emphasized the importance of removing the oil within a month to avoid complications such as macular edema or emulsification. On the other end of the spectrum, Dr. Kertes suggested a pneumatic retinopexy in both eyes on the same day, despite the level of pathology. He emphasized his high success rates, even with GRTs, and saw no need to delay treatment.

The Surgical Plan

After the discussion Dr. Nanda revealed the surgeon's actual management, which involved a vitrectomy with silicone oil and an encircling buckle for the GRT within 24 hours. The surgeon chose close follow-up to allow the left eye to recover before surgery on the right. By 1 week, however, the right eye was now 20/150 with foveal encroachment. The surgeon chose a vitrectomy with gas and an encircling buckle. The surgeon chose a buckle due to the patient's atypical presentation, possibility of an underlying vitreopathy, and lens status. Dr. Berrocal noted that pinhole glasses can sometimes be helpful in these bilateral cases to slow progression of an RD as an alternative to bilateral patching. Six months after oil removal and cataract surgery, the patient's VA was 20/40 OU.

CASE NO. 2: FOCAL AND MACULA-OFF

In the second case, the patient was pseudophakic with a small superonasal RD in the right eye and a more extensive superotemporal RD in the left eye (Figure 3). The right eye had no clear visible break, likely due to a limited view around the edge of the IOL. The left eye was macula-off with multiple breaks, both nasally and superotemporally.

The audience largely agreed on prioritizing the left eye. Dr. Charles recommended laser demarcation for the small, localized RD in the right eye and a vitrectomy with "medium-term" PFO in the left eye. He shared that he has used PFO in more than 1,300 cases in 23 years of practice and that it's particularly useful for inferior detachments. The benefit, he noted, is that patients can function normally for 2 weeks before staged PFO removal, with less discomfort and no induced refractive error. If the breaks are more superior (eg, 10 to 2 clock hours), he uses gas.

In terms of surgical timing, Dr. Berrocal said she typically operates within 1 week of macula-off symptoms. Dr. Levison prefers to get the patient to the OR within 3 days, if possible.

For the right eye, Dr. Kertes stated that if there is no visual field defect and the detachment is anterior to the equator, laser barricade is appropriate. Dr. Charles agreed, adding that only two to three confluent rows are typically needed for a sufficient barricade to prevent an iatrogenic scotoma. Although a pneumatic can be considered, especially with a superior RD, the panel generally agreed that laser break-through is rare.

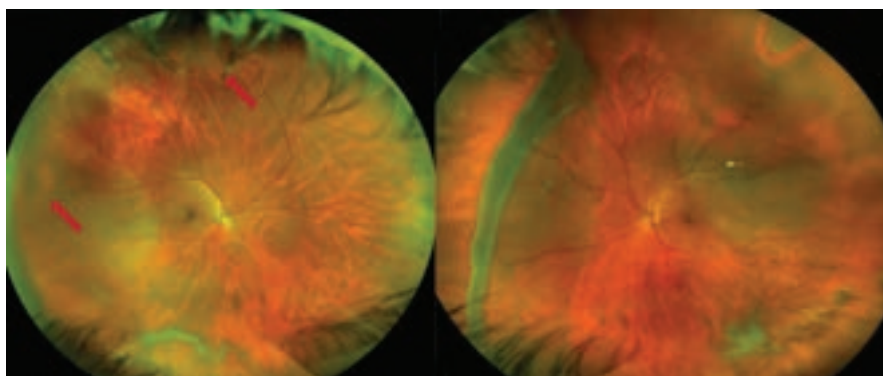


Figure 2. The VBS panel first discussed this patient, who presented with a focal superior detachment in the right eye and a GRT in the left eye.

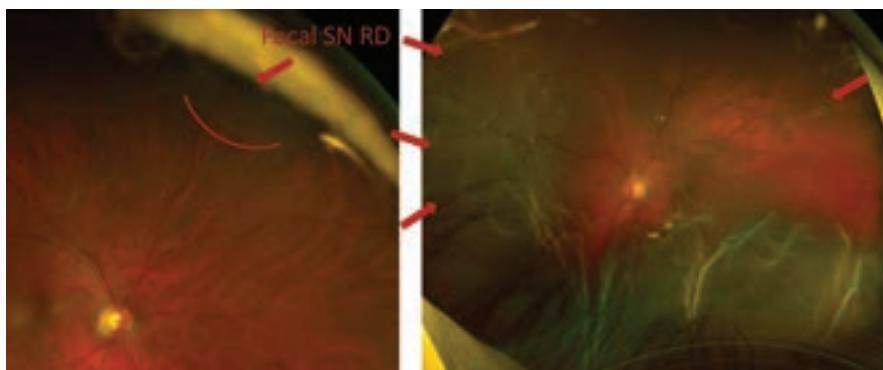


Figure 3. This pseudophakic patient presented with a small superonasal RD in the right eye and a superotemporal macula-off RD in the left eye with multiple breaks.

The majority of the audience chose a vitrectomy with gas for the left eye. For the right eye, the audience agreed with laser demarcation.

The Surgical Plan

Surgical management in this case included in-office laser for the right eye and a vitrectomy with endolaser and 15% C_3F_8 gas for the left eye. The panelists also discussed the long-term follow-up strategy for patients with RDs. Dr. Kertes rarely follows uncomplicated RD repairs more than 2 months. In contrast, Dr. Charles explained that visual improvement can continue up to 18 months post-surgery. From the audience, Yoshihiro Yonekawa, MD, shared data from his team's review of thousands of RD cases at Wills Eye Hospital in Philadelphia, noting that 1.4% of cases can redetach even after 1 year, more commonly after pneumatic retinopexies.

CASE NO. 3: PEDIATRIC RD

The third case involved a 15-year-old female patient who presented with a mild shadow in her vision. Examination noted bilateral, macula-on, inferonasal RDs, with multiple large retinal breaks (Figure 4). There was no posterior vitreous detachment (PVD) in either eye. There was no notable family history or ocular trauma.

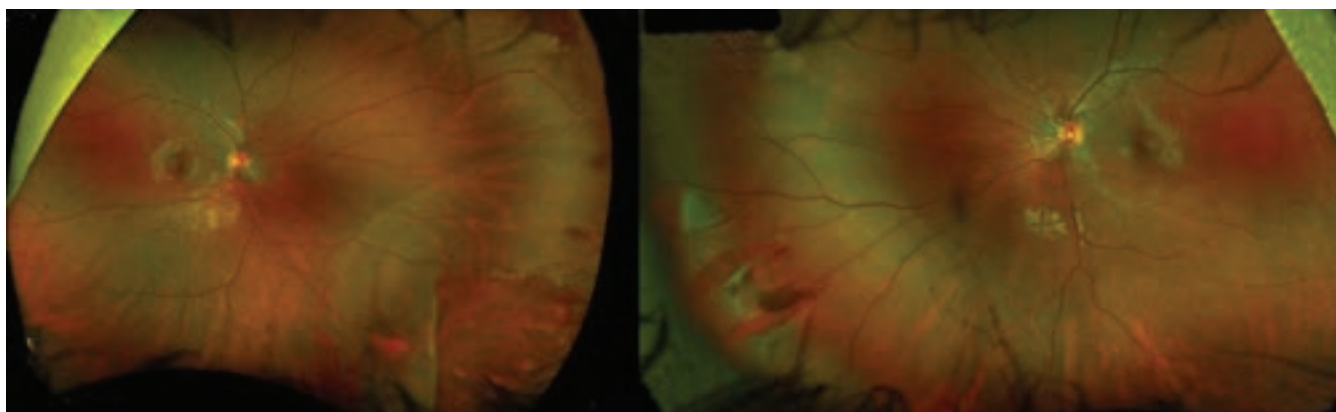


Figure 4. The final case discussed during the panel involved a 15-year-old patient who presented with bilateral inferonasal RDs and no PVD in either eye.

Dr. Berrocal recommended a staged approach with encircling scleral buckles in each eye. In a young patient with no PVD and atypical detachments, she saw the encircling buckle as the safest, most reliable approach. Timing between surgeries should be 2 to 3 days, she said, as opposed to simultaneous bilateral interventions in a young patient.

Dr. Kertes, on the other hand, proposed pneumatic retinopexy for each eye. He shared that the youngest pneumatic patient he has treated was 9 years old. Even with multiple inferonasal breaks, pneumatic retinopexy was effective, he said, and the lack of induced myopia or need for surgery made it preferable for the patient and their family.

The audience was in general agreement, with most recommending a primary buckle for both eyes.

The Surgical Plan

In this case, the surgeon proceeded with a scleral buckle and cryotherapy in the left eye within 1 week due to a greater “shadow” and larger breaks. One month later, a similar procedure with a scleral buckle and cryotherapy was performed in the right eye. There was no discernible progression over that timeframe.

In young patients without PVD, especially with inferior cases, some delay can be acceptable as long as symptoms are stable, the panelists agreed. However, Dr. Regillo cautioned that, in cases of Stickler syndrome or other heritable vitreoretinopathies, RDs may progress more rapidly. He advised considering genetic testing. The panelists also addressed the use of pneumatic retinopexy in young patients, acknowledging that gas can hasten PVD formation, increasing the risk of new breaks. They agreed that such cases require close follow-up when a pneumatic is performed.

SAVE THE DATE: April 9 – 11, 2026
14th Annual Vit-Buckle Society Meeting
 Las Vegas

WHAT'S YOUR BILATERAL RD APPROACH?

This session highlighted the spectrum of expert approaches to complex bilateral RD cases. While surgical philosophy varied, several consistent themes emerged. Scleral buckles remain polarizing: Drs. Berrocal and Regillo use them often, especially in young patients or those with inferior pathology, while Dr. Charles avoids them altogether. Pneumatic retinopexy received strong advocacy from Dr. Kertes, who argued for its broader use even in complex and bilateral settings. Dr. Charles supports the routine use of PFO as a valuable option for inferior detachments, particularly for functional preservation. Laser barricade remains a safe, effective strategy for small RDs, especially if they are anterior and without symptomatic field loss.

Long-term follow-up strategies varied based on practice models, but the consensus was that most redetachments happen within 2 months and that patients should be educated on that risk. Overall, the panel emphasized individualized care, early intervention, and patient-centered decision making as the cornerstones of success in managing bilateral RDs. ■

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Editorially independent supported by **abbvie** **REGENXBIO****SALLY S. ONG, MD****WHERE IT ALL BEGAN**

I grew up in a small town in Malaysia and received a full-ride scholarship to attend Duke University. During my freshman year, I studied global humanitarian challenges and volunteered for an eye care nonprofit at a remote village in China and a refugee camp in Ghana. There, I witnessed the life-changing effect of sight-restoring surgeries, which made me rethink my career aspirations.

Later, I had the opportunity to shadow Leon Herndon, MD, in clinic. The tremendous effect he had on his patients inspired me to become an ophthalmologist. After graduating from medical school at the Duke-National University of Singapore, I completed an ophthalmology residency at Duke and a retina fellowship at the Wilmer Eye Institute.

MY PATH TO RETINA

During my retina rotation in residency, I saw three patients with Coats disease and attended a journal club on Coats disease hosted by Prithvi Mruthyunjaya, MD, all within a few weeks. Given the rarity of this condition, I felt this was the universe pointing me toward retina! The constant development of innovative therapeutics and technologies in retina was very exciting, and Sharon Fekrat, MD, made sure we had access to them, even as residents. Dr. Fekrat and Xi Chen, MD, PhD, staffed my first vitrectomies and scleral buckles, and their endless encouragement and enthusiasm helped solidify my career choice. In addition, Cynthia A. Toth, MD, has been an influential mentor. She is an academic tour de force who has inspired me to be the best I can be with her impeccable standards for patient care, research, and teaching.

SUPPORT ALONG THE WAY

I am indebted to my mentors at Duke and all my fellowship mentors at Wilmer, in particular James T. Handa, MD; Zelia M. Correa, MD, PhD; Adrienne W. Scott, MD; David M. Wu, MD, PhD; Fernando Arevalo, MD, PhD; Sharon D. Solomon, MD; Mandeep S. Singh, MD, PhD; Peter A. Campochiaro, MD; and Neil M. Bressler, MD. Wilmer was an

inspiring place to be—I witnessed mentors transforming our field through their leadership in basic science research and clinical trials while still maintaining busy clinical workloads. They showed me what is possible with a lot of hard work and a sprinkling of good luck. I still reach out to them for advice on difficult cases, grant writing, and professional opportunities, and they continue to be supportive.

I am also grateful for the mentorship and support of Rebecca M. Sappington, PhD; Jian-Xing Ma, MD, PhD; and Craig M. Greven, MD, in my journey as a clinician-scientist at Wake Forest School of Medicine.



Dr. Ong's advice: Be kind to yourself and others. Retina is a challenging subspecialty—our patients can have tough pathology, difficult social situations, and, sometimes, personalities, and our hours are long and unpredictable; lean on your village when you need to and be that source of support for others.

AN EXPERIENCE TO REMEMBER

One of my patients is a 30-year-old woman who presented with severe tractional retinal detachments in both eyes from proliferative diabetic retinopathy. When we first met, she was in a wheelchair and completely dependent on others because she could not see. I observed the right eye since there had been no light perception for years and took her to surgery to repair the left retinal detachment. Her vision has recovered greatly since her surgery, and she now lives in her own apartment and, last year, volunteered to host Thanksgiving dinner for her family and friends. ■

Sally S. Ong, MD, is an assistant professor of Ophthalmology at the Wake Forest School of Medicine. She has served on advisory boards for EyePoint, Abbvie/Regenxbio, and Apellis. She has also received grant funding from the National Eye Institute, North Carolina Diabetes Research Center, International Retinal Research Foundation, and the Translational Eye and Vision Research Center at Wake Forest University. She can be reached at ssallyong@gmail.com.

FELLOWS' FOCUS

UNDERSTANDING—AND OVERCOMING—FELLOWSHIP CHALLENGES



Recent survey results can help us better understand the experiences of current and former vitreoretinal fellows.

BY VICENTE LORENZO CABAHO, MD, DPBO, AND ANDREW S.H. TSAI, MBBS, MCI, FRCOPHTH

Fellowship training in vitreoretinal surgery is like being thrown into the deep end of a pool—you either learn to swim quickly or you struggle to stay afloat. As a surgical retina fellow at Singapore National Eye Center, I've experienced firsthand the steep learning curve, the long hours, and, yes, those moments of self-doubt. But I've also discovered that these fellowship challenges are universal, shared by fellows across different programs and countries.

SURVEY INSIGHTS: WE'RE ALL IN THIS TOGETHER

To better understand these shared experiences, I (VLC) conducted a Google survey of 28 current and former retina fellows. The results were both validating and enlightening—I wasn't alone in my struggles.

Among the clinical challenges, 60% of fellows found surgical exposure to be very or most challenging (Figure 1). I remember my first vitrectomies, awkwardly maneuvering instruments while trying to maintain a mental map of what was happening inside the eye. Even more fellows (64%) rated managing complications as highly challenging. There's nothing quite like that moment of panic when something isn't going according to plan, and your attending is watching your every move. Patient load was another significant hurdle, with 57% rating it as very challenging. Between clinic responsibilities, surgery, and the pressure to conduct research, most fellows reported working 60 to 70 hours per week. No wonder 53% found work-life balance to be a major challenge, and 75% experienced moderate to severe burnout (Figure 2).

MENTORSHIP: DON'T BE AFRAID TO ASK

While 60% to 77% of fellows reported satisfaction with their supervision, a significant minority felt inadequately supported (Figure 3). The best advice I've received is simple: Don't be afraid to ask questions. A great mentor won't just

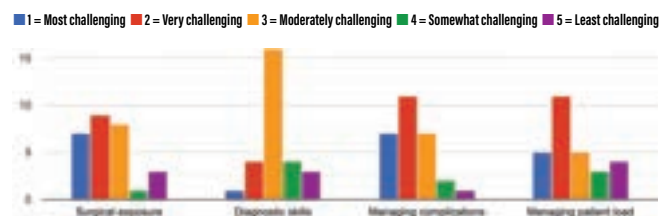


Figure 1. When asked to rank the clinical challenges they faced during fellowship, most fellows felt that surgical exposure and complications were the toughest to handle.

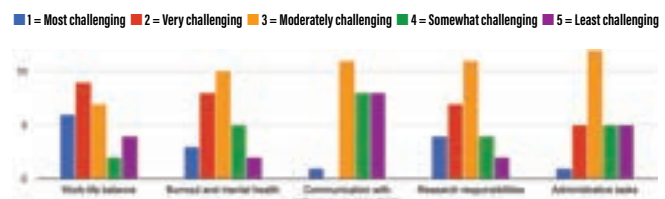


Figure 2. When asked about the biggest non-surgical challenges during fellowship, work-life balance topped the list for survey respondents.

teach you; they'll challenge you to grow.

Building personal relationships with your attendings makes a tremendous difference. I've found that seeking regular feedback—even when it's uncomfortable—accelerates improvement. Remember that every attending started exactly where you are now, fumbling through their first surgeries and making mistakes.

RESEARCH: START SMALL, BE REALISTIC

Research requirements often add another layer of stress to fellowship. Among survey respondents, 78% found research moderately to extremely challenging, with 53% feeling neutral about their research preparation (Figure 4).

My approach to research during fellowship has been to start small and be realistic. Focus on one or two meaningful

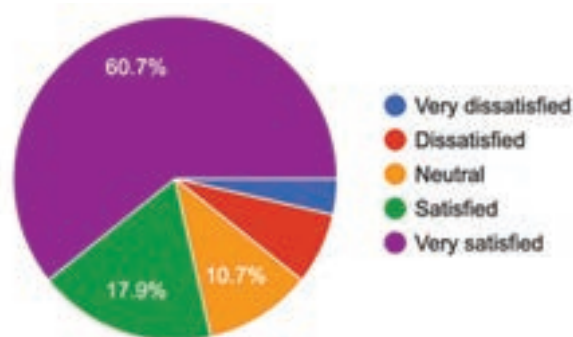


Figure 3. Fellows were asked to rank, on a scale from 1 to 5, how satisfied they were with their mentorship or supervision during their fellowship. Most of the survey respondents (nearly 61%) felt supported by their mentors.

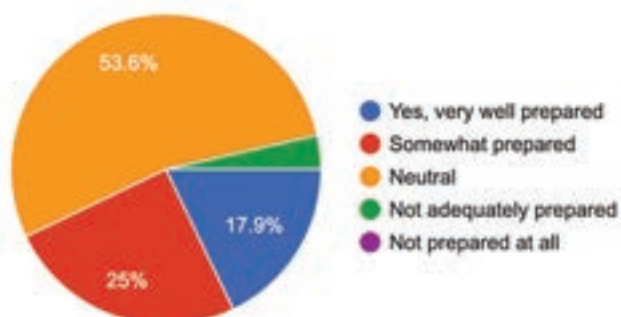


Figure 4. When asked if they felt fellowship adequately prepared them for research opportunities, approximately half of the fellows were ambivalent.

projects that you can complete, such as case reports or small retrospective studies. Don't feel pressured to publish groundbreaking research during fellowship—there's plenty of time to build your academic portfolio throughout your career.

WORK-LIFE BALANCE: A NECESSARY STRUGGLE

With 60- to 70-hour workweeks, maintaining any semblance of work-life balance feels like an impossible task. Yet, it is crucial for preventing burnout and preserving your passion for the field. I've learned to protect small pockets of time for activities that recharge me. Whether it's a quick video call with family back home in the Philippines, a short workout, or even a proper meal that doesn't come from the hospital cafeteria, these moments make a difference.

THE LEARNING CURVE: IT GETS BETTER (EVENTUALLY)

If I graphed my fellowship learning experience, it would look like a rollercoaster with an upward trajectory. The initial phase is slow while learning new techniques, adapting to unfamiliar equipment, and constantly asking, "Where's the break?!" in retinal detachment cases. Then comes the variable yet rapid learning phase, where some skills improve quickly while others lag behind. This is followed by a peak learning period when everything starts to click. Many vitreoretinal fellows experience a plateau or even a decline as fatigue sets in, before finally reaching a level of mastery (Figure 5).



Figure 5. This graph depicts the relationship between perceived surgical competence and surgical volume. The learning curve shows that competence initially increases rapidly and plateaus after approximately 200 cases. In regression analyses, an R^2 value of 0.69 indicates that 69% of the variation in the dependent variable (perceived surgical competence) can be explained by the independent variable (surgical volume).

The Association of University Professors of Ophthalmology recommends minimum surgical requirements of 100 vitrectomies and 20 scleral buckles over a 2-year fellowship.¹ But numbers don't tell the whole story—it's the quality of the experience that matters most.

FINAL THOUGHTS: IT'S WORTH IT

As my fellowship supervisor said, "Fellowship is tough, but it's worth it." I couldn't agree more. You're not just learning to be a surgeon—you're learning to be resilient, adaptable, and competent in the face of challenges.

When frustration hits (and it will), find ways to stay motivated. Every mistake, complication, or difficult situation is a learning experience that shapes your development as a surgeon. Perhaps the most comforting realization from my survey was that fellowship is only 1 to 2 years of your career. As you continue to practice for 5, 10, or 15+ years, this intense training period becomes just one chapter of your story. It will not define you as an eye surgeon. For me, success is the sum of small efforts repeated daily. So, keep showing up, keep learning, and remember that marginal gains are still gains. The curve will go up—I promise. ■

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UPDATES ABOUT IN THIS YEAR'S AMD PIPELINE POSTER



BY PETER K. KAISER, MD

Every year I update this poster—now in its fifth iteration (for those keeping score at home)—to give my fellow retina specialists a quick snapshot of where we stand in drug development. It's made for those of us juggling packed clinics and barely enough time to breathe. What should you know about? What should you keep an eye on? And what major changes to the treatment landscape and developmental pipeline are worth highlighting?

