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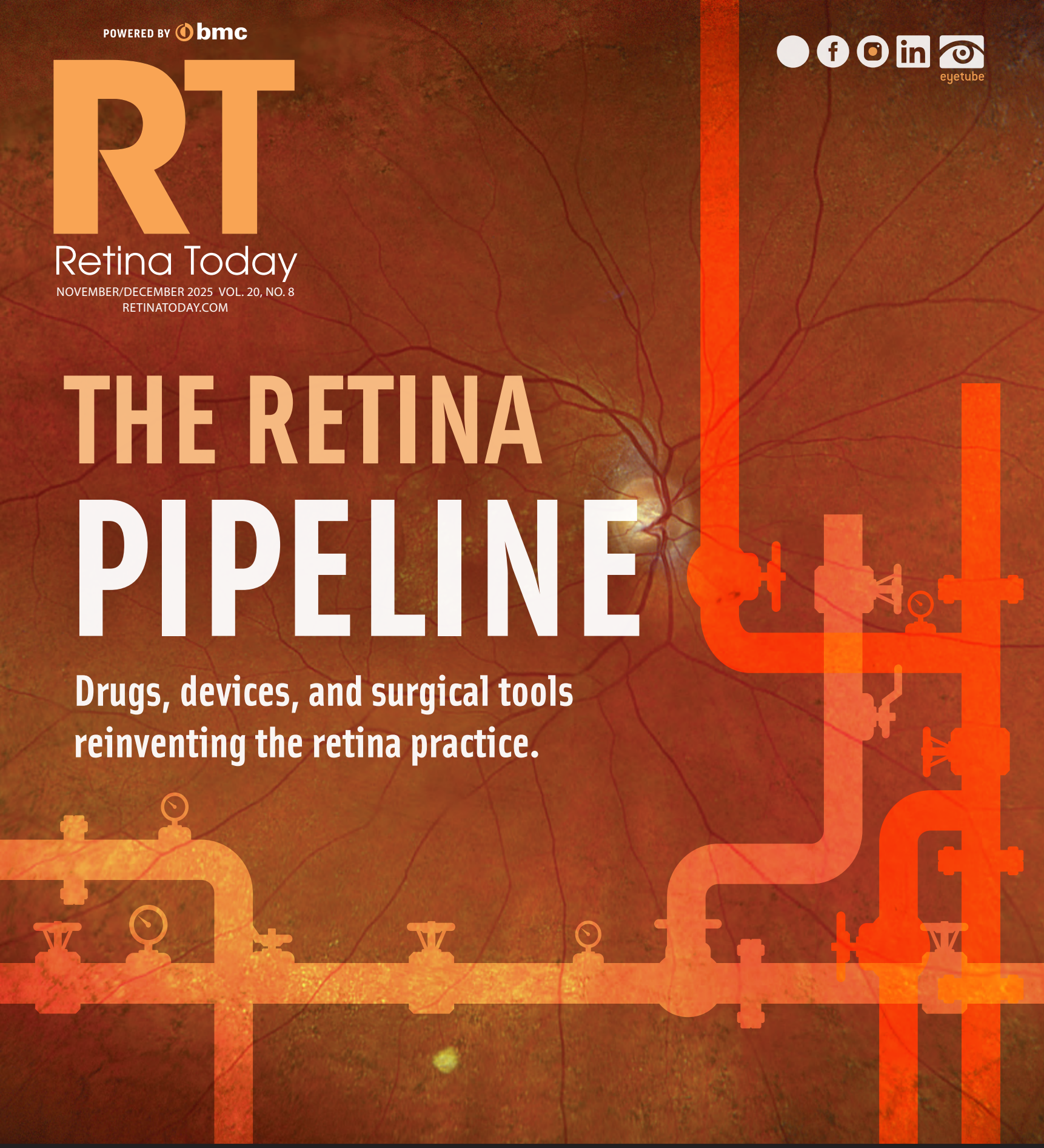
eyetube

THE RETINA PIPELINE

Drugs, devices, and surgical tools reinventing the retina practice.



TRIALS AND INNOVATIONS IN GA THERAPY | ROBOTICS FOR RETINAL SURGERY | ADVANCES IN TREATING DIABETIC EYE DISEASE

SYFOVRE slowed GA progression with **increasing effects over time**[1]

Through Year 2 (OAKS and DERBY), SYFOVRE slowed GA lesion growth (mm^2) vs sham pooled, with the greatest differences observed in the last 6 months[1]

- OAKS: **22%** (-0.87 mm^2 [-1.27 to -0.47]) monthly and **18%** (-0.72 mm^2 [-1.10 to -0.33]) EOM
- DERBY: **18%** (-0.73 mm^2 [-1.14 to -0.31]) monthly and **17%** (-0.70 mm^2 [-1.11 to -0.28]) EOM