In terms of wet age-related macular degeneration (AMD), I decided to remind my retina specialist colleagues about the redesigned Port Delivery System with Ranibizumab (Genentech/Roche). This technology is back in the treatment armamentarium for retina specialists (Spoiler alert: the new septum-overmold bond is sturdier and hopefully may prevent septum dislodgement). We also introduce readers to the *wingless integration* signaling pathway (Wnt, pronounced "wint"), which researchers have begun targeting. Although we are years away from

a potential treatment that leverages this pathway, we nevertheless should keep it on our radar.

The ever-expanding dry AMD section of this year's poster continues a familiar trend—steady growth in the pipeline. While we've seen a few failures, the number of new treatments, spanning a wide range of mechanisms, continues to climb.

Rethinking how to organize the summary of dry AMD treatments posed some unique challenges. For example, the longest list of pipeline treatments falls under the "Suppress Inflammation" section, and to square the realities of print layout and page real estate, we placed it most prominently on the left side of the poster. This does not mean, however, that these options are furthest upstream in the dry AMD treatment flowchart, nor are they more legitimate than options that appear elsewhere on the poster.

I'd like to call your attention to the box titled, "New Evidence on the Efficacy of AREDS Supplements in

AMD," which explores a recent study showing that certain combinations of oral micronutrient supplementation could play an important role in mitigating the risk of vision loss in patients with GA.¹ AREDS vitamins remain one of our oldest options, but age has not made them any less useful. If you're looking for a surprising update, don't skip this callout box. ■

As always, we are eager to hear your suggestions, comments, and criticisms of this annual poster. If you need to reach the team that assembles this project so that we can consider your input next year, email me, Peter K. Kaiser, MD, at pkkaiser@gmail.com or Cara Deming, Executive Director of Special Projects at Bryn Mawr Communications, at cdeming@bmctoday.com.

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AI CHATBOTS IN RETINA



With proper foresight, this technology has the potential to enhance clinical efficiency and patient care.

BY MATTEO MARIO CARLÀ, MD, AND STANISLAO RIZZO, MD

The advent of AI is set to redefine the landscape of eye care. This transformative technology, especially using AI chatbots powered by large language models (LLMs) such as ChatGPT and Google Gemini, promises a new era of efficiency and precision in diagnosing and treating retinal diseases. The integration of these advanced tools into clinical practice could significantly enhance patient management, streamline workflows, and improve overall outcomes. Although the potential benefits are vast, several challenges must be addressed before AI can seamlessly integrate into everyday clinical practice.¹

EXAMPLES OF AI IN RETINA

Several AI-powered devices based on deep-learning algorithms have already received regulatory approval and have been implemented into retinal imaging software. For example, RetinAI Discovery (Retinai) works with color fundus photography and OCT to identify biomarkers in diseases such as diabetic retinopathy, AMD, and epiretinal membranes. In addition, VUNO Med-Fundus AI (Vuno) identifies biomarkers and provides heatmaps of abnormal findings for these conditions. RetInSight Fluid Monitor (RetInSight) quantifies intraretinal and subretinal fluid on OCT images to assist physicians in managing neovascular AMD. Finally, the Scanly Home OCT Monitoring Program (Notal Vision) uses AI to enable more frequent monitoring of AMD, diabetic macular edema, and retinal vein occlusion by automating the detection of retinal fluid.²

These applications have demonstrated the practical value of AI in enhancing diagnostic accuracy and treatment planning. By segmenting OCT images and linking them to real-world referral recommendations, AI contributes to more proactive interventions and, potentially, better outcomes for patients. However, more research is needed to ensure these devices are safe and effective, which requires collaboration between clinicians, researchers, and regulatory bodies.

ADVANTAGES OF AI IN DIAGNOSTICS

AI tools can assist in the diagnostic process by automating routine tasks, analyzing imaging data, flagging potential abnormalities, and providing detailed reports. Moreover, the

ability of AI to analyze vast amounts of data and identify patterns facilitates the development of personalized treatment plans by considering individual patient characteristics and predicting disease progression. To this point, AI chatbots have demonstrated remarkable capabilities in suggesting surgical plans for retinal detachment (RD) based on the analysis of RD records. In our study, we found that ChatGPT-4 achieved an 84% agreement with expert vitreoretinal surgeons when proposing plans for RD repair (Figure).³

While impressive, these results were inherently limited by a lack of multimodal integration of data from diverse sources, which is key for real-world application of LLMs.³ These shortfalls have been addressed in newer chatbots, which now offer the ability to integrate data from numerous sources. In a more recent study from our group, ChatGPT-4's diagnostic capabilities were tested on OCT and OCT angiography scans and achieved a 78% accuracy rate for various retinal diseases, outperforming Gemini Advanced.⁴ These findings underscored the cutting-edge potential of AI-assisted diagnosis.

CHALLENGES WITH AI

Integrating AI into clinical workflows presents several hurdles, such as the limited diagnostic capability of current LLMs. While it can excel at identifying common retinal conditions, it often struggles with rarer diseases or complex cases. This limitation suggests there is a need for continuous training and refinement of algorithms to expand their diagnostic capabilities. In addition, realizing the full potential of AI requires the seamless integration of various data sources, including the patient's clinical history, tests and imaging, genetic information, and lifestyle factors. A holistic understanding of the patient's condition is essential for developing precise and personalized treatment strategies.⁵

Various ethical considerations loom large in the adoption of AI in health care, such as data privacy, algorithmic bias, and potential misuse, which cannot be ignored. Establishing robust ethical frameworks and guidelines is warranted to ensure responsible development and deployment of these tools.⁶ It is crucial to emphasize that AI chatbots should augment, never replace, the role of ophthalmologists; maintaining human oversight remains essential for patient

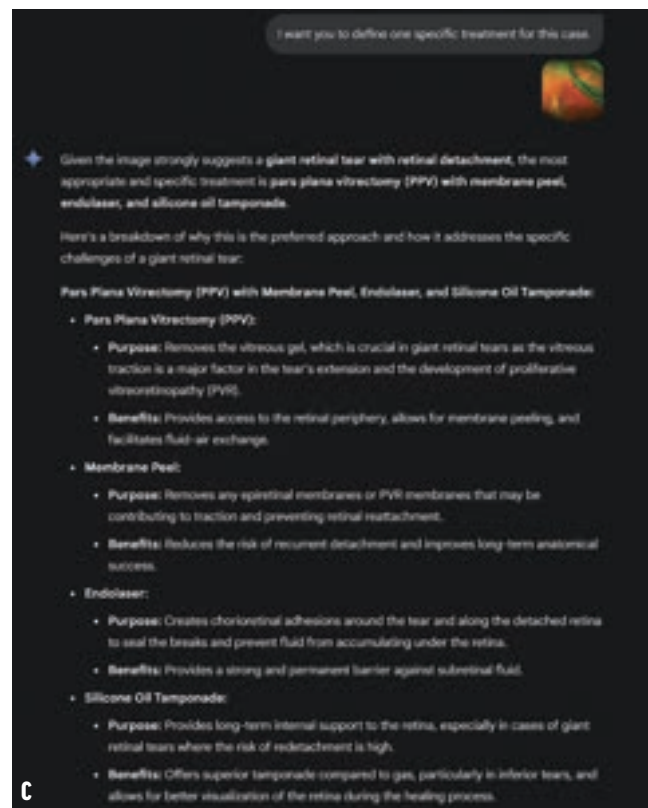
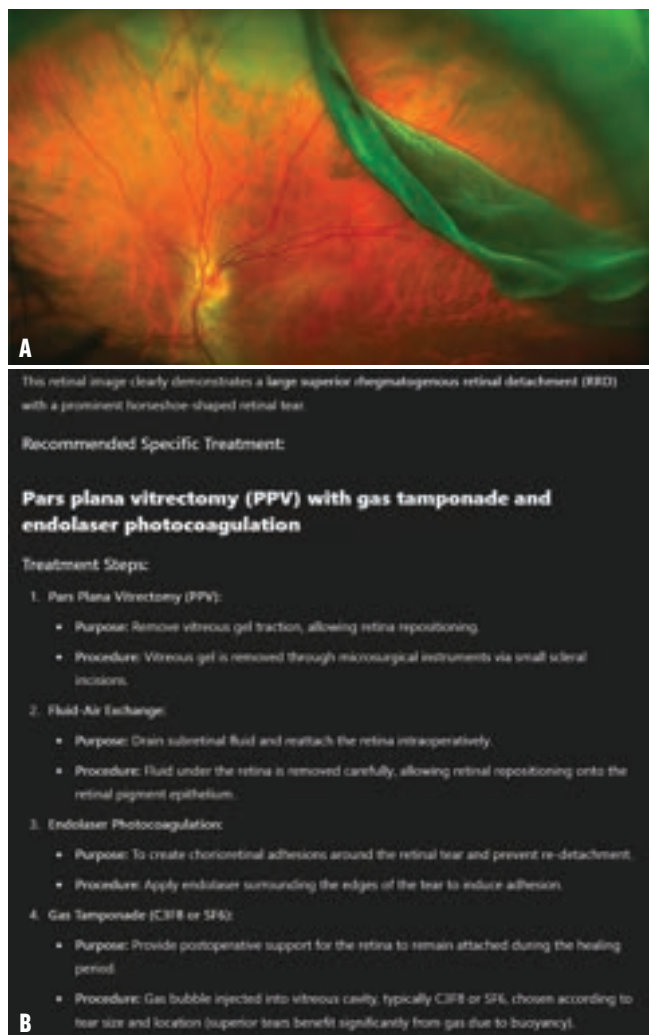


Figure. An image of a rhegmatogenous RD with a giant tear (A) was fed to two AI chatbots, ChatGPT-4.5 (B) and Gemini 2.0 (C), which provided suggestions for surgical management.

safety and the appropriate application of AI insights.

Another factor is the lack of a standardized regulatory pathway for AI-enabled medical devices, which poses potential risks related to patient safety and efficacy.

A critical aspect of AI integration is the development of a collaborative ecosystem in which AI and human expertise work in synergy. As AI technology evolves, the capabilities of these chatbots to analyze increasingly complex data, including multimodal inputs such as videos and photos, will expand. This future necessitates ongoing research and development to address current limitations, refine algorithms, and expand the scope of AI applications in retina care.

THE FUTURE IS HERE

The integration of AI chatbots into the retina care offer the potential to revolutionize patient management by enhancing efficiency, precision, and personalization in treatment strategies. However, realizing this potential requires overcoming several challenges, including expanding diagnostic capabilities, ensuring multimodal

data integration, and establishing robust regulatory and ethical frameworks. The journey toward fully integrating AI into retina care is only beginning, but the goal is clear: a future in which AI augments human expertise to deliver better patient outcomes. ■

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Emerging (Durable) Therapies for Wet AMD

New approaches are helping us care for patients while reducing their treatment burden.

By Jacob S. Heng, MD, PhD, and Adrienne W. Scott, MD



Although anti-VEGF therapy is the mainstay of wet AMD treatment, many patients require sustained VEGF suppression with treatment every 4 to 8 weeks to maintain disease control—a treatment approach that is not always sustainable due to patient circumstances.

Fortunately, much progress has been made to address durable VEGF suppression (Table 1). In addition, therapies that may provide even more durable VEGF suppression are being developed (Table 2), including tyrosine kinase inhibitors (TKIs) and gene therapies (see *Gene Therapy Approach*).

DURABLE ANTI-VEGF THERAPIES

The port delivery system (PDS; Susvimo, Genentech/Roche) is a surgically-implanted, refillable device that allows sustained release of ranibizumab. In the phase 3 ARCHWAY study, patients with wet AMD were randomly assigned 3:2 to treatment with the PDS with refill-exchanges every 24 weeks (Q24W) or intravitreal ranibizumab (Lucentis, Genentech/Roche) every 4 weeks (Q4W).¹ PDS Q24W showed noninferior BCVA gains compared with ranibizumab Q4W. Of patients with the PDS, 98.4% did not require supplemental injections before the first refill-exchange procedure. However, 19% of PDS patients had pre-specified ocular adverse events compared with 6% of patients receiving ranibizumab.¹

Another new therapy promising extended duration of effect is 8 mg aflibercept (Eylea HD, Regeneron). In the phase 3 PULSAR study, patients with wet AMD were randomly assigned 1:1:1 to 8 mg aflibercept every 12 weeks (Q12W), 8 mg aflibercept every 16 weeks (Q16W), or 2 mg aflibercept (Eylea, Regeneron) every 8 weeks (Q8W) following three monthly loading doses of each respective

AT A GLANCE

- ▶ When first-generation anti-VEGF agents do not provide satisfactory outcomes, consider switching to faricimab (Vabysmo, Genentech/Roche) or 8 mg aflibercept (Eylea HD, Regeneron).
- ▶ The port delivery system (Susvimo, Genentech/Roche) is a promising approach for treatment intervals of 6 months or more.
- ▶ Many therapies touting longer treatment effect are under investigation, including EYP-1901 (Duravyu, Eyepoint Pharmaceuticals), OTX-TKI (Axpaxli, Ocular Therapeutix), CLS-AX (Clearside Biomedical), AR-14034 (Alcon), and KHK4951 (Kyowa Kirin).



TABLE 1. APPROVED THERAPIES FOR WET AMD				
Agent (Company)	Target	Type of Molecule	FDA Approval	Target Dosing Frequency
Bevacizumab (Avastin, Genentech/Roche)	VEGF-A	IgG1 antibody	Off-label	4-8 weeks
Ranibizumab (Lucentis, Genentech/Roche)	VEGF-A	Antibody fragment (Fab)	2006	4-8 weeks
2 mg Aflibercept (Eylea, Regeneron/Bayer)	VEGF-A and -B; placental growth factor	VEGFR-1 and -2 ligand domain and IgG Fc fusion protein	2011	4-8 weeks
Brolucizumab (Beovu, Novartis)	VEGF-A	Single-chain variable fragment	2019	8-12 weeks
8 mg Aflibercept (Eylea HD, Regeneron/Bayer)	VEGF-A and -B; placental growth factor	VEGFR-1 and -2 ligand domain and IgG Fc fusion protein	2023	8-16 weeks
Faricimab (Vabsymo, Genentech/Roche)	VEGF-A; Ang-2	Bispecific antibody	2022	4-16 weeks
Port Delivery System (Susvimo, Genentech/Roche)	VEGF-A	Antibody fragment (Fab) with sustained release from refillable device	2021	6 months

TABLE 2. DURABLE THERAPIES IN DEVELOPMENT FOR WET AMD					
Agent (Company)	Target	Type of Molecule	Route of Delivery	Target Dosing Frequency	Trial phase
EYP-1901 (Eyepoint Pharmaceuticals)	VEGF-A, -B, and -C; platelet derived growth factor receptor	TKI (vorolanib) in bioerodable implant	Intravitreal	6 months	Phase 3
OTX-TKI (Ocular Therapeutix)	VEGFR-1, -2, and -3	TKI (axitinib) in hydrogel implant	Intravitreal	9-12 months	Phase 3
CLS-AX (Clearside Biomedical)	VEGFR-1, -2, and -3	TKI (axitinib) suspension	Suprachoroidal	12-24 weeks	Phase 2b
AR-14034 (Alcon)	VEGFR-1, -2, and -3	TKI (axitinib) in bioerodible polymer implant	Intravitreal	10 weeks or more	Phase 2
KHK4951 (Kyowa Kirin)	VEGFR-1, -2, and -3	TKI (tivozanib) in nanocrystals	Eye drop	3 times daily	Phase 2

treatment.² Patients receiving 8 mg aflibercept Q12W and Q16W achieved noninferior BCVA gains compared with those receiving 2 mg aflibercept Q8W, with a similar incidence of ocular adverse events across all groups.²

Faricimab (Vabsymo, Genentech/Roche) is a bispecific antibody targeting VEGF-A and Ang-2. Ang-2 is a soluble protein associated with vascular destabilization by binding to the Tie2 receptor on vascular endothelial cells. Faricimab was evaluated for wet AMD in the TENAYA and LUCERNE trials, where patients with wet AMD were randomly assigned 1:1 to receive intravitreal faricimab up to Q16W (after four loading doses) compared with 2 mg aflibercept dosed Q8W (after three loading doses).³ Faricimab dosing intervals up to week 60 were fixed at Q8W, Q12W, or Q16W based on strict protocol-defined disease activity criteria; between week 60 and week 108, a treat-and-extend regimen was used. BCVA change and ocular adverse events were comparable between the faricimab and aflibercept groups. At week 112, 74.1% and 81.2% of patients receiving faricimab achieved Q12W or longer dosing, while 59.0% and 66.9% achieved Q16W dosing in TENAYA and LUCERNE, respectively.³

EXTENDING THE TREATMENT INTERVAL

The most common first-line anti-VEGF agent is off-label bevacizumab (Avastin, Genentech/Roche).⁴ Recently, many payers, including Aetna,¹ have mandated step therapy, which dictates that patients first be treated with bevacizumab and switch to ranibizumab (or a biosimilar such as ranibizumab-nuna [Byooviz, Samsung Bioepis/Biogen]) or 2 mg aflibercept only when there is an inadequate therapeutic response. The CATT trial found similar visual acuity gains between wet AMD patients treated with bevacizumab compared with those treated with ranibizumab.² However, no prospective study has compared aflibercept with ranibizumab and bevacizumab in wet AMD.

In diabetic macular edema (DME), however, the DRCR Retina Network Protocol T found that 2 mg aflibercept resulted in better visual gains compared with ranibizumab and bevacizumab when the presenting BCVA was 20/50 or worse.³ Furthermore, DRCR Retina Network Protocol AC found that step therapy starting with bevacizumab and switching to 2 mg aflibercept achieved similar visual acuity gains at 2 years compared with aflibercept monotherapy

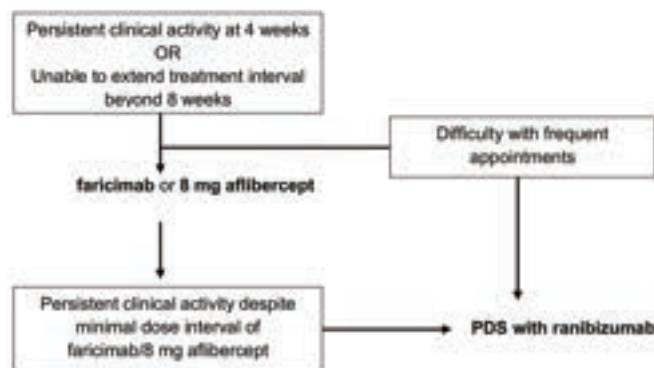


Figure 1. This is our approach to extending the treatment interval for patients with wet AMD.

in DME patients.⁵ Extrapolating these results to wet AMD and considering the CATT trial, step therapy starting with bevacizumab and switching to 2 mg aflibercept would seem to be a logical choice.

When treatment with these first-generation agents every 4 weeks does not result in satisfactory drying of the retina, switching to faricimab or 8 mg aflibercept may be considered (Figures 1 and 2). Of note, faricimab can be given as frequently as every 4 weeks after four monthly doses, whereas 8 mg aflibercept can only be given every 8 weeks after three monthly doses.^{6,7} In addition, switching therapies may also benefit patients who cannot be extended to treatment intervals of 8 weeks and beyond. However, no head-to-head study has compared faricimab with 8 mg aflibercept, although a network meta-analysis using data from the phase 3 clinical trials (TENAYA/LUCERNE and PULSAR) suggests that faricimab may have a superior drying effect.⁸

Finally, for patients already receiving faricimab or 8 mg aflibercept at the minimum dosing interval with persistent disease activity, the PDS may offer more consistent and durable VEGF suppression. The PDS could also be considered for patients with a high treatment burden who cannot attend frequent injection appointments.

DURABLE THERAPIES IN DEVELOPMENT

EYP-1901 (Duravyu, Eyepoint Pharmaceuticals) is a bioerodible sustained delivery platform that delivers vorolanib, a TKI that inhibits VEGFR-1, -2, and -3 and platelet-derived growth factor receptor. In the phase 2 DAVIO trial, patients receiving EYP-1901 achieved noninferior changes in BCVA compared with 2 mg aflibercept Q8W, with almost two-thirds of patients not requiring supplemental anti-VEGF injections at 6 months and an over 80% reduction in the annualized anti-VEGF injection rate.⁵ The global phase 3 LUGANO (NCT06668064) and LUCIA (NCT06683742) clinical trials are underway.

OTX-TKI (Axpaxli, Ocular Therapeutix) incorporates axitinib, a TKI targeting VEGFR-1, -2 and -3, into a hydrogel implant that bioresorbs in approximately 9 months. In a phase 1 trial, OTX-TKI achieved BCVA gains similar to 2 mg

Gene Therapy Approach

Several gene therapies are under investigation for the treatment of wet AMD, including the following:

- ABBV-RGX-314 (Regenxbio/Abbvie)
- Ixo-vec (ixoberogene soroparvovec, Adverum Biotechnologies)
- 4D-150 (4D Molecular Therapeutics)
- KH631 (Chengdu Origen Biotechnology)
- FT-003 (Frontera Therapeutics)
- HG202 (HuidaGene Therapeutics)
- EXG102-031/EXG202 (Exegenesis Bio)

To learn more about these therapies, check out *Gene Therapy for AMD: What You Need to Know*, on page 26.

aflibercept Q8W at 12 months, resulting in an 89% reduction in anti-VEGF injections.⁶ Two phase 3 trials, SOL-1 (NCT06223958) and SOL-R (NCT06495918), are active.

CLS-AX (Clearside Biomedical) delivers an axitinib suspension using a proprietary suprachoroidal microinjector. Topline data from the phase 2 ODYSSEY trial showed an 84% reduction in treatment burden over 6 months, with 67% of treated patients not requiring supplemental treatment up to 6 months.⁷ The company is planning two phase 3 trials.⁸

AR-14034 (Alcon) contains axitinib in a bioerodible polymer implant that can be injected intravitreally.⁹ AR-14034 is being evaluated in the phase 1/2 NOVA-1 study as a supplement to an initial dose of 2 mg aflibercept.

KHK4951 (Kyowa Kirin) packages tivozanib, a TKI targeting VEGFR-1, -2 and -3, in nanocrystals as an eye drop that allows penetration into the posterior segment.¹⁰ While not a sustained-release therapy, KHK4951 could potentially be an at-home therapy. A phase 2 trial (NCT06116890) is underway to evaluate its safety and efficacy.

MEETING AN UNMET NEED

Current durable anti-VEGF therapies for wet AMD include faricimab, 8 mg aflibercept, and the PDS. While faricimab and 8 mg aflibercept offer some extension of the treatment interval in most patients, many do not reach the extended intervals seen in clinical trials.^{9,10} The PDS is a promising approach for treatment intervals of 6 months or more, but

(Continued on page 42)

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REGENXBIO



CLAUDIA GÓMEZ HOOTEN, MD

WHERE IT ALL BEGAN

I was born in Santiago, Chile, and immigrated to the United States as a young child. Growing up in Texas in a family with two physician parents, I was introduced to medicine at an early age, which naturally set the stage for my own career in health care. I attended Rice University for my undergraduate studies, then began my medical education at the University of Texas Medical Branch in Galveston. After my second year, I transferred to the University of Florida College of Medicine, where my husband was stationed for his military training. This move allowed me to continue my medical journey while also supporting his career.

MY PATH TO RETINA

My initial plan was to follow in my father's footsteps and pursue general surgery. However, during my third year of medical school, an unexpected opportunity arose when a rotation in ophthalmology became available, and I seized the chance. On the first day of the rotation, I found myself in the OR watching a membrane peel, and I was hooked. In that moment, I knew immediately that ophthalmology was the field I wanted to pursue.

SUPPORT ALONG THE WAY

I have been fortunate to have had mentors at every stage of my training, and I remain in close contact with all of them. During residency, I was guided by Garvin H. Davis, MD, MPH; Judianne Kellaway, MD; and Helen Mintz-Hittner, MD. In fellowship, Rajiv Edlagan Shah, MD; Vishak J. John, MD; and Craig M. Greven, MD, played pivotal roles in shaping my skills and perspectives. Now, as an associate at Retina Group of Washington, I am constantly learning from Reginald Sanders, MD. Beyond providing invaluable education and technical expertise, these mentors have also shared life philosophies and offered crucial advice on navigating my career as a vitreoretinal surgeon while staying grounded.

AN EXPERIENCE TO REMEMBER

It's difficult to pinpoint a single memorable experience, as there have been so many meaningful moments throughout my career. What stands out most to me, however, are the



Dr. Hooten's advice: Maintain your compassion and empathy toward your patients. Remember, retina is more than technical skills.

relationships I have built with my patients—from the infants in the NICU and their families to the elderly adults I see in clinic. These connections are incredibly rewarding. Equally important are the relationships I have developed with my peers and mentors. I continue to collaborate with them daily, sharing cases, exchanging ideas, and supporting one another through both professional challenges and life events. ■

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Gene Therapy for AMD: What You Need to Know

Several candidates with varying mechanisms of action and delivery methods are in clinical trials.

By Szilárd Kiss, MD, FASRS, and Peyman Razavi, MD



Unlike current treatment approaches for AMD (Figures 1 and 2), which focus on managing symptoms, gene therapy offers a promising avenue for long-term—and potentially curative—interventions. Here, we provide an overview of the latest advances in the field (Table).

GENE THERAPY CANDIDATES FOR WET AMD

ABBV-RGX-314 (Regenxbio/Abbvie) uses an AAV vector to deliver a gene encoding an anti-VEGF antibody fragment similar to ranibizumab.¹ The phase 2 AAVIATE trial (NCT04514653) is studying suprachoroidal ABBV-RGX-314 compared with ranibizumab (Lucentis, Genentech/Roche). Interim 6-month results in 115 patients across three dose levels indicated no serious adverse events. In patients treated at the highest dose level, the therapy has resulted in an 80% decrease in the annualized injection rate and 50% of patients remaining injection-free. Additionally, no cases of intraocular inflammation were observed with a short course of prophylactic topical steroid eye drops.² An ongoing observational trial (NCT05210803) is following patients for 5 years to assess long-term safety and efficacy.

The phase 3 ASCENT clinical trial (NCT05407636) and the phase 2/3 ATMOSPHERE (NCT04704921) trial are assessing the administration of ABBV-RGX-314 via subretinal delivery

compared with 2 mg aflibercept (Eylea, Regeneron) and ranibizumab, respectively. A long-term study (NCT03999801) is following participants for up to 5 years after a single subretinal administration of ABBV-RGX-314.

Ixo-vec (ixoberogene soroparvovec, Adverum Biotechnologies) employs an AAV capsid, AAV.7m8, to intravitreally deliver the genetic code for aflibercept,

AT A GLANCE

- ▶ Gene therapy offers a promising avenue for long-term—and potentially curative—interventions for wet AMD and geographic atrophy (GA).
- ▶ At least six gene therapies are under investigation for the treatment of wet AMD with intravitreal, subretinal, and suprachoroidal delivery methods. Early data suggest some of them could decrease the annualized injection rate by 80% or more.
- ▶ Several companies are in the early phases of exploring gene therapy for GA. Preliminary results show promise, with a slowing of GA lesion growth rates for some drug candidates.



TABLE. ACTIVE CLINICAL TRIALS INVESTIGATING GENE THERAPY CANDIDATES IN AMD				
Agent (Company)	Delivery	NCT Number	Phase	Completion
Wet AMD				
ABBV-RGX-314 (Regenxbio/Abbvie)	Suprachoroidal	NCT05210803	Long-term	March 2028
	Subretinal	NCT03999801	Long-term	December 2028
	Subretinal	NCT05407636	Phase 3	November 2025
	Subretinal	NCT04704921	Phase 2/3	May 2025
	Suprachoroidal	NCT04514653	Phase 2	October 2025
Ixo-vec (Adverum Biotechnologies)	Intravitreal	NCT04645212	Long-term	June 2025
	Intravitreal	NCT06856577	Phase 3	March 2030
	Intravitreal	NCT05536973	Phase 2	August 2028
4D-150 (4D Molecular Therapeutics)	Intravitreal	NCT06864988	Phase 3	June 2027
	Intravitreal	NCT05197270	Phase 1/2	November 2025
KH631 (Chengdu Origen Biotechnology)	Intravitreal	NCT05672121	Phase 1/2	December 2026
	Intravitreal	NCT05657301	Phase 1	September 2026
KH658 (Chengdu Origen Biotechnology/Vanotech)	Suprachoroidal	NCT06825858	Phase 1	TBD
FT-003 (Frontera Therapeutics)	Intravitreal	NCT06492863	Phase 1/2	October 2024
	Intravitreal	NCT05611424	Phase 1	November 2024
HG202 (HuidaGene Therapeutics)	Subretinal	NCT06623279	Phase 1	February 2027
	Subretinal	NCT06031727	Phase 1	December 2024
EXG102-031 (Exegenes Bio)	Subretinal	NCT05903794	Phase 1	December 2024
EXG202 (Exegenes Bio)	Intravitreal	NCT06888492	Phase 1	April 2026
Geographic Atrophy				
JNJ-1887 (Janssen)	Intravitreal	NCT06635148	Long-term	August 2029
	Intravitreal	NCT05811351	Phase 2	July 2025
OCU410 (Ocugen)	Subretinal	NCT06018558	Phase 1/2	September 2025

enabling transduced retinal cells to continuously produce therapeutic levels of aflibercept. Preliminary 4-year data from the ongoing OPTIC extension study (NCT04645212) show an 86% reduction in annualized anti-VEGF injections compared with baseline. Nearly half of the participants remained injection-free, and 78% of those who were injection-free after the first year maintained that status through year 4.³

Preliminary results from the phase 2 LUNA trial (NCT05536973) show that ixo-vec reduced the need for anti-VEGF injections by 88% to 92% from baseline in 60 patients across two dose cohorts, 6E10 vg/eye and 2E11 vg/eye, respectively. At the two tested doses, 1-year injection-free rates were 54% and 69%, respectively.³ At 52 weeks, with prophylactic topical steroids, no inflammation was observed

in patients receiving the low dose of ixo-vec.³ The phase 3 ARTEMIS study (NCT06856577) is enrolling 284 patients in a double-masked, randomized trial comparing ixo-vec (6E10 vg/eye) with 2 mg aflibercept.⁴

4D-150 (4D Molecular Therapeutics) delivers aflibercept and a VEGF inhibitory miRNA through intravitreal injection of an AAV variant.⁵ In the phase 1/2 PRISM trial (NCT05197270), participants are administered either high- or low-dose gene therapy, while the control group receives bimonthly aflibercept injections. An interim analysis at 24 weeks revealed a more than 80% reduction in injection frequency across both treatment groups.⁶ Visual acuity remained stable in both groups, and no significant adverse events were reported.⁶ The company is recruiting for the

Advances in AMD

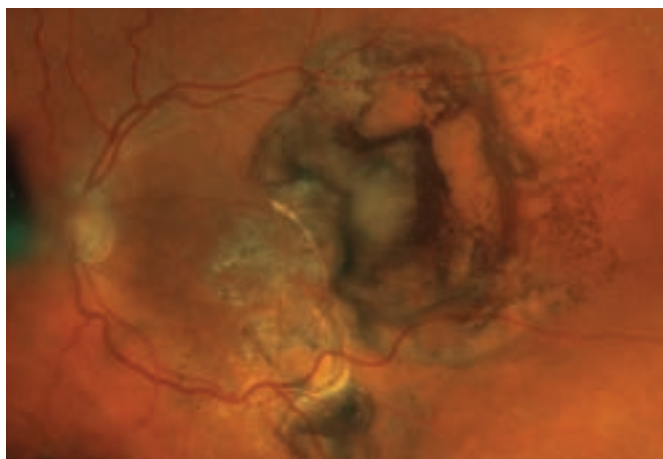


Figure 1. Gene therapies under investigation for wet AMD may one day allow patients such as these to have a one-and-done treatment.

4FRONT-1 phase 3 trial (NCT06864988).

KH631 (Chengdu Origen Biotechnology) uses an AAV vector to deliver a gene encoding a VEGF receptor fusion protein, which binds to VEGF.⁷ In preclinical studies, KH631 demonstrated prolonged retention of the therapeutic protein in the retina and effectively prevented disease progression in wet AMD models.⁷ Phase 1 (NCT05657301) and phase 1/2 (NCT05672121) clinical trials are evaluating its safety and efficacy in wet AMD.

In addition, Chengdu Origen Biotechnology/Vanotech recently announced the first patient with wet AMD dosed in a phase 1 trial (NCT06825858) for KH658, another recombinant AAV vector that encodes a VEGF receptor fusion protein that is delivered into the suprachroidal space.⁸

FT-003 (Frontera Therapeutics) is an AAV gene expression system designed to stimulate retina cells to produce a humanized recombinant fusion protein similar to aflibercept.⁹ Phase 1 (NCT05611424) and phase 1/2 (NCT06492863) clinical trials are assessing its safety and efficacy in wet AMD.

HG202 (HuidaGene Therapeutics) is an RNA-editing treatment using the CRISPR/Cas13 system, delivered via a single AAV vector. The therapy is designed to reduce VEGF expression and prevent the development of choroidal neovascularization (CNV) in AMD. Preclinical studies showed an 87% reduction in CNV area, which surpasses current anti-VEGF treatments.¹⁰ Two ongoing phase 1 trials—SIGHT-I (NCT06031727) and BRIGHT (NCT06623279)—are assessing safety, tolerability, and efficacy at different doses. Initial data from the SIGHT-I trial indicated that a patient with a history of non-responsiveness to anti-VEGF injections showed significant improvement in retinal fluid, central retinal thickness, and visual acuity after a low-dose injection, with no adverse events or dose-limiting toxicity observed.¹¹

EXG102-031 (Exegenesis Bio) is an AAV vector expressing a fusion protein that binds all four subtypes of VEGF and

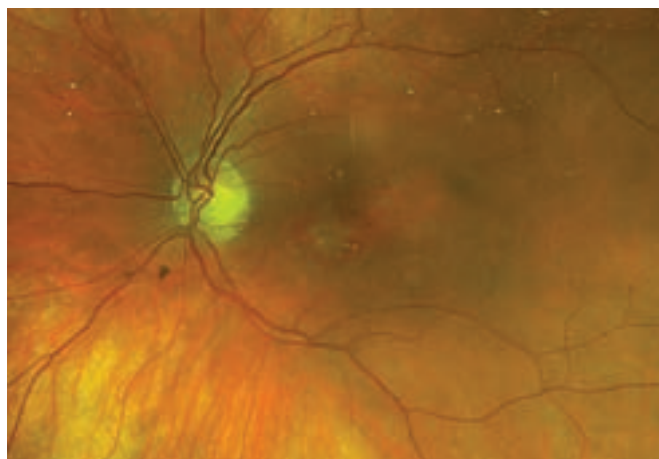


Figure 2. Patients with dry AMD, such as this one, now have FDA-approved treatment options and the promise of gene therapies that are currently under investigation.

Ang-2 delivered subretinally. EXG202 (Exegenesis Bio) uses the same fusion protein-expressing transgene but is packaged in an ocular-specific capsid that enables a three- to five-fold increase in transduction efficiency in retinal cells, allowing administration via intravitreal injection.¹² Both EXG102-031 and EXG202 are in phase 1 trials (NCT05903794 and NCT06888492, respectively).

GENE THERAPY CANDIDATES FOR GEOGRAPHIC ATROPHY

JNJ-1887 (JNJ-81201887/AAVCAGsCD59, Janssen) employs an AAV vector to enhance the expression of soluble CD59, an antiinflammatory protein that inhibits the formation of the membrane attack complex in the complement pathway.¹³ JNJ-1887 is delivered via a single intravitreal injection. The phase 1 study demonstrated that the gene therapy was well-tolerated across all dose levels in 17 patients, with no significant safety concerns. Notably,



Gene Therapy Defined

- **Gene replacement therapy** introduces a functional gene copy to compensate for a defective one. It requires knowledge of the specific genetic mutation and is less effective for polygenic diseases such as AMD.¹
- **Gene silencing** uses siRNAs or miRNAs to degrade specific mRNAs, preventing the production of harmful proteins.
- **Gene editing** uses CRISPR/Cas9 to directly modify DNA mutations or reduce the expression of mutated proteins.
- **Modifier gene therapy** regulates upstream or downstream genes that affect the expression of the malfunctioning gene.
- The **ocular “biofactory”** delivers genes encoding therapeutic agents directly to ocular cells, enabling them to produce these agents locally, reducing the need for intraocular injections.
- **Neuroprotective gene therapy** delivers factors such as pigment epithelium-derived factor (PEDF) to prevent retinal cell degeneration. In an AMD mouse model, delivery of PEDF with miRNAs effectively reduces choroidal neovascularization.²
- **Optogenetics** introduces light-sensitive opsins, such as melanopsin, into retinal cells to treat photoreceptor degeneration, showing promising efficacy in preclinical studies.³

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patients in the high-dose cohort exhibited a continuous decline in geographic atrophy (GA) lesion growth rates over 24 months.¹⁴ Janssen initiated a phase 2 clinical trial (NCT05811351) to assess the change in GA lesion growth in eyes treated with JNJ-1887 compared with sham. Additionally, a long-term extension study (NCT06635148) is underway to monitor the drug’s sustained effects and safety. OCU410 (AAV5-hRORA, Ocugen) is designed to restore the expression of the *RORA* gene, which is involved in lipid

metabolism and oxidative stress regulation.¹⁵ Early results from the phase 1 portion of the phase 1/2 clinical trial (NCT06018558), which includes nine participants with GA across three dosage levels, reported no serious side effects at 6 months. The treated eyes exhibited a 21.4% reduction in lesion growth compared with untreated eyes.¹⁶

BETTER VISION, FEWER TREATMENTS

There is a wealth of promising therapies in development for both wet and dry AMD (Figures 1 and 2). As research pushes forward, treatments for AMD could soon feature leading options that employ a multifaceted approach using various delivery techniques—all of which aim to preserve patients’ vision and extend treatment duration. ■

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- TRIESENCE® Suspension is also contraindicated in patients with hypersensitivity to corticosteroids or any component of TRIESENCE® Suspension. Rare instances of anaphylactoid reactions have occurred in patients receiving corticosteroid therapy.

Warnings and Precautions

- TRIESENCE® is a suspension; it should not be administered intravenously.
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- Elevated blood pressure, salt and water retention, and hypokalemia: Monitor blood pressure and sodium, potassium serum levels.
- GI perforation: Increased risk in patients with certain GI disorders.
- Behavioral and mood disturbances: May include euphoria, insomnia, mood swings, personality changes, severe depression, and psychosis.
- Decreases in bone density: Monitor bone density in patients receiving long term corticosteroid therapy.
- Live or live attenuated vaccines: Do not administer to patients receiving immunosuppressive doses of corticosteroids.

- Negative effects on growth and development: Monitor pediatric patients on long-term corticosteroid therapy.
- Use in pregnancy: Fetal harm can occur with first trimester use.
- Weight gain: May cause increased appetite.

Adverse Reactions

- Based on a review of the available literature, the most commonly reported adverse events following ocular administration of triamcinolone acetonide were elevated intraocular pressure and cataract progression. These events have been reported to occur in 20-60% of patients.
- Less common reactions occurring in up to 2% of patients include: endophthalmitis (infectious and non-infectious), hypopyon, injection site reactions (described as blurring and transient discomfort), glaucoma, vitreous floaters, detachment of retinal pigment epithelium, optic disc vascular disorder, eye inflammation, conjunctival hemorrhage and visual acuity reduced. Cases of exophthalmos have also been reported.

Drug Interactions

- Anticoagulant Agents - Corticosteroids may enhance or diminish the anticoagulant effect of anticoagulant agents. Coagulation indices should be monitored.
- Antidiabetic Agents - Corticosteroids may increase blood glucose concentrations. Dose adjustments of antidiabetic agents may be required.
- CYP 3A4 Inducers and Inhibitors - CYP 3A4 inducers and inhibitors may respectively increase or decrease clearance of corticosteroids, necessitating dose adjustment.
- NSAIDs - Concomitant use of NSAIDs, including aspirin and salicylates, with a corticosteroid may increase the risk of GI side effects.

For additional Important Safety Information about TRIESENCE® Suspension, please see the Full Prescribing Information at triesencehcp.com.



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- Hypothalamic-pituitary-adrenal (HPA) axis suppression, Cushing's syndrome, and hyperglycemia: Monitor patients for these conditions and taper doses gradually.
- Infections: Increased susceptibility to new infection and increased risk of exacerbation, dissemination, or reactivation of latent infection.
- Elevated blood pressure, salt and water retention, and hypokalemia: Monitor blood pressure and sodium, and potassium serum levels.
- GI perforation: Increased risk in patients with certain GI disorders.
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ADVERSE REACTIONS

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DRUG INTERACTIONS

- *Anticoagulant Agents* – Corticosteroids may enhance or diminish the anticoagulant effect of anticoagulant agents. Coagulation indices should be monitored.
- *Antidiabetic Agents* – Corticosteroids may increase blood glucose concentrations. Dose adjustments of antidiabetic agents may be required.
- *CYP 3A4 Inducers and Inhibitors* – CYP 3A4 inducers and inhibitors may respectively increase or decrease clearance of corticosteroids, necessitating dose adjustment.
- *NSAIDs* – Concomitant use of NSAIDs, including aspirin and salicylates, with a corticosteroid may increase the risk of GI side effects.

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

Two prospective case control studies showed decreased birth weight in infants exposed to maternal corticosteroids in utero. Triamcinolone acetonide was shown to be teratogenic in rats, rabbits, and monkeys at inhalation doses of 0.02 mg/kg and above and in monkeys, triamcinolone acetonide was teratogenic at an inhalation dose of 0.5 mg/kg (1/4 and 7 times the recommended human dose). Corticosteroids should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. Infants born to mothers who received corticosteroids during pregnancy should be carefully observed for signs of hypoadrenalism.

Nursing Mothers

Corticosteroids are secreted in human milk. The risk of infant exposure to steroids through breast milk should be weighed against the known benefits of breastfeeding for both the mother and baby.

Pediatric Use

The efficacy and safety of corticosteroids in the pediatric population are based on the well-established course of effect of corticosteroids which is similar in pediatric and adult populations. The adverse effects of corticosteroids in pediatric patients are similar to those in adults.

Geriatric Use

No overall differences in safety or effectiveness were observed between elderly subjects and younger subjects, and other reported clinical experience with triamcinolone has not identified differences in responses between the elderly and younger patients.

PATIENT COUNSELING INFORMATION

Patients should discuss with their physician if they have had recent or ongoing infections or if they have recently received a vaccine.

Patients should be advised of common adverse reactions that could occur with corticosteroid use such as elevated intraocular pressure, cataracts, fluid retention, alteration in glucose tolerance, elevation in blood pressure, behavioral and mood changes, increased appetite, and weight gain.



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TRI-00004 06/24

Beyond Complement: Emerging Therapeutics for Dry AMD

Targeting inflammation, mitochondrial health, and neuroprotection.

By Aumer Shughoury, MD, and Thomas A. Ciulla, MD, MBA



A better understanding of complement dysregulation in AMD has led to the first approved therapies targeting the complement system to slow the progression of geographic atrophy (GA).¹ However, beyond complement inhibition, several novel therapeutic strategies are emerging that target the diverse pathogenic mechanisms of dry AMD (Figure 1).² These include therapies that suppress chronic inflammation, enhance mitochondrial health and function, and protect against cellular apoptosis to slow retinal degeneration.

TARGETING INFLAMMATION

Chronic, low-grade inflammation is a critical driver of AMD pathogenesis. Increased chemokine, cytokine, and complement cascade signaling results in pathologic accumulation of activated macrophages, microglia, and complement factors in the subretinal space. This dysregulated immune response promotes progressive retinal tissue injury and photoreceptor degeneration as AMD progresses (Figure 2).³⁻⁶

Mature cells of the innate immune system express a family of receptors called sialic acid-binding immunoglobulin-type lectins (siglecs), which modulate immune activity in response to specific sialic acid patterns on the cell membranes. Because certain siglecs function as immune checkpoints to recognize “self” sialic acid patterns and dampen local inflammatory activity against host tissues, they represent

promising targets to reduce inflammatory damage to retinal tissue in the development of AMD.^{6,7}

AVD-104 (Aviceda Therapeutics) is a glycomimetic siglec-agonist nanoparticle designed to reduce retinal inflammation in GA by binding select siglec subtypes on activated macrophages and microglia in the subretinal space, repolarizing them to a neuroprotective state and reducing the production of proinflammatory cytokines to curtail local retinal injury.⁸ AVD-104 also directly disrupts the

AT A GLANCE

- ▶ Chronic inflammation is a critical driver of AMD pathogenesis. Thus, AVD-104 (Aviceda Therapeutics) and tonabersat (Xiflam, InflammX Therapeutics) aim to improve inflammatory modulation in the retina.
- ▶ Elamipretide (SS-31, Stealth Biotherapeutics) and photobiomodulation with the Valeda Light Delivery System (LumiThera) both focus on improving mitochondrial health and function.
- ▶ ONL1204 (ONL Therapeutics) and CT1812 (Zervimesine, Cognition Therapeutics) are neuroprotective therapies being explored for the treatment of dry AMD.

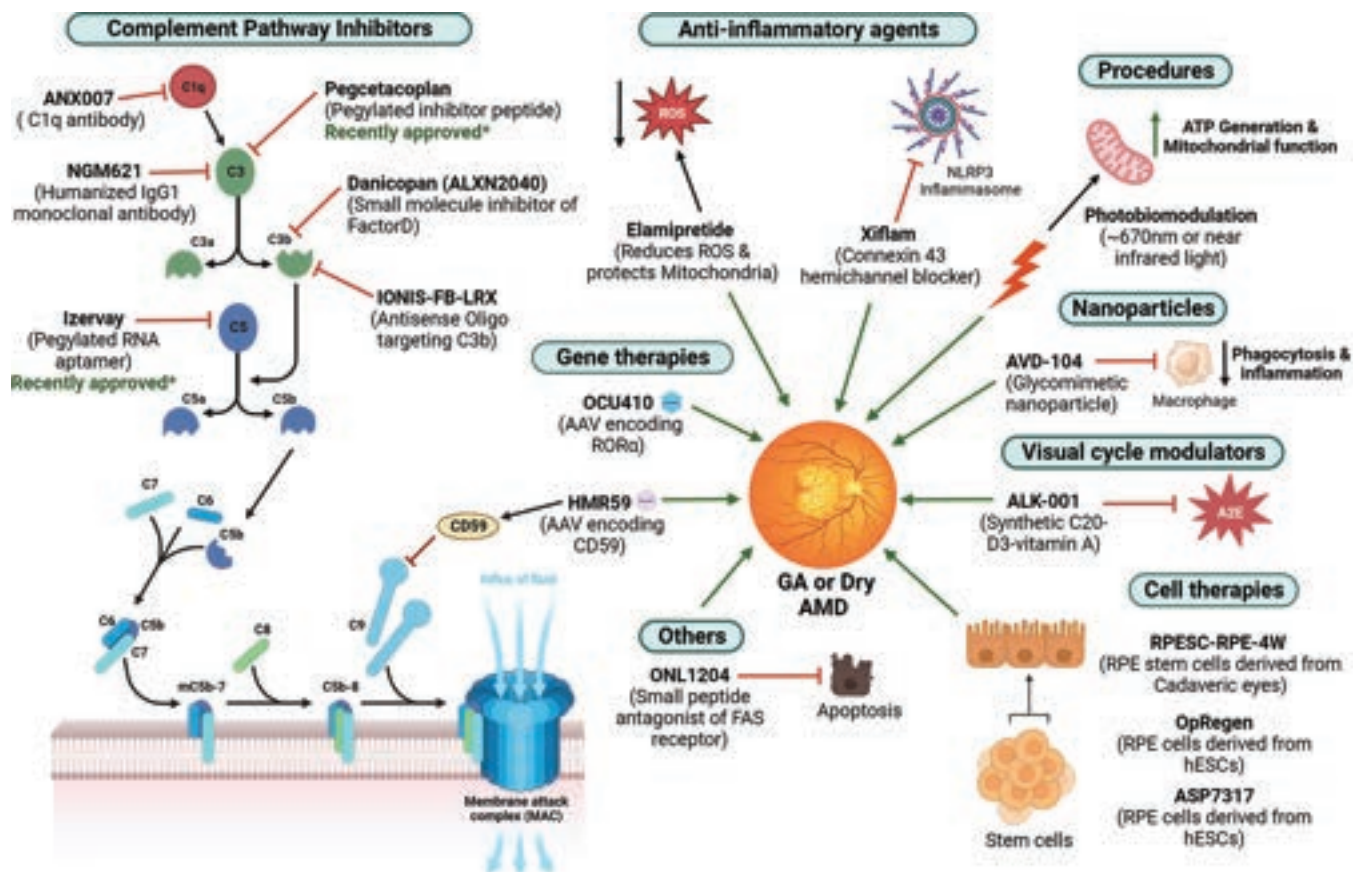


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Figure 1. In addition to complement pathway inhibitors, several emerging therapies target other mechanisms of dry AMD pathogenesis.

complement cascade by binding and activating complement factor H to suppress C3 activity.⁹ Preliminary data from the phase 2/3 SIGLEC trial (NCT05839041) suggest that AVD-104 therapy in patients with GA may be well tolerated with significant reduction in GA growth rate at 3 months.¹⁰

Tonabersat (Xiflam, InflammX Therapeutics) is an oral inhibitor of the connexin43 hemichannel, which plays a critical role in ocular inflammation through the assembly and activation of the NLRP3 inflammasome pathway within immune cells.^{11,12} Connexin43-mediated activation of the NLRP3 inflammasome triggers cytokine release, while connexin43-driven ATP secretion perpetuates the NLRP3 pathway.¹² A phase 2 trial (NCT05727891) is assessing tonabersat in diabetic macular edema, and the company is planning a phase 2 trial for patients with intermediate AMD.¹³

ENHANCING MITOCHONDRIAL HEALTH AND FUNCTION

Chronic inflammation in AMD is thought to be driven primarily by an imbalance between the generation and elimination of reactive oxygen species (ROS) in retinal tissue, subjecting retinal pigment epithelium (RPE) and photoreceptor cells to chronic oxidative stress and accumulation of toxic metabolic byproducts.¹⁴ This metabolic stress causes progressive mitochondrial damage,

energy depletion, and, ultimately, apoptotic cell death.

Therapies aimed at correcting such metabolic imbalances in AMD seek to slow retinal degeneration by enhancing mitochondrial function and reducing oxidative damage.

Photobiomodulation (PBM) employs low-intensity light, typically 590 nm to 850 nm, to reduce oxidative stress associated with chronic retinal diseases.¹⁵ Exposure to these wavelengths is thought to activate mitochondrial cytochrome c oxidase in retinal cells to enhance cellular respiration, increasing ATP production and limiting toxic ROS.¹⁶ Together, these effects may protect retinal cells against oxidative injury and progressive degeneration.¹⁵⁻¹⁷

The Valeda Light Delivery System (LumiThera), which received FDA De Novo authorization for treating dry AMD, delivers simultaneous 590 nm, 660 nm, and 850 nm wavelengths of light in brief sessions multiple times per week over the course of several months. The LIGHTSITE III trial (NCT03878420) showed significant and clinically meaningful improvements in visual acuity, with gains of ≥ 5 letters in more than 55%, ≥ 10 letters in 26.4%, and ≥ 15 letters in 5.5% of PBM-treated eyes.^{18,19} An open-label extension study, LIGHTSITE IIIB (NCT06229665), is assessing the efficacy of PBM in this cohort over an additional 13 months.

Elamipretide (SS-31, Stealth Biotherapeutics) is a



The **#1 PRESCRIBED** FDA-approved treatment for new GA patients*

*Based on Symphony data from 3/24-1/25. May not represent entire patient population



When you see GA, start IZERVAY

Learn more at **IZERVAYecp.com**.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Increase in Intraocular Pressure

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

ADVERSE REACTIONS

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

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

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 dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days).

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 pooled across GATHER1 and GATHER2, are listed below in Table 1.

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

Adverse Drug Reactions	IZERVAY N=292	Sham N=332
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
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.

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 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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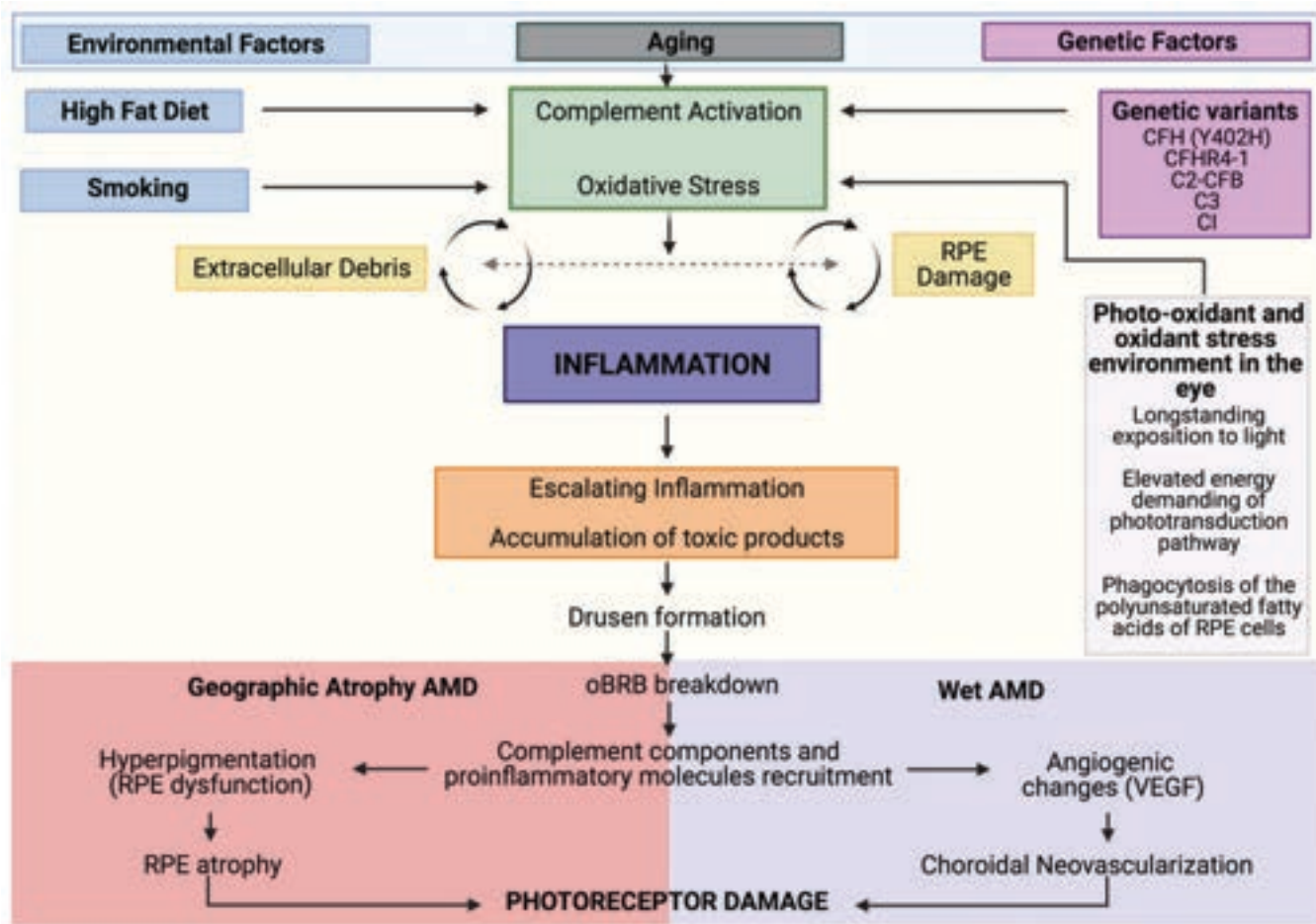


Figure 2. AMD pathogenesis and progression is thought to be largely driven by chronic, low-grade inflammation in the aging retina. Environmental, genetic, and age-related factors trigger complement activation, oxidative stress, and escalating inflammation, ultimately driving RPE dysfunction, drusen formation, and photoreceptor degeneration.

subcutaneous tetrapeptide designed to mitigate oxidative damage by promoting efficient cellular respiration.²⁰ Elamipretide selectively binds cardiolipin (a lipid found on the inner mitochondrial membrane) to stabilize the electron transport chain, thus increasing ATP production and reducing ROS generation during cellular respiration.^{20,21} By improving mitochondrial function in RPE cells under oxidative stress, elamipretide may slow or even reverse retinal degeneration in AMD.²²⁻²⁴ Although a phase 1 trial (NCT02848313) showed that daily elamipretide may improve visual function over 24 weeks, the phase 2 trial (NCT03891875) did not meet primary endpoints of change in low-luminance visual acuity or GA area after 48 weeks.²⁴⁻²⁶ A phase 3 trial (NCT06373731) is in development.²⁷

THE ROLE OF NEUROPROTECTION

Chronic inflammatory and oxidative injury in AMD cause progressive RPE dysfunction and photoreceptor degeneration as the disease progresses.²⁸ Neuroprotective strategies to promote RPE and photoreceptor survival may therefore mitigate progressive retinal degeneration in AMD.

The Fas receptor (CD95), a transmembrane protein of the tumor necrosis factor receptor family, serves as a key trigger of cellular apoptosis in response to environmental stressors. When bound by its ligand, Fas activates the extrinsic apoptosis pathway via caspase-8, culminating in cell death.²⁹ Fas activation additionally results in the production of chemokines and cytokines that recruit immune cells and enhance local inflammation. Preclinical studies in mice have found that overactivation in the RPE results in increased susceptibility to inflammatory stimuli and oxidative stress, promoting progressive photoreceptor degeneration.³⁰ The Fas receptor has therefore emerged as a potential target for neuroprotective prevention of photoreceptor degeneration in AMD.²⁹

ONL1204 (ONL Therapeutics) is an intravitreal small-molecule Fas inhibitor that protects against RPE and photoreceptor apoptosis.³¹ Preliminary data from a phase 1 study in patients with GA (NCT04744662) suggest that ONL1204 is well tolerated and may result in a dose-dependent reduction in GA growth rate at 6 months.³² A multicenter phase 2 trial (NCT06659445) is further assessing the safety and efficacy of ONL1204 in GA with various dosing regimens.

Gene Therapy Approach

Two gene therapies are under investigation for the treatment of GA: OCU410 (AAV5-hRORA, Ocugen) and JNJ-1887 (JNJ-81201887/AAVCAGsCD59, Janssen). To learn more about these therapies, check out *Gene Therapy for AMD: What You Need to Know*, on page 26.

CT1812 (Zervimesine, Cognition Therapeutics) is an oral drug that displaces toxic protein oligomers from the sigma-2 receptor complex on the endoplasmic reticulum, which plays a role in cellular protein/lipid trafficking and homeostasis. In preclinical AMD models, CT1812 showed an ability to reverse the pathologic effects of oxidative stress on RPE cells, restoring RPE homeostasis and normalizing RPE-mediated phagocytosis and trafficking of photoreceptor outer segments.³³ A phase 2 trial (NCT05893537) is ongoing to assess daily oral CT1812 therapy in patients with GA.

FUTURE DIRECTIONS AND CLINICAL OUTLOOK

Many emerging therapeutic strategies for dry AMD are rapidly expanding our approach beyond complement inhibition. With novel drugs in development that aim to reduce chronic inflammation, enhance mitochondrial health, and promote retinal cell survival, clinicians may one day have the ability to proactively intervene on multiple mechanisms of AMD pathogenesis to prevent disease progression. Sustained innovation in this field is likely to continue shifting our approach to AMD from supportive care toward multimodal, patient-tailored therapy aimed at preventing vision loss and enhancing quality of life in our aging population. ■

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Imaging Biomarkers for GA Progression

Our study identified a set of OCT parameters that can predict a faster growth rate.

By Maxwell S. Mayeda, MD, and Talisa E. de Carlo Forest, MD



With two FDA-approved complement inhibitors—pegcetacoplan (Syfovre, Apellis) and avacincaptad pegol (Izervay, Astellas)—on the market to slow the progression of

geographic atrophy (GA) secondary to AMD, the question is, which patients do we treat? Understanding which patients with dry AMD are at the highest risk for the fastest progression is especially important for effective long-term patient management.

Many studies have explored multimodal imaging biomarkers, and OCT in particular, to predict progression of intermediate AMD to GA, but few have investigated biomarkers that help predict faster GA progression.^{1,2}

Existing studies on GA growth rate have focused on baseline GA characteristics, AI and computational models, and quantitative imaging biomarkers.³⁻¹² While these measures can be effective, they are also time-consuming, expensive, or unavailable in most retina practices. To better care for our patients, we need readily accessible imaging biomarkers to help clinicians determine which patients with GA will rapidly progress and may be good candidates for treatment. In this article, we share our study findings that reveal demographic data and imaging biomarkers that are associated with a faster GA growth rate.¹³

AT A GLANCE

- Using the University of Colorado AMD Registry, we evaluated 121 eyes of 66 patients with geographic atrophy (GA) without concurrent choroidal neovascularization to determine which demographic data and imaging biomarkers are associated with a faster GA growth rate.
- Nonexudative subretinal fluid, subretinal hyperreflective material or acquired vitelliform lesions, and incomplete retinal pigment epithelium and outer retina atrophy were positively associated with higher GA growth rates.
- These biomarkers, along with a thin choroid, can easily be identified on OCT and should alert providers to an increased risk of faster disease progression, especially in the setting of larger and multifocal GA lesions, older age, and female sex.



REGISTRY DATA

The University of Colorado AMD Registry has been enrolling patients longitudinally since 2014 to dynamically evaluate the interplay between changes in multimodal imaging biomarkers, dysregulation of systemic inflammation, and genetics in patients with AMD. Using this registry, we evaluated 121 eyes of 66 patients with GA without concurrent choroidal neovascularization to determine which demographic data and imaging biomarkers are associated with a faster GA growth rate. We evaluated simple and mainly qualitative imaging biomarkers that can assist in accurate and concise clinical decision making.¹³

We reviewed spectral-domain OCT, color fundus photographs, and fundus autofluorescence images for a variety of imaging biomarkers and baseline GA lesion characteristics. We then calculated the square-root transformed GA growth rate, a commonly accepted measure that helps neutralize the effects of initial GA lesion size. We evaluated associations between square-root transformed GA growth rate and imaging biomarkers, baseline lesion characteristics, and patient demographics using linear regression models.¹³

KEY FINDINGS

Older age and female sex were associated with increased rates of GA progression. A patient's body mass index was weakly negatively associated with GA growth rate. Smoking history was not associated with GA growth rate.¹³

Larger areas of GA were associated with increased rates of progression. Multifocal and extrafoveal GA lesions had faster, but not statistically significant, growth rates. These findings support the hypotheses of faster centrifugal growth and the importance of the GA perimeter.¹³

Nonexudative subretinal fluid (SRF), subretinal hyperreflective material (SHRM) or acquired vitelliform lesions (AVLs), and incomplete retinal pigment epithelium (RPE) and outer retina atrophy (iRORA) were positively associated with higher GA growth rates. While iRORA is a known precursor for GA, less is known about nonexudative SRF and SHRM/AVLs in dry AMD. We believe these biomarkers also precede new GA lesions, increasing the overall GA perimeter area and the rate of GA growth.¹³

One study in the literature investigated nonexudative SRF in GA and observed a high percentage of progression to GA in areas of SRF overlying drusen and drusenoid

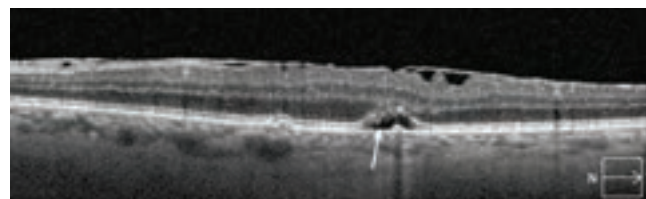


Figure 1. The arrow points to nonexudative SRF with overlying ellipsoid zone attenuation that later progressed to GA (A).

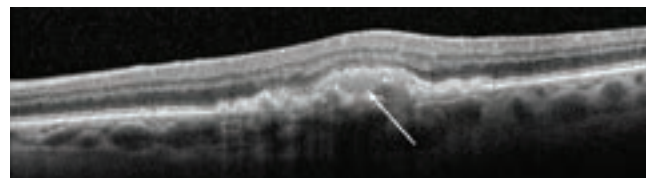


Figure 2. The arrow points to a hyperreflective area representative of SHRM/AVLs that later progressed to GA.

pigment epithelial detachments.¹⁴ Our findings corroborate that these areas of nonexudative SRF likely represent a degenerative space beneath the retina, rather than an exudative fluid process, and are risk factors for progression to GA (Figure 1).¹³ SHRM/AVLs in the setting of dry AMD have more recently been hypothesized to represent an accumulation of various breakdown materials due to significant RPE stress and dysfunction or to act as a physical barrier for nutrient exchange, accelerating photoreceptor degeneration and GA progression (Figure 2).^{15,16}

Our study's third and most intuitive biomarker was iRORA. Once this pattern of damage starts, our study demonstrated that progression to complete RPE and outer retina atrophy (cRORA) is accelerated.¹³

Retinal pseudocysts and subfoveal choroidal thickness were significantly negatively associated with higher GA progression (Figure 3); this significance held true even after adjusting for age, which has long been associated with choroidal thinning and AMD. Retinal pseudocysts are degenerative, nonexudative retinal cysts that have been hypothesized to correspond to Müller cell degeneration and are commonly found in the inner nuclear layer overlying preexisting GA. There is little research on why these lesions would be associated with a lower GA growth rate, but we hypothesize that they may represent a burning out of the disease process or are protective in some way.¹³

Interestingly, imaging biomarkers traditionally associated with the development of GA were not associated with

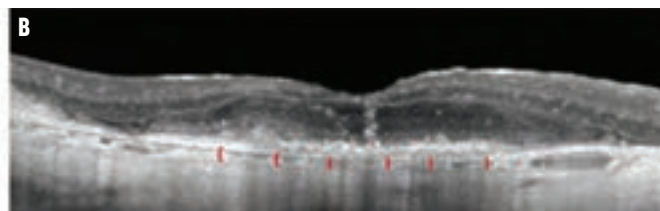


Figure 3. This OCT image (A) shows multiple retinal pseudocysts (arrow) in the internal nuclear layer overlying an area of cRORA as evidenced by signal hypertransmission (*), an area of cRORA of at least 250 μ m (black bracket), and an area of iRORA (white bracket). The red brackets on another OCT image denote the boundaries of a thin choroid (B).

increased rates of GA progression in our study. Reticular pseudodrusen, outer retinal tubulation, drusenoid pigment epithelial detachments, and calcified drusen may only be associated with initial GA formation and not play a large role in progression. Investigation with larger sample sizes would be helpful to better evaluate these relationships.¹³

DISCUSSION

When counseling and selecting GA patients for therapeutic intervention, there are many considerations to keep in mind. While a faster GA growth rate is only one piece of the overall picture, it can help guide referrals and discussions. SHRM/AVLs, nonexudative SRF, iRORA, and a thin choroid are biomarkers that can be easily identified on OCT and should alert providers to an increased risk of faster disease progression, especially in the setting of larger and multifocal GA lesions, older age, and female sex.

Further studies investigating choroidal thickness, nonexudative SRF, SHRM/AVLs, and iRORA can help establish reliable indicators of disease progression risk and analyze the efficacy of future GA therapies. ■

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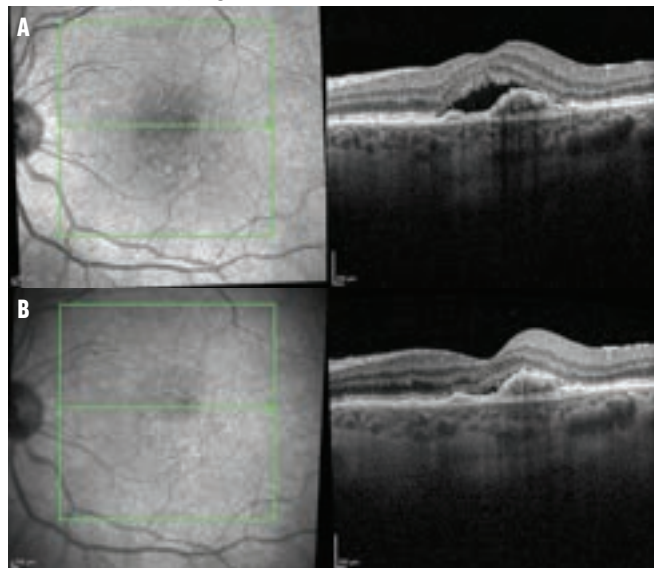


Figure 2. This patient with wet AMD being treated with 2 mg aflibercept had less than ideal fluid control (A). After three monthly doses of faricimab, the patient's OCT imaging showed significant improvement (B).

it carries associated surgical risks that require careful patient counseling. Many alternative strategies for sustained VEGF suppression are currently under development.

All these approaches show promise in early clinical trials but must stand up to scrutiny against the high bar of current anti-VEGF therapies. ■

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Managing DME With Subthreshold Laser



In many cases, laser treatment offers myriad advantages and few downsides.

BY LIHTEH WU, MD

The treatment of choice for diabetic macular edema (DME) is anti-VEGF therapy which has largely superseded macular laser photocoagulation (MLP).

However, not all patients respond equally to this therapy, and not all patients can afford it. At the same time, macular laser therapies have evolved from destructive thermal techniques to subthreshold ones that are tissue-sparing and non-thermal, such as Lumibird Medical's SubLiminal[®] Treatment mode (Figure 1A and B). Thus, there are certain instances where MLP remains a useful tool, such as in eyes with non-center-involved DME, in center-involved DME with good visual acuity, or in center-involved DME with a central macular thickness (CMT) of $\leq 400 \mu\text{m}$.

Most cases of non-center-involved DME can be managed by observation. However, in cases where patients are non-compliant, have difficulty traveling to doctor appointments, or live in areas with limited resources, MLP may be an option. Case 1 (described on the next page) illustrates this scenario.

CENTER-INVOLVED DME WITH GOOD VISUAL ACUITY ($\geq 20/25$): PROTOCOL V OF THE DRCR NETWORK

The Diabetic Retinopathy Clinical Research (DRCR) Protocol V concluded that in eyes with center-involved DME and a good baseline visual acuity ($\geq 20/25$), initial

treatment with MLP yields equivalent visual acuity outcomes to initial treatment with intravitreal aflibercept (Eylea, Regeneron) or observation.¹ However, MLP was associated with significant cost-savings relative to anti-VEGF therapy or observation.²

In the Protocol V study, patients were randomized to initial treatment with aflibercept injection, conventional MLP, or observation. If the visual acuity of patients in either the observation group or the MLP treatment group decreased from baseline, they were rescued with aflibercept. Of the 236 eyes assigned to observation, 80 (34%) received aflibercept within the 2-year study period, and in the laser photocoagulation group, aflibercept was initiated in 25% (60/240).¹ The cumulative probability of receiving aflibercept by 2 years was 26% in the MLP group and 36% in the observation group.¹

After 2 years of follow-up, the mean visual acuity was 20/20 in each group. Furthermore, the investigators determined that the percentage of patients with a greater than 5-letter decrease in visual acuity at 2 years was not statistically significantly different between the groups initially managed with aflibercept (16%), laser photocoagulation (17%), or observation (19%).¹

In a follow-up report, the investigators calculated the total per-person cost of each approach over 10 years (in US dollars),

including the cost of clinic visits, diagnostic testing, study interventions such as injection and laser, and additional interventions and complications over the 2-year period.² Because the study followed patients for only 2 years, the researchers extrapolated data for years 3 to 10, assuming that each patient would attend three clinic visits, undergo three OCT scans, and receive 0.5 injections per year in all groups. In the aflibercept-first group, the cost was almost \$30 billion. MLP, at just 50% of the cost of aflibercept, was the most economical intervention, even better than the observation-first approach. Moreover, a sensitivity analysis revealed that the cost of treating DME is largely driven by the cost of aflibercept.

EFFICACY OF THE SUBTHRESHOLD LASER FOR TREATING DME

Over the past decade, numerous studies have validated the safety and efficacy of the subthreshold laser for treating DME. The data suggest that the subthreshold laser achieves at least equivalent clinical outcomes as conventional MLP, but with less iatrogenic trauma to retinal tissue.

Mansouri et al reported that the best results of subthreshold laser application in eyes with DME are obtained when the CMT is $< 400 \mu\text{m}$.³ After 12 months, the eyes with a CMT of $< 400 \mu\text{m}$ ($n = 33$) experienced an average of

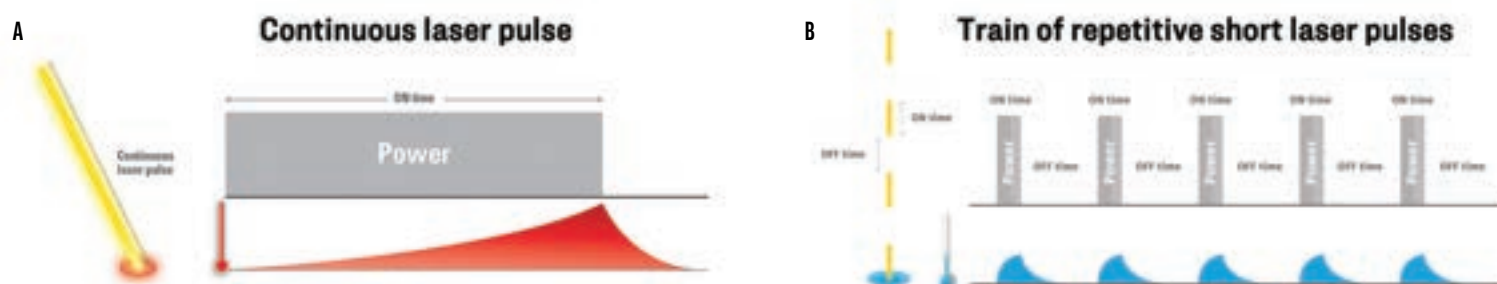


Figure 1. Thermal laser therapy (A) vs Lumibird Medical's subthreshold laser therapy (B).

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MEDICAL

CASE 1:

A 75-year-old man with a 33-year history of type 2 diabetes had a visual acuity of 20/40 in both eyes. He was noted to have non-center-involved DME OS. The patient lived far from the clinic and could not return regularly to get monitored. I decided to treat him with subthreshold laser therapy from Lumibird Medical. Four months after treatment, his left eye showed a complete resolution of the retinal thickening (Figure).

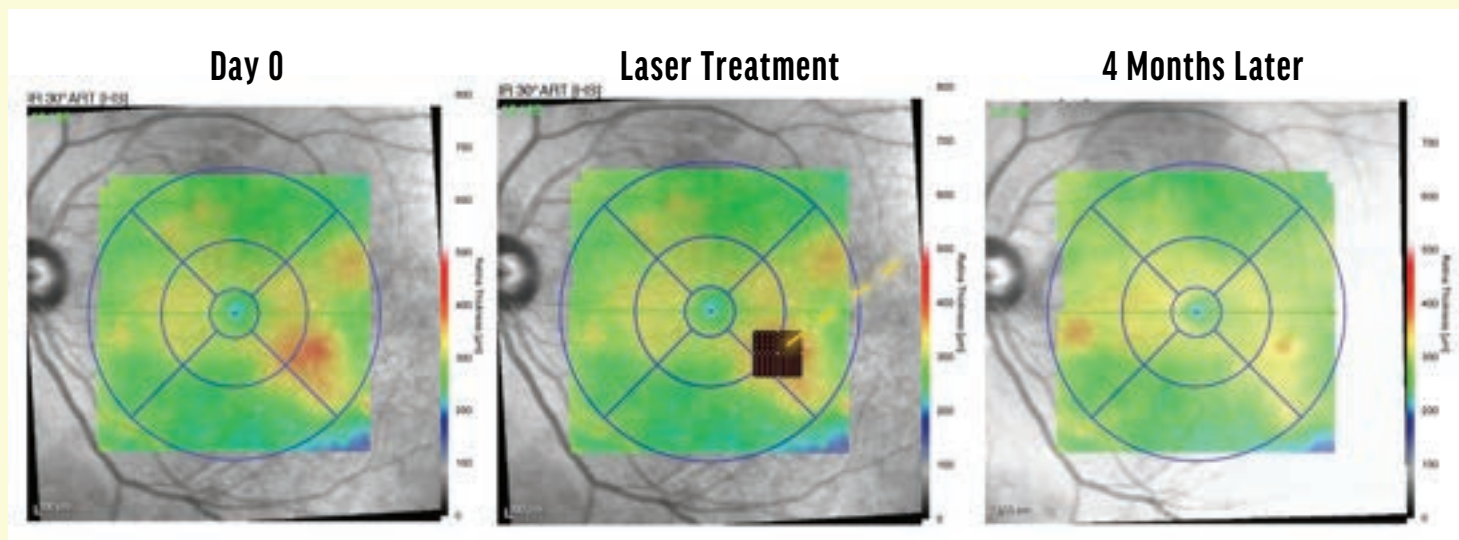


Figure. Subthreshold laser therapy on day 0 (left), the retinal area treated by laser (middle), and 4 months postoperatively (right).

a 55- μ m reduction in CMT and a 0.2 logMAR gain in visual acuity; additionally, no patients required rescue therapy with anti-VEGF injections. By comparison, there was no change in CMT or visual acuity in eyes with a CMT of $> 400 \mu\text{m}$ ($n = 30$) by month 6. By month 12, all eyes had received rescue therapy with bevacizumab (Avastin, Genentech).³

More recently, a double-masked, randomized, multicenter, noninferiority study conducted in the UK compared the outcomes of the subthreshold laser versus standard MLP for treating DME in eyes with a CMT of $\leq 400 \mu\text{m}$.⁴ The mean change in BCVA at 24 months was the primary outcome.

At month 24, the mean change in BCVA from baseline was -2.43 ± 8.30 letters in the subthreshold laser group and -0.45 ± 6.72 letters in the MLP group. The subthreshold laser was deemed to be not only noninferior, but equivalent to MLP in efficacy. And, in a cost analysis, the investigators found no difference between the two treatments.⁴

A meta-analysis performed in 2016 of six randomized, controlled clinical trials that evaluated the efficacy of conventional MLP versus the subthreshold laser for treating DME showed that there was no difference in the resolution of DME between the two treatment regimens at 12 months after

treatment. The subthreshold laser delivered superior visual outcomes, suggesting that perhaps the subthreshold laser causes less iatrogenic macular damage, as evidenced by microperimetry.⁵

Other studies have similarly shown that the subthreshold laser may diminish the anti-VEGF treatment burden.⁶⁻⁸ In one meta-analysis, researchers reported that there were significantly fewer anti-VEGF injections in eyes that were treated with a combination of laser and intravitreal anti-VEGF injections versus anti-VEGF monotherapy.⁹

MECHANISM OF ACTION OF THE SUBTHRESHOLD LASER

Two studies published by Midena et al in Italy have demonstrated that changes in inflammatory and vaso-active biomarkers of the aqueous humor following the application of the subthreshold laser implicate activated microglia and Müller cells in the pathogenesis of DME. After treatment with the laser,

"MACULAR LASER THERAPY, AT JUST 50% OF THE COST OF AFLIBERCEPT, WAS THE MOST ECONOMICAL INTERVENTION, EVEN BETTER THAN THE OBSERVATION-FIRST APPROACH."

CASE 2:

A 67-year-old man with diabetes noted on screening presented with a visual acuity of 20/30 OD. He was diagnosed with center-involved DME in the right eye. I decided to treat the eye with subthreshold laser therapy from Lumibird Medical. Six months after treatment, the visual acuity of the patient improved to 20/20, and his eye showed a complete resolution of the retinal thickening (Figure).

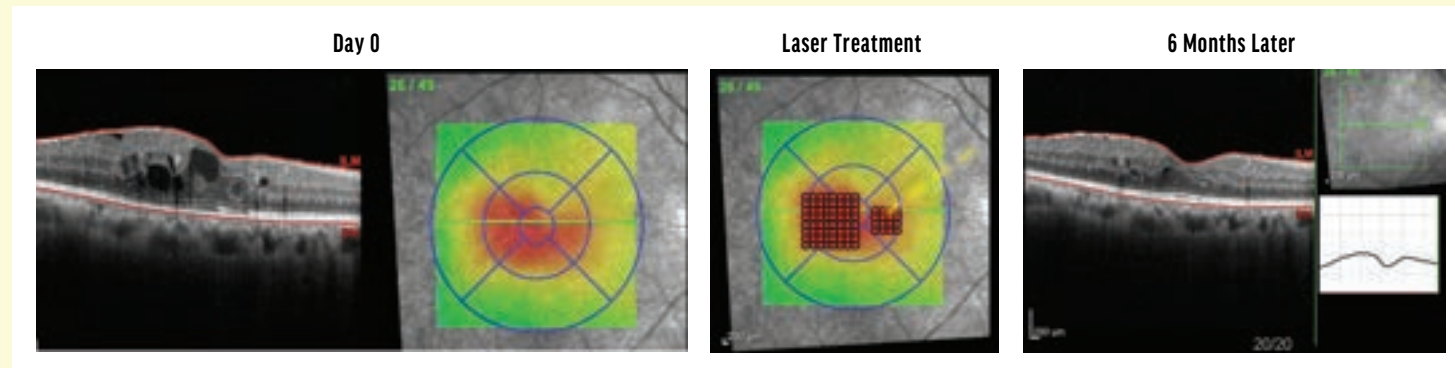


Figure. Subthreshold laser therapy showed on day 0 (left), during laser treatment (middle), and 6 months postoperatively (right).

inflammatory cytokines mainly produced from activated microglia were significantly reduced^{10,11} (see case 2).

SUMMARY

In select cases of non-central DME, center-involved DME with a good visual acuity, and center-involved DME with a CMT of $\leq 400 \mu\text{m}$, when patients are non-compliant, have difficulty traveling to doctor appointments, or live in areas with limited resources, MLP may be indicated for DME. Subthreshold laser photocoagulation is equivalent to conventional MLP in terms of efficacy. I recommend using the subthreshold laser if available in lieu of MLP, since it does not burn the retina, and the studies described

herein have indicated that it may deactivate microglial cells and Müller cells. ■

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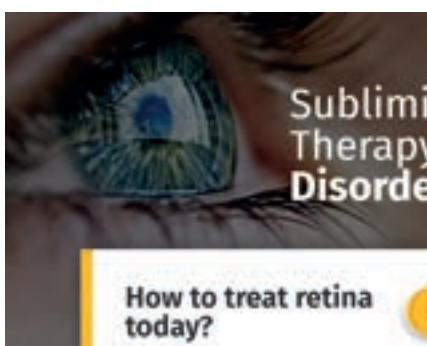
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FDA Guidance: What it Means for AMD Trials

Industry leaders discuss the shifts in clinical trial designs
and their recent interactions with the FDA.

By **Nadia K. Waheed, MD, MPH; Ramiro Ribeiro, MD, PhD;
Victor Chong, MD, MBA, FARVO; Lanita C. Scott, MD; and David J. Tanzer, MD**



In 2023, the FDA issued draft guidance regarding drug development programs for wet AMD. These nonbinding guidelines are meant to offer “current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited.”¹ The document goes on to state, “The word *should* in Agency guidances means that something is suggested or recommended but not required.”

It is important to note that FDA representatives have said that a sponsor may use an alternative approach, if it satisfies the applicable requirements, and the FDA encourages discussion.

“[The document] was put out as a starting point for comments; it was not meant for implementation,” said Wiley Chambers, MD.² “When there are different interpretations, it means that the document needs further clarity. The Agency encourages comments to point out where there is confusion.” Dr. Chambers, the former supervisory medical officer in Ophthalmology for the Center

for Drug Evaluation and Research at the FDA for more than 36 years, is now a consultant for Ocular Advisors.

Here, Chief Medical Officers Nadia K. Waheed, MD, MPH,

AT A GLANCE

- ▶ The FDA’s 2023 draft guidance (not for implementation) suggests that intravitreal ranibizumab (Lucentis, Genentech/Roche) every 4 weeks or 2 mg aflibercept (Eylea, Regeneron) every 4 or 8 weeks (after three monthly injections) be used for comparison in noninferiority trials.
- ▶ The FDA draft guidance indicates that sponsors should have at least one other comparative arm in which the dosing frequency, criteria for dosing adjustments, and criteria for interventions are the same for each investigational drug arm.
- ▶ A decrease in the number of administrations of available effective therapies alone is not sufficient to demonstrate efficacy.

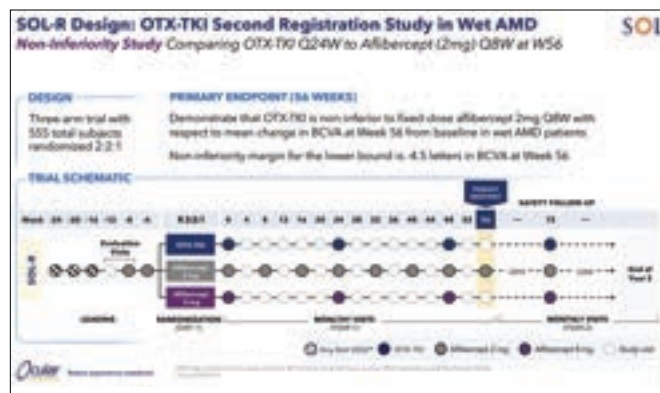
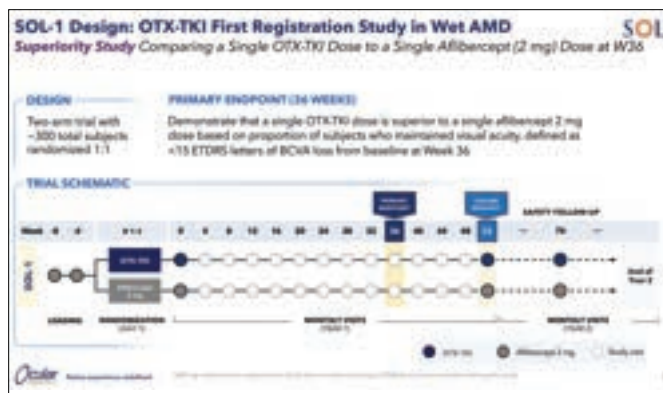


Figure 1. The SOL-1 clinical trial is designed as a superiority study to better assess the increased durability of OTX-TKI. The SOL-R clinical trial is a noninferiority study comparing OTX-TKI with 2 mg aflibercept every 8 weeks for 56 weeks.

(Ocular Therapeutix); Ramiro Ribeiro, MD, PhD, (EyePoint Pharmaceuticals); and Victor Chong, MD, MBA, (Clearside Biomedical) discuss how these guidelines are influencing their development programs. As a clinical trial partner, Lexitas' Senior Vice President of Medical and Clinical Sciences Lanita C. Scott, MD, and Chief Medical Officer David J. Tanzer, MD, share their insight on the current landscape of wet AMD clinical trials.

THE DRAFT GUIDANCE, IN BRIEF

Some of the notable considerations outlined in the draft document include the following¹:

- The FDA suggests that intravitreal injection of ranibizumab (Lucentis, Genentech/Roche) every 4 weeks or 2 mg aflibercept (Eylea, Regeneron) every 4 or 8 weeks (after three monthly injections) be used for comparison in noninferiority trials. For superiority trials, however, the agency offers no discussion on the therapeutic options for the control group.
- The guidance indicates that sponsors should have at least one other comparator arm in which the dosing frequency, criteria for dosing adjustments, and criteria for interventions are the same for each investigational drug arm.
- In terms of drug efficacy, sponsors should consider one of the following:
 - A statistically significant smaller percentage of patients with a doubling of the visual angle (ie, equivalent to a decrease of 15 ETDRS letters or more) in best-corrected distance visual acuity (BCDVA) at 9 months or later.
 - A statistically significant larger percentage of patients with a halving of the visual angle (ie, equivalent to an increase of 15 ETDRS letters or more) in BCDVA at 9 months or later.
 - A statistically significant difference between groups in mean BCDVA of 15 or more letters at 9 months or later after the start of drug administration.

- Two-sided, 95% confidence interval at 9 months or later after the start of drug administration: greater than or equal to -4.5 letters.
- A decrease in the number of administrations of available effective therapies alone is not sufficient to demonstrate efficacy, according to the agency.

A WORLD WITHOUT SHAM

By Nadia K. Waheed, MD, MPH

Implicit in the FDA's draft guidance is that at least one comparator arm should follow the same dosing schedule as the investigational drug. Although not discussed in the draft guidance, recent interactions with the FDA have also indicated that the Agency does not recommend sham injections as adequate masking.^{3,4} This is a major shift from the early foundational noninferiority anti-VEGF studies that allowed sham injections in the control arm as a masking strategy.

Although anti-VEGF agents are incredibly efficacious, the global unmet need at this point is reducing treatment burden. However, reduced treatment burden is not, in and of itself, basis for approval and labeling.

OTX-TKI (Axpaxli, Ocular Therapeutix) is under investigation as a sustained-release option designed for 6 to 12 months of efficacy (Figure 1). How do we appropriately evaluate durability, given the FDA guidance that sham injections are not adequate for masking? Ultimately, we mitigated this challenge by using a superiority design for the phase 3 SOL-1 study (NCT06223958) to answer a true efficacy and durability question.

CLINICAL TRIAL DESIGNS

For a closer look at the trial designs for SOL-1, SOL-R, LUGANO, LUCIA, and CLS-AX, view this article on the web at retinatoday.com by scanning the code:



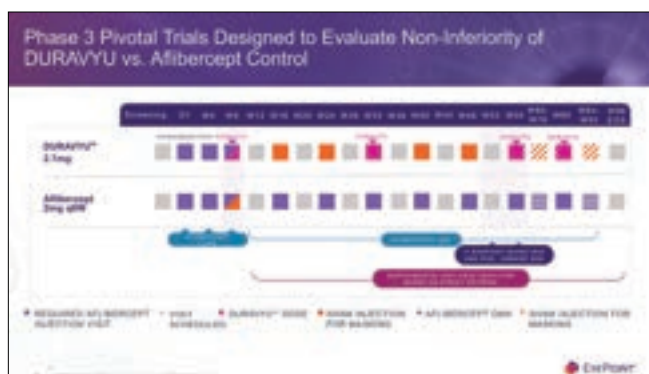


Figure 2. EyePoint Pharmaceuticals chose to pursue a noninferiority trial design for its LUGANO and LUCIA phase 3 trials.

The SOL-R noninferiority study (NCT06495918) uses three arms: 8 mg aflibercept (Eylea HD, Regeneron) dosed approximately every 6 months after the initial induction phase, OTX-TKI dosed approximately every 6 months, and 2 mg aflibercept dosed every 2 months. Per FDA guidance, sponsors should have at least one other comparator arm in which the dosing frequency, criteria for dosing adjustments, and criteria for interventions are the same as the investigational agent; thus, the 8 mg aflibercept every 6 months arm was introduced to comply with these criteria and mask the OTX-TKI arm.

We feel that this complementary study design approach provides two adequately controlled studies and a totality of evidence acceptable for eventual New Drug Application (NDA) submission.

Depending on the mechanism of action of any given drug, the FDA draft guidance could present review challenges. Thus, sponsors must keep the lines of communication open with the FDA. For example, we sought a special protocol assessment for SOL-1, in which the FDA has a more stringent assessment, and we were informed that the design met the criteria for a registrational clinical trial. That process was instrumental in aligning our trial designs with FDA guidance.

STAY THE COURSE

By Ramiro Ribeiro, MD, PhD

In general, and predating this draft guidance, a noninferiority trial design is one of the four designs acceptable to provide evidence of efficacy, and it is recognized globally as a scientifically sound option. In wet AMD, the clinical goal is to diagnose and treat patients as early as possible, ideally when vision is still good and may be preserved. Thus, the noninferiority trial design appropriately represents current clinical practices.

We are conducting two identical, global, noninferiority studies for EYP-1901 (Duravyu, Eyepoint Pharmaceuticals), consistent with registration studies in wet AMD for the past 2 decades (Figure 2). The guidance specifies the

margin of effect over control of 4.5 letters. When we designed the phase 3 LUGANO (NCT06668064) and LUCIA (NCT06683742) studies, we took this guidance into account and obtained concurrence during our FDA interactions.

The objective of the LUGANO and LUCIA studies is to demonstrate that EYP-1901 can maintain vision compared with 2 mg aflibercept while reducing the treatment burden—an important key secondary endpoint for our study. While the guidance does state that the treatment burden itself is not an approvable primary endpoint, we believe a therapy that can lead to similar vision as current anti-VEGF drugs while reducing the treatment burden is important for patients and physicians.

In terms of masking, the FDA guidance requires sponsors attempt to minimize bias in trials, and we believe a sham injection remains the best approach. This masking strategy is supported by evidence in the literature demonstrating that patients cannot tell the difference between an injection with an active treatment and a sham injection.⁵ Importantly, we have had numerous conversations with the FDA, and they have accepted our masking strategy.

Our pipeline is following the typical path of noninferiority study designs, with a technology designed to decrease treatment burden and align with current clinical practice of preserving vision. When we complete our submission for our phase 3 clinical trials to the FDA, our discussions with the Agency will serve as a further learning opportunity for our industry.

BALANCING EFFICACY WITH DURATION

By Victor Chong, MD, MBA, FARVO

The draft guidance, which specifically states it is not for implementation, does not change the well-accepted trial designs in wet AMD. It always comes down to each sponsor working with the FDA to tailor its program's specific needs.

However, there is some confusion in the industry regarding the position of superiority trials in terms of what is approvable and what is good practice. Superiority must be determined in comparison with standard of care when a good therapy is available. The FDA stated that BCDVA should be the primary endpoint for wet AMD registrational studies—superiority in terms of duration is not approvable on its own. The agency offered a noninferiority study design to allow noninferiority on BCDVA with various treatment frequencies. Both designs described in the guidance have caused ambiguity for sponsors.

The question of sham injections was not discussed in the guidance, but the key concern is adequate masking. For a potential treatment delivered by intravitreal injection, sham injection might not provide complete masking. Luckily, the inability to mask does not necessarily stop approval (eg, for gene therapy that requires surgery, such as voretigene neparvovec [Luxturna, Spark Therapeutics]).



We are analyzing our phase 2 ODYSSEY results and planning our phase 3 program in consultation with the FDA. We seek to produce data supportive of a label with dosing between 3 and 6 months in the maintenance phase to align with the wet AMD treatment approach desired by most retinal physicians. Repeat CLS-AX dosing data in ODYSSEY has informed the phase 3 design and provides further support for NDA submission. The phase 3 trials are likely to include two similar noninferiority studies with 2 mg aflibercept as the comparator (Figure 3).

The agency has indicated that it is moving away from sham injections as adequate masking, which presents a challenge to trial design. Eliminating bias becomes harder as the frequency of treatment decreases, making it difficult to maintain the double-masked nature of certain clinical trials.

Collaboration with the FDA is crucial regarding study design to find a path forward that blends masking and durability. The Agency has shown a willingness to provide feedback and engage in discussions to ensure safety and adequate trial designs. Given the continued uncertainty (made apparent by the disparate interpretations of the draft guidance highlighted here), a collaborative approach is essential as we navigate the complexities of developing new treatments for wet AMD. ■

- Financial disclosure: Employee (Lexitas)

IMPLANTABLE DRUG DELIVERY: A LOOK AT PHARMACOKINETICS



Novel approaches are showing promise for addressing treatment burden in retinal disease.

BY CHARLES C. WYKOFF, MD, PHD, FASRS, FACS

The pharmacokinetics, pharmacodynamics, and delivery methods of intraocular drugs are important considerations in the management of retinal disease and in drug development. The successful delivery of novel therapeutics to the retina has been a challenge for development programs, and while various methods have been explored, many have led to subtherapeutic levels of drug delivered to the target tissue.¹

Currently, the most common retinal drug delivery method is intravitreal injection, widely used for delivering anti-VEGF biologics for the treatment of a host of exudative retinal diseases, including wet AMD and diabetic macular edema (DME). However, in many patients, frequent anti-VEGF injections are required, which can present meaningful treatment and adherence burdens. As such, adherence rates are often suboptimal, and injections are frequently administered at longer intervals than may be ideal, limiting their effectiveness and compromising long-term patient outcomes.¹

Additionally, while regular injections may be feasible for compounds such as anti-VEGF proteins, which have half-lives on the order of days, this approach is less feasible for small-molecule drugs, which typically have much shorter intraocular half-lives and may require unrealistic dosing frequencies.¹ To address this need, several implantable sustained drug delivery methods are currently under investigation for retinal pathologies. These methods hold promise to reduce treatment burden and maximize long-term visual outcomes through increased adherence and reduced disease fluctuation with more consistent delivery of drug at therapeutic levels.

WET AMD

Although anti-VEGF therapy constituted a paradigm shift in the treatment of wet AMD, therapeutic outcomes in routine clinical practice often lag behind those achieved in clinical trials, and reduced frequency of injections appears to be a key factor.² A large-scale study of practice

data found that only about one-third of eyes treated with anti-VEGF agents had injection intervals of less than 8 weeks by the end of the first year of treatment and more than 40% had discontinued treatment by year 3. These reductions in treatment frequency may translate to poorer visual acuity outcomes over time.³

Despite the widespread use of anti-VEGF therapy, our understanding of the pharmacokinetics at the patient level remains limited, hindering our ability to create optimal dosing strategies for individual patients. For example, the optimal frequency of administration likely depends on the agent's half-life, which may vary between patients due to factors that could affect individual clearance rates.⁴

Tyrosine kinase inhibitors (TKIs) are under investigation as a new treatment approach for wet AMD that differ from available anti-VEGF biologics in their intracellular multitarget inhibition of tyrosine kinase receptors, including VEGF receptors. Many of the TKIs in development have demonstrated promising pharmacokinetic profiles; two late-stage programs with clinical data to date are

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BY CHARLES C. WYKOFF, MD, PHD, FASRS, FACS

The pharmacokinetics, pharmacodynamics, and delivery methods of intraocular drugs are important considerations in the management of retinal disease and in drug development. The successful delivery of novel therapeutics to the retina has been a challenge for development programs, and while various methods have been explored, many have led to subtherapeutic levels of drug delivered to the target tissue.¹

Currently, the most common retinal drug delivery method is intravitreal injection, widely used for delivering anti-VEGF biologics for the treatment of a host of exudative retinal diseases, including wet AMD and diabetic macular edema (DME). However, in many patients, frequent anti-VEGF injections are required, which can present meaningful treatment and adherence burdens. As such, adherence rates are often suboptimal, and injections are frequently administered at longer intervals than may be ideal, limiting their effectiveness and compromising long-term patient outcomes.¹

Additionally, while regular injections may be feasible for compounds such as anti-VEGF proteins, which have half-lives on the order of days, this approach is less feasible for small-molecule drugs, which typically have much shorter intraocular half-lives and may require unrealistic dosing frequencies.¹ To address this need, several implantable sustained drug delivery methods are currently under investigation for retinal pathologies. These methods hold promise to reduce treatment burden and maximize long-term visual outcomes through increased adherence and reduced disease fluctuation with more consistent delivery of drug at therapeutic levels.

WET AMD

Although anti-VEGF therapy constituted a paradigm shift in the treatment of wet AMD, therapeutic outcomes in routine clinical practice often lag behind those achieved in clinical trials, and reduced frequency of injections appears to be a key factor.² A large-scale study of practice

data found that only about one-third of eyes treated with anti-VEGF agents had injection intervals of less than 8 weeks by the end of the first year of treatment and more than 40% had discontinued treatment by year 3. These reductions in treatment frequency may translate to poorer visual acuity outcomes over time.³

Despite the widespread use of anti-VEGF therapy, our understanding of the pharmacokinetics at the patient level remains limited, hindering our ability to create optimal dosing strategies for individual patients. For example, the optimal frequency of administration likely depends on the agent's half-life, which may vary between patients due to factors that could affect individual clearance rates.⁴

Tyrosine kinase inhibitors (TKIs) are under investigation as a new treatment approach for wet AMD that differ from available anti-VEGF biologics in their intracellular multitarget inhibition of tyrosine kinase receptors, including VEGF receptors. Many of the TKIs in development have demonstrated promising pharmacokinetic profiles; two late-stage programs with clinical data to date are

**TACTICS AIMED AT ENHANCING
THE PHARMACOKINETICS OF
EXISTING AND FUTURE RETINAL
THERAPEUTICS HAVE THE
POTENTIAL TO MEANINGFULLY
IMPROVE PATIENTS' LIVES.**

MACULAR TELANGIECTASIA TYPE 2

The use of ciliary neurotrophic factor (CNTF) has been found to significantly slow the progression of retinal degeneration in two randomized prospective trials involving patients with macular telangiectasia (MacTel) type 2.¹ From a pharmacokinetic standpoint, however, delivery of CNTF has some challenges. Its intraocular half-life is extremely short (estimated between 1 to 3 minutes), making treatment with bolus injections of CNTF non-viable. Additionally, it is a protein, making it challenging to use in polymer release systems, which are traditionally optimized for the delivery of small molecules, and it does not readily penetrate the blood-retina barrier.²

To address these issues, an encapsulated cell technology, revakinagene tarorectel-lwey (Encelto, Neurotech Pharmaceuticals), has been developed to continuously deliver CNTF inside the vitreous cavity and can remain productive for many years. The therapy consists of a semipermeable polymer membrane capsule

that contains a genetically engineered human retinal pigment epithelial cell line designed to express CNTF at a consistent rate. The capsule is surgically implanted into the vitreous cavity and anchored to the overlying sclera using a prolene suture.

Early studies of revakinagene tarorectel-lwey found that it consistently produced CNTF over a 2-year period.² More recently, revakinagene tarorectel-lwey demonstrated efficacy in MacTel patients in two phase 3 clinical trials, and safety studies have demonstrated it is generally well tolerated.³ The device was recently approved by the FDA for use in patients with MacTel type 2.⁴

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EYP-1901 (Duravyu, Eyepoint Pharmaceuticals), which releases vorolanib,^{5,6} and OTX-TKI (Axpaxli, Ocular Therapeutix), which releases axitinib.^{7,8} EYP-1901 has demonstrated zero-order kinetics in preclinical studies, with near steady-state drug levels achieved within 4 hours of dosing and maintained through 8 months.⁹ Preclinical studies of OTX-TKI have demonstrated steady-state drug levels and consistency in axitinib concentrations across retinal and choroidal tissues 6 months after a single injection of OTX-TKI.⁷ TKIs have also been investigated in nonproliferative diabetic retinopathy and DME.¹⁰

The port delivery system (PDS; Susvimo, Genentech/Roche) is a surgically implanted device designed for in-office refills and can deliver a continuous supply of ranibizumab to patients, with refills given in-office every 6 months in the phase 3 wet AMD trial.¹¹ Data from a population pharmacokinetics model showed release of ranibizumab from the PDS with an estimated half-life of 106 days.¹² The PDS is currently FDA-approved for the treatment of wet AMD and DME.¹¹

DIABETIC MACULAR EDEMA

At a population level, patients with DME have demonstrated lower adherence rates with treatment than patients with wet AMD, and approximately two-thirds of patients with DME experience at least one barrier to treatment or attending a medical visit.¹³ Patients with DME who receive anti-VEGF therapy have been reported to require a median of 15 or 16 injections over a 2-year period,¹⁴ further highlighting the need for strategies that can reduce the number of treatments in this patient population.

One approach that has been explored for bridging this gap

is the use of a fluocinolone acetonide intravitreal implant (Iluvien, ANI Pharmaceuticals), which is indicated for the treatment of DME in patients who have not manifested an IOP response to prior corticosteroid treatment. This implant is nonbiodegradable and can release fluocinolone acetonide for up to 3 years, potentially reducing retinal thickness fluctuations.¹⁵ Most importantly for this therapeutic, the ongoing prospective, randomized NEW DAY trial is analyzing its use for first-line therapy in eyes with DME compared with 2 mg aflibercept (Eylea, Regeneron).¹⁶

The dexamethasone intravitreal implant (Ozurdex, Abbvie) is also approved for the treatment of DME and uses a propriety drug delivery system with a polymer matrix.¹⁷ Preclinical pharmacokinetic models with and without vitrectomy have indicated the presence of dexamethasone for a minimum of 31 days.¹⁸

In patients with DME and diabetic retinopathy treated with the PDS, pharmacokinetic data showed that continuous delivery was achieved over an every-24-week refill interval. The PDS facilitates continuous drug release into the vitreous through passive diffusion.¹⁹

LOOKING AHEAD

Beyond sustained-release implants, other strategies being explored to enhance the intraocular pharmacokinetics of retinal therapies include gene therapies; the relatively simplistic approach of dose escalation, which has been found to reduce the number of required intravitreal injections in some cases; the use of micro- and nanoparticles; and periocular routes of administration, such as suprachoroidal delivery.²⁰

(Continued on page 55)

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Prethy Rao, MD
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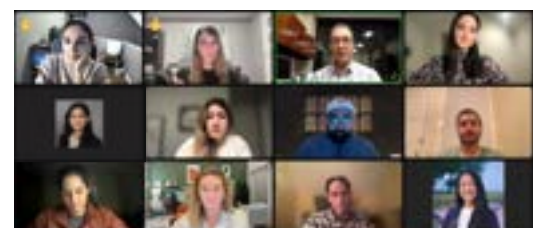
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A NEW TECHNIQUE FOR MYOPIC TRACTION MACULOPATHY



Learn about wristwatch macular buckling and how we have optimized the procedure.

BY NIKOLOZ LABAURI, MD; TEKLA MAMAGISHVILI, MD; MONIKA ZALINIAN, MD; AND SUPRIYA DABIR, MD, PHD

Myopic traction maculopathy (MTM) involves a spectrum of pathological changes to the macula in high myopia and is caused by two main mechanisms: 1) internal traction due to a posterior hyaloid membrane, rigid vasculature of the neurosensory retina, and/or an epiretinal membrane and 2) external outpouching of the thinned posterior scleral wall (ie, posterior staphyloma).¹ MTM comprises numerous posterior retinal abnormalities and can manifest in isolation or combined with posterior vitreoschisis, epiretinal membrane, foveoschisis, lamellar macular hole, full-thickness macular hole, and/or posterior retinal detachment.²

Surgical treatment focuses on addressing the causative mechanisms of MTM and takes two main approaches: 1) an internal approach with pars plana vitrectomy to relieve internal traction by removing the vitreous, epiretinal membrane, or internal limiting membrane and 2) an external approach with posterior scleral indentation (macular buckling) to shorten the axial length of the eye and oppose the sclera, choroid, and retinal pigment epithelium posteriorly toward the photoreceptors of the neurosensory retina.³⁻⁷ MTM can be observed or treated either with macular buckling, vitrectomy, or a combination of both.

Here, we describe a novel device and implantation technique—wristwatch macular buckling—that has proven successful in our OR.

THE PROCEDURE

The device, assembled by the operating surgeon prior to implantation, is made of solid silicone rubber that is trephined with a 7 mm corneal punch to harvest a round 7 mm silicone rubber head (Figure 1A). It has a concave internal surface and a preplaced 2.5 mm groove on its external surface made for the silicone band placement.

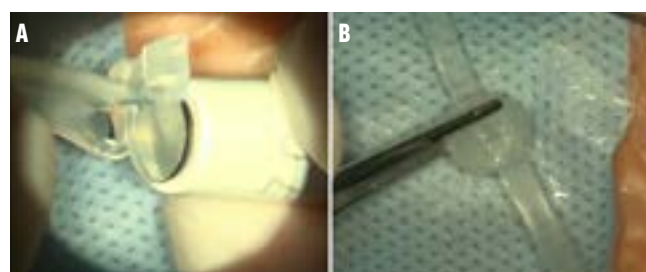


Figure 1. A 7 mm corneal trephine cuts a round indenting head from the silicone (A). The assembled buckling device resembles a wristwatch (B).

Use a 2 mm crescent knife to make partial-thickness tunnels at both ends of the external groove, through which the silicone band is passed and firmly fixated. The assembled device resembles a wristwatch, hence its name (Figure 1B).

Perform a circumferential 360° conjunctival peritomy to isolate and sling (using 4-0 silk traction sutures) all recti muscles. Pass the proximal end of the silicone band under the superior oblique and superior rectus muscles and bring it from the superotemporal to the superonasal quadrant. Next, pass the distal end of the silicone band under the lateral rectus and the inferior oblique muscles. Repeat these steps with the inferior rectus. Pull the proximal and distal ends of the silicone band nasally to slide the indenting 7 mm head across the sclera and bring it under the foveal projection.

Confirm the appropriate position of the buckle head through transvitreal observation. Then, use a 2 mm crescent knife to make two partial-thickness scleral tunnels in an oblique fashion in the superonasal and inferonasal quadrants. Pass both ends of the band through the appropriate scleral tunnels and secure them using a Watzke sleeve. Lastly, adjust both ends of the band to center the head of the implant under the fovea while applying mild indentation over the macular region to flatten the posterior staphyloma and

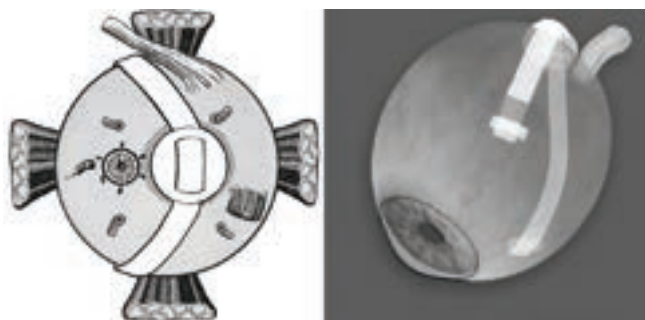


Figure 2. A drawing of the buckling element shows the head indenting the foveal zone and the ends of the band passing through the scleral tunnels, secured with Watzke sleeves.

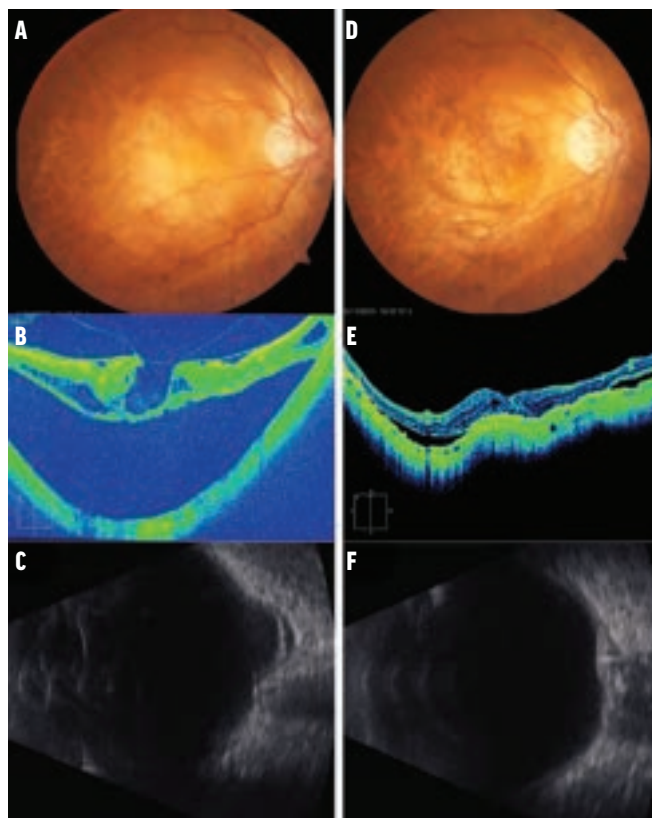


Figure 3. This patient's MTM involves vitreomacular traction (A), an epiretinal membrane (B), foveoschisis, and posterior retinal detachment (C). Seven months post-vitreotomy and supplementary macular buckling, the retina is attached with minimal subretinal and intraretinal fluid (D and E). B-scan echography shows a posterior scleral outpouching and a reshaped staphyloma due to the buckle indentation (F).

reshape the eye wall. Adjust the Watzke sleeves to prevent the band from slipping and help maintain the constant indenting position (Figure 2).

If vitrectomy and membrane peeling is planned in combination with wristwatch macular buckling, place the buckle implant first and center it properly before conducting the vitrectomy, membrane peeling, and tightening of the buckle to achieve adequate indentation after the vitreous cavity is completely filled with air and prior to the air-gas exchange. Finally, trim the silicone band at both sides,

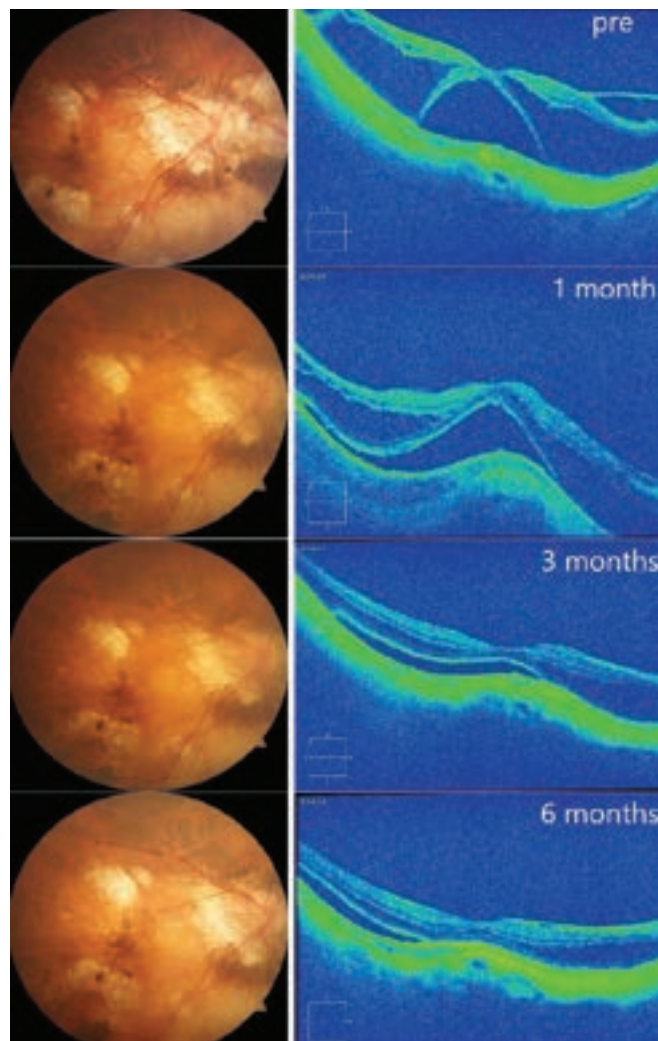


Figure 4. This patient has preoperative vitreoschisis, retinoschisis, and a posterior retinal detachment. Postoperative months 1, 3, and 6 show reabsorption of subretinal fluid and reduction of retinoschisis that is directly related to gradual improvement in visual acuity.

remove the traction sutures from the recti muscles, and ensure Tenon capsule and the conjunctiva are closed.

This buckling method has numerous advantages, including:

- The concave indenting head provides flat indentation, inducing minimal, if any, metamorphopsia.
- Because the indenting head has a large diameter (7 mm), it captures the foveal zone more easily.
- During the procedure, the two-point fixation of the plomb provides flexibility in adjusting both ends of the band and quick centration of the indenting head.
- The procedure doesn't require lateral muscle resection to access the posterior pole.
- The implant is not related to conjunctival bulging; thus, there is a lesser probability of extrusion.
- The buckle is fixed onto the sclera without sutures.
- The device does not require customized manufacturing and is cost-effective.

CASE STUDIES

At our center, we operated on seven eyes of six MTM patients between April 2023 and November 2024. We performed wristwatch macular buckling with pars plana vitrectomy and membrane peeling in six eyes and macular buckling alone in one eye.

All patients achieved good functional and structural outcomes, including retinal reattachment, macular hole closure, and retinoschisis resolution. Visual acuity improved in all except one patient, in which the retina was reattached and the central scotoma disappeared but BCVA didn't change from baseline (Figure 3). In the case where standalone macular buckling was performed, intra- and subretinal fluid is still in the process of reabsorption (Figure 4).

Macular buckling is beneficial in certain cases of MTM where retinal tissue is insufficient and unable to cover the broad area of posterior staphyloma, making macular hole closure difficult. Mastering this procedure requires a learning curve to avoid damaging the optic nerve and inducing excessive metamorphopsia related to high buckle indentation. ■

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(Continued from page 51)

Tactics aimed at enhancing the pharmacokinetics of existing and future retinal therapeutics have the potential to meaningfully improve patients' lives. This space is evolving, and it is exciting to participate in the development of these therapies, especially in concert with the potential role for remote monitoring approaches, such as home OCT. ■

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RISING STARS IN RETINA

RT
Retina Today

YoungMD>Connect

Get to know outstanding retina fellows from the class of 2025.



Adrian Au, MD, PhD

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

I first knew I wanted to become a retina specialist when I was in medical school and had the chance to see the retina with indirect ophthalmoscopy—that first experience sealed it for me. It is the most elegant and beautiful organ, whether you see it in normal or pathologic states.

In addition, being able to identify and treat disease, improve vision, and make a meaningful difference in someone's life remains the greatest reward of becoming a retina specialist.

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

I have been fortunate enough to be mentored by many outstanding clinicians and scientists along my journey. Among them I include Allan E. Kreiger, MD; David Sarraf, MD; Steven Schwartz, MD; Pradeep S. Prasad, MD, MBA; Hamid Hosseini, MD; Irena Tsui, MD; Jayanth Sridhar, MD; Colin A. McCannel, MD; Tara A. McCannel, MD, PhD; Kirk Hou, MD, PhD; Edmund Tsui, MD, MS;

Michael S. Ip, MD; Michael B. Gorin, MD, PhD; Hajir Dadgostar, MD; and Rishi P. Singh, MD. Each has shown me how to treat patients—and the retina—with the utmost respect and care.

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

One of the most memorable moments of my fellowship was celebrating the life of Dr. Kreiger. Witnessing the profound effect he had on his patients, the fellows he mentored, and the field of retina was

to diagnostic and therapeutic innovations that enable us to treat patients more effectively, advancing the boundaries of what's possible in retina care.

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

Push yourself to continuously grow and adapt. Retina is a rapidly evolving field, and the knowledge you gain during training serves as a foundation, not a limit. Stay curious, embrace new developments, and strive to refine your skills to provide the best care for your patients. ■



FIRST CAREER MILESTONE

Dr. Au is joining the faculty at the University of California, Los Angeles.

truly inspiring. It was a humbling reminder of how a single individual can leave an enduring legacy through exceptional care, mentorship, and innovation in retinal surgery.

RT: What are you hoping to accomplish once you are in practice?

In 5 to 10 years, I envision myself practicing at an academic institution, delivering the highest level of clinical and surgical care. I aspire to mentor residents and fellows and foster the next generation of retina specialists. Additionally, I hope to contribute

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EXPANDED TRANSFER OF CARE POLICIES IN RETINA



Here's what's old and how to implement what's new.

BY JOY WOODKE, COE, OCS, OCSR

Beginning in 2025, the Centers for Medicare and Medicaid Services broadened their policies related to transfer of care during the global period.¹ Their goal is to improve the accuracy of the global surgery payment and tracking processes.

WHAT'S THE SAME?

There is no change to the documentation requirements or coding for a formal, documented transfer of care agreement, or comanagement. Primarily reported with cataract-related procedures, ophthalmology uses a few transfer of care modifiers, including:

- Modifier -54: Surgical care only
- Modifier -55: Postoperative management only

When an external physician is the sole provider of preoperative care, modifier -56 is used; however, it is rarely used in ophthalmology.

Formal comanagement arrangements are initiated by patient request. For example, a surgical patient might request such an arrangement if they live 2 hours from the surgical site and wish to minimize their travel time for postoperative visits. Both the patient and the nonoperating practitioner must agree to the arrangement.

After surgery, there is a formal transfer of care documented by the surgeon. This should include the date of transfer and relevant clinical information.

The coding and claim submission would reflect this arrangement to accurately report the global days provided. For example, if a patient is comanaged for a vitrectomy

(CPT code 67036) performed on April 1 in the right eye and the surgeon provided 7 of the 90 days of postoperative care before transferring care, the surgeon's claim should be reported as:

- 67036 -54-RT
- 67036 -55-RT – prorated fee
 - Report prorated date range in item 19: 4/2/25–4/8/25

The comanaging clinician's claim should be reported as:

- 67036 -55-RT – prorated fee
 - Report prorated date range in item 19: 4/9/25–6/30/25

There are additional compliance, ethical, and legal pitfalls to avoid related to comanagement. AAO members can explore additional guidance in the AAO's Comprehensive Guidelines for the Co-Management of Ophthalmic Postoperative Care.²

WHAT'S NEW?

When the retina specialist provides only the surgical component of the global package, modifier -54 must be reported with the CPT code for the surgery. This is an expansion from the previously established formal comanagement agreement, which now includes an informal, nondocumented but expected transfer of care.

If, for example, the patient notifies the surgeon that they will be moving out of state and will not be coming back for postoperative care, modifier -54 is required for the surgical claim. There are no requirements for the use of modifiers

BEGINNING IN 2025, THE CENTERS FOR MEDICARE AND MEDICAID SERVICES BROADENED THEIR POLICIES RELATED TO TRANSFER OF CARE DURING THE GLOBAL PERIOD. THEIR GOAL IS TO IMPROVE THE ACCURACY OF THE GLOBAL SURGERY PAYMENT AND TRACKING PROCESSES.

-55 and -56 for external providers in these cases, which continue to be used when there is a formal, documented transfer of care established prior to surgery.

E/M ADD-ON CODE

Medicare also implemented a new E/M add-on code, HCPCS code G0559, which is defined as: Postoperative follow-up visit complexity inherent to evaluation and management services addressing surgical procedure(s), provided by a physician or qualified health care professional who is not the practitioner who performed the procedure (or in the same group practice) and is of the same or a different specialty than the practitioner who performed the procedure, within the 90-day global period of the procedure(s), once per 90-day global period, when there has not been a formal transfer of care.

The reimbursement for this code captures the additional time and resources it takes to provide postoperative care when the retina specialist themselves did not perform the surgery or was not involved in a formal, documented transfer of care agreement.

There are four elements that must be confirmed through documentation when reporting this code:

1. Request and review the surgical operative report and other chart documentation to confirm relevant clinical details.
2. For a procedure outside the physician's specialty, research the procedure, expected postoperative care, and possible complications.
3. Document the examination and postoperative progression.
4. Communicate the patient's status to the surgeon who performed the procedure.

This add-on code was designated by Medicare and is associated with a total relative value unit of 0.27, which translates to a national average payment of \$8.73.

HCPCS code G0559 should not be reported:

- by the surgeon who performed the surgery,

- by any provider in the same practice as the surgeon,
- by the surgeon or co-managing physician when a formal agreement has been executed,
- more than once during the 90-day global period,
- with an eye visit code (92002, 92012, 92004, 92014), or
- to any payers other than Medicare Part B, unless they have a published coverage policy.

G0559 Case Study

A Medicare Part B patient who had a retinal detachment repair (CPT code 67108) 1 month ago by a retina specialist in a different state presents with visual disturbances. The retina specialist seeing the patient now requests and reviews the patient's chart notes and the operative report. The provider evaluates the patient, documents their postoperative status, and sends a letter to the surgeon.

This office visit meets all the requirements for HCPCS code G0559 and should be billed with an appropriate level of E/M.

The patient returns in 1 week for a follow-up visit. G0559 should not be reported for this encounter, as it can only be billed once during the entire 90-day global period.

STAY IN THE KNOW

Remain updated and learn more about retina coding by visiting aao.org/retinapm. ■

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GEOGRAPHIC ATROPHY AND VISUAL PROGNOSIS

Complement inhibitor therapies do not reverse vision loss, but they may help preserve patients' functional vision longer.

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By Daniel K. Bennett, MD

When it comes to educating patients about the visual prognosis associated with geographic atrophy (GA), I tend to be a

hopeless optimist—I focus on what available treatments can do rather than what they cannot. Based on clinical trial evidence, we know that complement inhibition slows the rate of lesion progression, thereby helping preserve viable retina and retain useful vision. As a result, we cannot promise patients they will restore vision, but we can assure them there is a good chance therapy can extend the time with useful vision to enjoy normal daily activities.



Discussing Visual Prognosis

Many patients we encounter have already experienced some element of vision loss, so they understand this is a pathology with real-world implications. If they have not yet experienced vision loss, it can be a difficult message to convey. Our focus is on having an honest dialogue that properly conveys the appropriate goals and outcomes of initiating therapy. This means being honest that currently available complement inhibitors are not designed to stop the condition; rather they are designed to slow the pathology. Furthermore, it means relaying our goal is to keep them as functional as possible for as long as possible.

While current treatments for GA are not perfect, they are often better than doing nothing. We are still in the nascent era of GA treatment, and I have every confidence the eye care community will learn to utilize the available treatments more effectively in real-world practice. This includes gaining better insights into patient selection and when to start therapy, which should translate to better outcomes. As well, the pipeline of GA treatments is rich and deep—the current modalities may be temporizing agents, but they may also be adequate to stabilize our patients long enough for regenerative and restorative agents to become clinically available.

FUNCTIONAL TESTING MODALITIES

1

Microperimetry – A visual field test that incorporates perimetry and retinal imaging to allow direct mapping of the stimulus in the region of interest, thus providing the ability to correlate functional information with structural data.

2

Low-Luminance Visual Acuity – Visual acuity testing that is performed with a significantly reduced light level, typically using a neutral density filter placed in front of the eye; differences between normal visual acuity and low luminance visual acuity can indicate early signs of retinal damage.

3

Reading Speed Test – Typically assessed by measuring the number of words an individual can read correctly in a specific timeframe, often using standardized reading charts. Reading speed tests may be more sensitive to functional impairments compared to BCVA alone.



What Is The Role of Measuring Vision?

Whenever possible, we want to base our clinical management decisions on objective data. The problem we face in real-world practice is the methods for measuring functional visual acuity in the clinic are subjective and unreliable. For example, we use ETDRS charts in our lanes as opposed to Snellen visual acuity charts. The problem is patients can memorize the letters on the ETDRS chart or use eccentric fixation to read the chart. As a consequence, visual acuity measurements are not a good barometer for the risk of progression, nor do they tell us much about what the patient is experiencing in their everyday world.

A number of more objective functional assessments are currently being investigated for potential clinical use (see *Functional Testing Modalities*). In particular, microperimetry testing is a modality that may highlight areas of functional loss not appreciated by conventional testing. Likewise, low-luminance visual acuity and testing reading speed are much better ways of quantitatively determining functional limitations versus relying on patient reported symptoms.

In our experience, however, functional testing is more valuable as a research tool than as a diagnostic tool to guide clinical decision making. A large issue with functional testing is incorporating it into a busy clinical

schedule can be a rate-limiting step: the time it takes to perform such testing does not justify the yield. Fundamentally, the results of functional testing would not affect the decisions we make in the clinic on a daily basis.

Conclusion

Functional testing in patients with GA, as currently construed, has limited clinical value in terms of guiding management decisions. As more research is done, and perhaps as AI makes inroads into clinical practice, the calculus will change. Certainly, functional testing has the theoretical advantage of picking up nascent GA before objective imaging studies. At the current time, however, what we learn from functional testing is not correlated with the risk of progression or potential for vision loss. Modalities that guide patient conversations in this regard are certainly welcome, but we simply need more data before they are implemented in real-world practice. ■

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- Financial disclosures: Speakers Bureau (Genentech)

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POSTERIOR PLACOID CHANGES DUE TO NUTRITIONAL DEFICIENCY



Low levels of vitamin A may be the culprit behind this ocular condition.

BY ERIC W. LAI, MD; BRIAN K. DO, MD; AND SIDNEY A. SCHECHET, MD

Posterior placoid changes (PPC) are an uncommon clinical finding characterized by large, yellow-white circular inflammatory lesions in the posterior pole that affect the outer retinal layers, retinal pigment epithelium (RPE), and underlying choriocapillaris.^{1,2} Acute syphilitic posterior placoid chorioretinitis has been well documented in the literature and remains at the top of the differential in its association with PPC.^{3,4} Other ocular diseases on the differential for PPC include tuberculous chorioretinitis, acute posterior multifocal placoid pigment epitheliopathy, persistent placoid maculopathy, serpiginous choroiditis, multifocal choroiditis, cancer-associated retinopathy, and more.^{5,6}

PPC has yet to be well described in association with nutritional deficiencies. In this article, we describe an interesting case of a patient with a history of hepatic malignancy in remission who presented with bilateral PPC and a unilateral macular hole in the setting of underlying vitamin A deficiency.

CASE REPORT

A 72-year-old pseudophakic man with a history of hepatocellular carcinoma (HCC) in remission was referred to our retina clinic for a macular hole in his right eye and dry AMD in each eye. He described symptoms of dry eyes, decreased night vision, and overall worsening vision in each eye for 1 year. On review of systems, he reported a 3-week rash on his ankle and had generally felt unwell for several months prior to presentation.

Examination Findings

His BCVA was 20/60 OD and 20/50 OS, and Ishihara color plates were 1/15 OU. On anterior examination, each eye had significant punctate epithelial erosions but no signs of anterior uveitis. Posterior examination revealed subtle, well-circumscribed, hypopigmented placoid-like lesions in the posterior pole of each eye, which appeared

diffusely hypoautofluorescent on fundus autofluorescence (FAF). In the peripheral retina, there were numerous, scattered, yellow-white punctate drusenoid deposits in each eye, corresponding to a mottled appearance on FAF. OCT identified a stage 2 full-thickness macular hole with trace cystoid macular edema in his right eye and focal RPE detachment in his left eye; furthermore, each eye showed diffuse outer nuclear layer attenuation, external limiting membrane disruption, ellipsoid zone loss, and mottled RPE changes (Figures 1 and 2).

Fluorescein angiography (FA) revealed early hypofluorescence throughout the posterior pole with distinct outer round margins in each eye and stippled hyperfluorescence and late staining with late disc leakage in each eye. ICG angiography was unremarkable.

Further Workup

The patient denied any history of syphilis, tuberculosis, or family history of retinal disease. He was advised to present to the emergency department to complete occult infectious, inflammatory, and paraneoplastic workup. However, he left against medical advice prior to completing this workup; 2 months later he was evaluated by a uveitis specialist due to his VA worsening to 20/200 OD and 20/100 OS. His repeat retinal examination was unchanged, other than worsening outer retinal disruption on macular OCT in each eye. An electroretinogram (ERG) showed extinguished rod and cone responses, delayed a-waves on full-field ERG, and diffuse macular depression on multifocal ERG in each eye. He was again advised to complete the laboratory workup and to follow up with his medical oncologist to ensure stable remission of HCC.

Systemic workup was eventually completed, which revealed negative fluorescent treponemal antibody absorption, rapid plasma reagin, interferon-gamma release assay, HLA-A29, antinuclear antibody, rheumatoid factor, angiotensin-converting enzyme, and Lyme testing. His liver

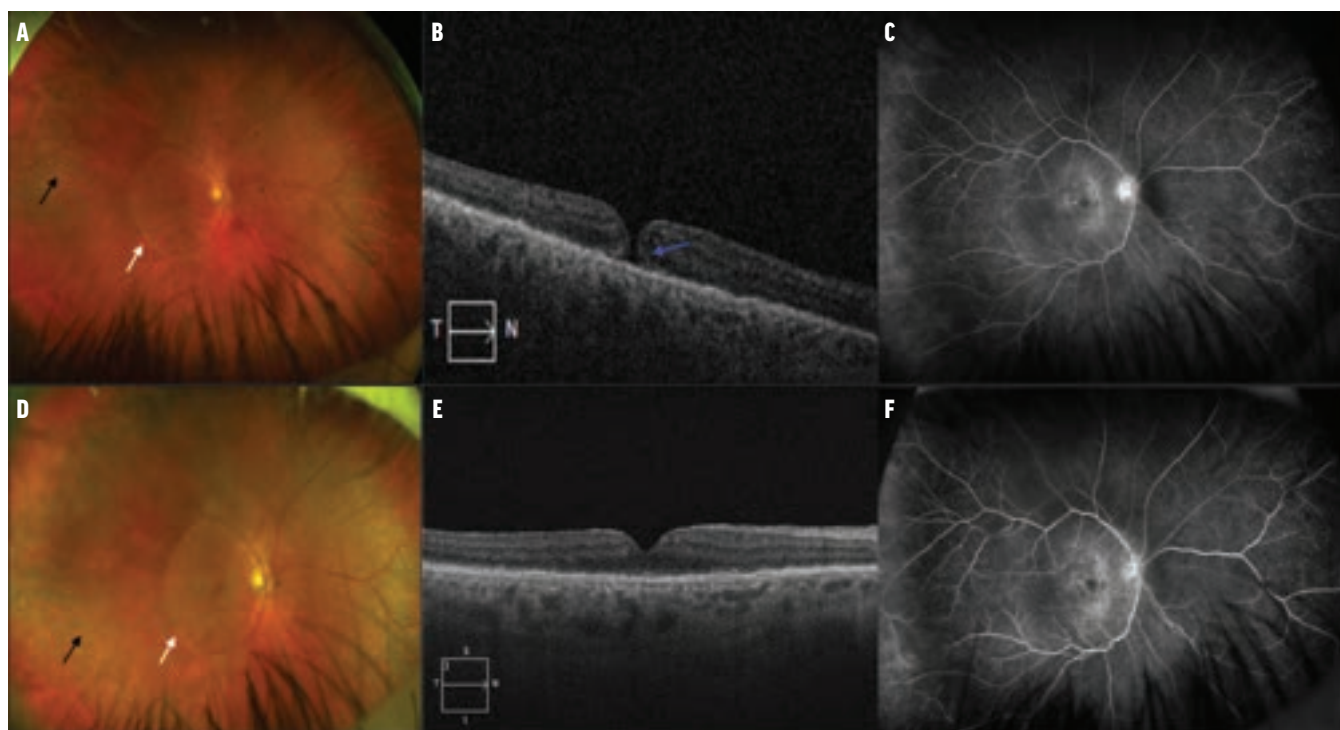


Figure 1. Fundus photography, OCT, and FA of the right eye were obtained at presentation (A-C) and 2 months post-vitamin A repletion (D-F). Fundus photography showed a faint, well circumscribed placoid-like lesion (A and D, white arrows) in the posterior pole, as well as peripheral yellow-white lesions (A and D, black arrows). OCT showed a stage 2 full-thickness macular hole (B, blue arrow), diffuse outer layer attenuation, external limiting membrane disruption, ellipsoid zone loss, and RPE mottling. OCT findings improved after vitamin A repletion (E). Late-phase FA showed disc leakage (C) with stippled hyperfluorescence and staining throughout the posterior pole, with less distinct margins and less disc leakage after initiation of vitamin A supplementation (F).

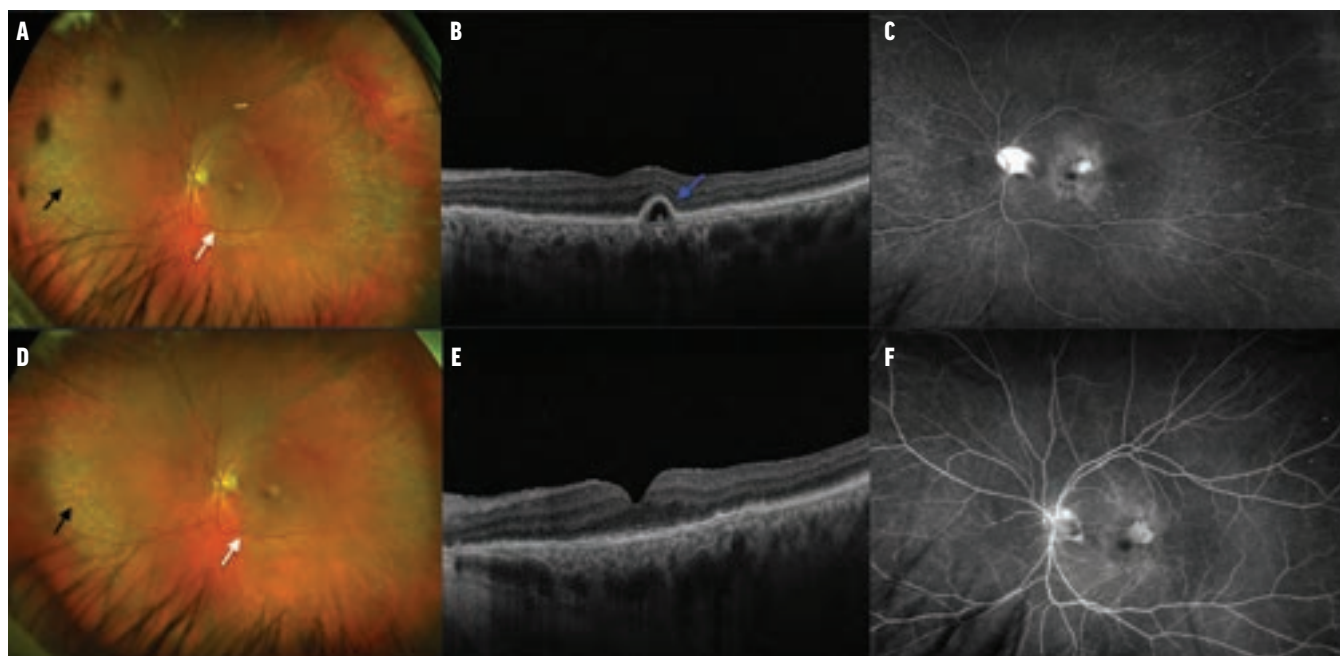


Figure 2. Fundus photography, OCT imaging, and FA of the left eye obtained at presentation (A-C) and 2 months post-vitamin A repletion (D-F) showed similar findings and improvements as was seen in the right eye. Fundus photography showed a faint, well circumscribed placoid-like lesion (A and D, white arrows) and peripheral yellow-white lesions (A and D, black arrows). OCT showed a serous pigment epithelium detachment (B, blue arrow) that improved with supplementation (E). Similar to the right eye, late-phase FA showed disc leakage (C) with stippled hyperfluorescence and staining, with improvement after vitamin A supplementation (F).

enzymes were at baseline, and HCC was found to be stable, per his oncologist. Unexpectedly, he was found to have a severely low vitamin A level (6.2 µg/dL, reference range 22.0 µg/dL – 69.5 µg/dL).

The patient was started on vitamin A supplementation 50,000 units via intramuscular delivery weekly with transition to oral repletion.

Follow-Up

Six weeks later, he subjectively reported improvements in nyctalopia, dry eyes, and general fatigue. His serum vitamin A level raised to 11.9 µg/dL, and his BCVA improved to 20/50 OD and 20/40 OS. There were fewer distinct placoid-like macular lesions in each eye and decreased disk leakage on FA. Interestingly, on OCT, the macular hole in the right eye had closed without pharmacologic (topical) or surgical intervention.

Three months later, his vitamin A level was 22.3 µg/dL. Repeat ERG post-vitamin A repletion showed significant improvement in rod and cone function. His BCVA improved to 20/30 OU, and Ishihara color plate testing was 5/15 in each eye.

VITAMIN A AND VISION

Vitamin A is a fat-soluble vitamin that serves an important role in visual phototransduction and maintaining conjunctival and corneal epithelium health.⁷ In the United States, gastrointestinal (GI) malabsorption resulting from conditions such as inflammatory bowel disease, Celiac disease, or bariatric surgery is the most common cause of vitamin A deficiency.⁸ Vitamin A is stored in the liver; thus, patients with hepatobiliary disease, as was the case presented here, have poor reserve to begin with.⁹

Symptoms of vitamin A deficiency include nyctalopia, fatigue, and decreased vision, while associated anterior examination findings include conjunctival xerosis, Bitot spots, and keratomalacia.^{10,11} Retinal findings are typically described as multiple round, yellow-white lesions in the macula and midperiphery.^{12,13} OCT findings typically include subretinal hyperreflective deposits alongside complete RPE and outer retinal atrophy.¹⁴ Repletion with vitamin A typically reverses these clinical findings and symptoms.¹¹ Interestingly, there are no standardized guidelines for routine screening of vitamin A deficiency in patients with GI comorbidities.¹⁵

While posterior placoid changes have been documented in association with many diseases including syphilis, tuberculosis, and inflammatory white-dot syndromes, PPC and macular hole have not been well described in association with vitamin A deficiency.

Macular holes and cystoid macular edema have also not been associated with vitamin A deficiency.¹⁶ As vitamin A deficiency has been described in the literature in

association with atrophic changes in the RPE, it is possible that a similar process could have caused a full-thickness macular hole to form over time, which subsequently closed with repletion.¹⁷

THOROUGH WORKUP IS WARRANTED

Bilateral placoid lesions in the retina often point to systemic etiologies and should be worked up for infectious, inflammatory, autoimmune, and paraneoplastic causes. In patients with GI comorbidities who describe general fatigue, nyctalopia, and progressively worsening vision, consider vitamin A deficiency as an underlying etiology. Early detection and vitamin A repletion can prevent permanent retinal injury and lead to significant visual improvement. ■

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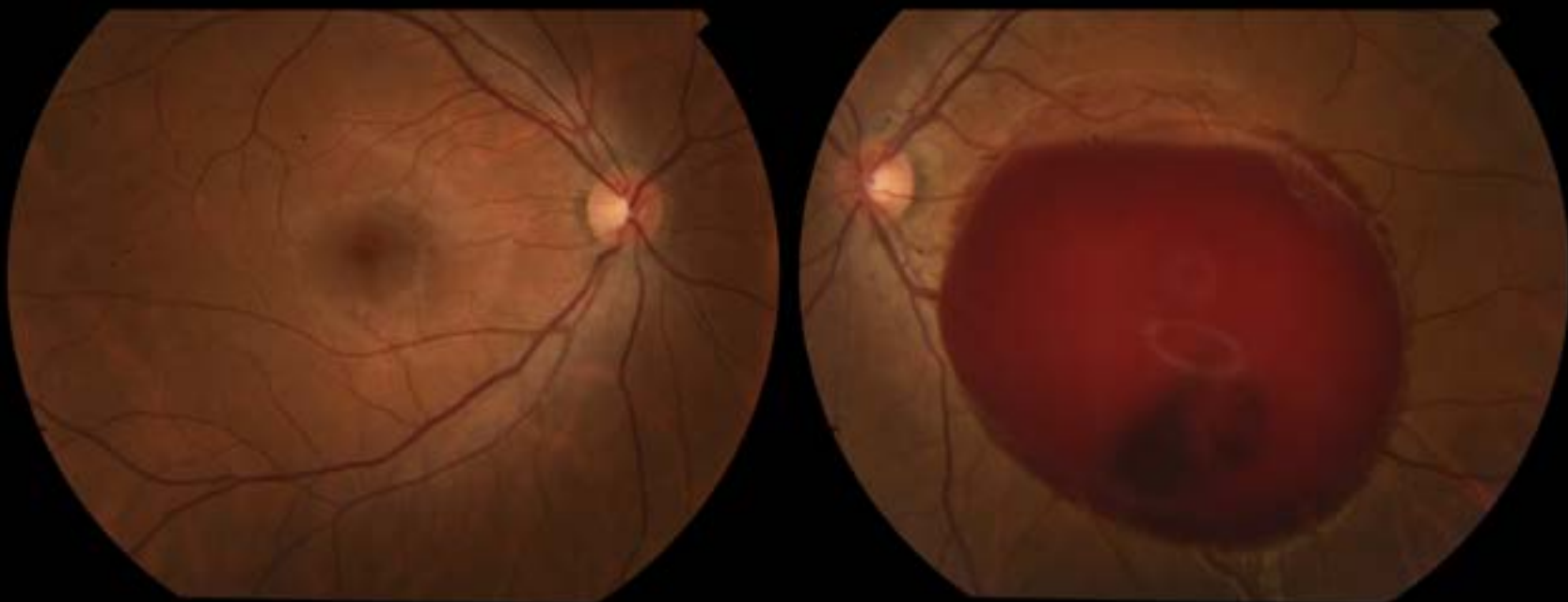


FIGURE 1

VALSALVA RETINOPATHY: THE SILENT BLEEDER

A rare, potentially severe retinal hemorrhage can occur as a result of certain activities.

BY INÊS CERDEIRA LUDOVICO, MD; PATRÍCIA SILVA, MD; JOANA FERREIRA, MD; ANA LUÍSA BASÍLIO, MD;
AND CARLOS BATALHA, MD

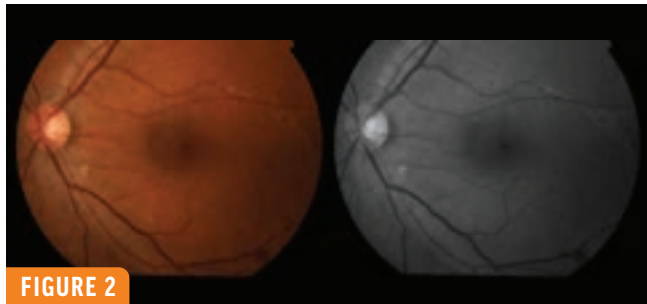
Valsalva retinopathy is a rare condition first described in 1972 as a preretinal hemorrhage with a clinical presentation of mild to severe unilateral visual loss.¹ It typically occurs in otherwise healthy individuals after an event that raises intrathoracic or intraabdominal pressure, such as coughing, vomiting, weightlifting, straining for bowel movement, sexual intercourse, or childbirth.

There is no known sex, race, or age predilection described in the literature. It results from forcible expiration against a closed glottis, causing a rise in venous blood pressure. In individuals with incompetent valves in the venous systems of the head and neck, this pressure can trigger a

spontaneous rupture of perifoveal superficial retinal blood vessels with consequent hemorrhagic detachment of the internal limiting membrane or onto the subhyaloid space.²

CASE REPORT

A 26-year-old man with no relevant history presented to our emergency department with sudden visual acuity loss in his left eye accompanied by a reddish hue in his vision after intense vomiting due to acute gastroenteritis. His BCVA was hand motion at 3 feet OS. The slit-lamp examination and his IOP measurements were unremarkable. Fundoscopic examination of the left eye revealed a large, round premacular hemorrhage approximately 6 disc areas

**FIGURE 2**

in size containing bright red preretinal blood with a convex surface toward the vitreous with some movement (Figure 1).

We initially performed a Nd:YAG laser hyaloidectomy to release the blood into the inferior vitreous cavity for a faster recovery, but the treatment was unsuccessful, likely due to blood coagulation. After 1 week, the patient underwent pars plana vitrectomy with restoration of his BCVA to 20/20 OS (Figure 2). ■

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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 taroretsel-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 $\geq 2\%$ patients and with higher frequency in ENCELTO group compared to Sham group in Study 1 and Study 2.

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

Adverse Reactions	ENCELTO	Sham
	(N=117)	(N=111)
	n (%)	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.

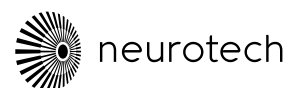
Geriatric Use

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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NOW APPROVED

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



Harness the tech with the survival effect ON PHOTORECEPTORS¹



See the data behind ENCELTO

Scan the QR code or visit
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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

ENCELTO is contraindicated in patients with active or suspected ocular or periocular infections, and in patients with known hypersensitivity to Endothelial Serum Free Media (Endo-SFM).

WARNINGS AND PRECAUTIONS

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

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

The most common adverse reactions ($\geq 2\%$) 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 following pages.

Reference: ENCELTO [prescribing information]. Cumberland, RI. Neurotech Pharmaceuticals, Inc.