SEE WHY EARLY TREATMENT MATTERS TO SLOW GA PROGRESSION
StartSYFOVREearly.com

GALE Trial Limitations: The analysis for GALE utilized a projected sham and may not reflect rate of change of all patients with GA. Projected sham assumes linear growth rate from Years 2–4, based on the average of the mean rate of change of each 6-month period of sham treatment in OAKS and DERBY. This is a prespecified analysis with no statistical testing hierarchy; results need to be interpreted with caution. Open-label studies can allow for selection bias.[2,3]

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 AMD) with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE EOM, sham monthly, or sham EOM, for 2 years. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[1,4]

GALE Trial Design: GALE (N=792) 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 GA secondary to AMD. 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 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 within 60 days of the final visit in OAKS and DERBY.[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.

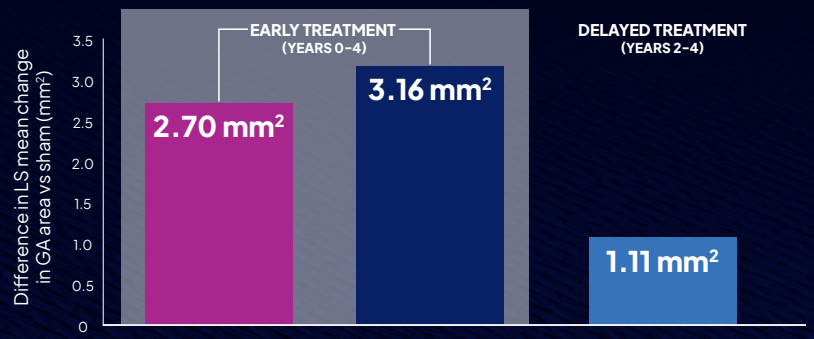
WARNINGS AND PRECAUTIONS

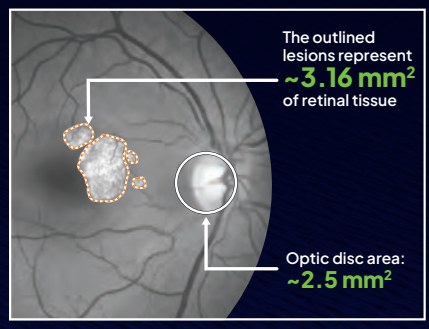
- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients 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.

In a post hoc analysis of patients without subfoveal involvement treated over 4 years,

Retinal tissue preservation was observed with Early SYFOVRE Treatment[3]

DIFFERENCES IN GA AREA GROWTH AT YEAR 4 (SYFOVRE VS SHAM/PROJECTED SHAM)[3]





3.16 mm²: The Equivalent of ~1.5 Optic Disc Areas[3]

*Pooled crossover includes patients from both monthly and EOM sham arms in OAKS and DERBY who crossed over into SYFOVRE monthly and EOM treatment in GALE, respectively.[3]

This is a post hoc analysis with no control for type 1 error and should be interpreted with caution. The first 2-year analysis of GALE used a projected sham assuming a linear growth rate. No conclusions can be drawn from this analysis.[3]

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

- **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.

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2024. **2.** Wykoff CC, Holz FG, Chiang A, et al. Pegcetacoplan treatment for geographic atrophy in age-related macular degeneration over 36 months: data from OAKS, DERBY, and GALE. *Am J Ophthalmol*. 2025;276:350–364. doi:10.1016/j.ajo.2025.04.016. Online ahead of print. **3.** Data on file. Apellis Pharmaceuticals, Inc. **4.** Heier JS, Lad EM, Holz FG, et al. Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials. *Lancet*. 2023;402(10411):1434–1448. doi:10.1016/S0140-6736(23)01520-9.

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

AMD=age-related macular degeneration; EOM=every other month; GA=geographic atrophy.

Apellis

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Ocular or Periocular Infections
SYFOVRE is contraindicated in patients with ocular or periocular infections.
Active Intraocular Inflammation
SYFOVRE is contraindicated in patients with active intraocular inflammation.
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.
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Waltham, MA 02451

SYF-PI-20Dec2024-3.0

12/24 US-PEGGA-2400436 v1.0

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FEATURED ARTICLES

DEPARTMENTS

Harnessing the Power of Light

The **first and only** FDA-authorized treatment for Dry AMD* to improve vision[1]

*Dry AMD eyes with: 3 medium drusen, or 1 large drusen, or non-central involving GA; and with BCVA between 20/32 – 20/70

Valeda Important Product Information
Indications for Use
The Valeda Light Delivery System is intended to provide improved visual acuity in patients with best-corrected visual acuity of 20/32 through 20/70 and who have dry age-related macular degeneration (AMD) characterized by:
• The presence of at least 3 medium drusen (> 63 µm and = 125 µm in diameter), or large drusen (> 125 µm in diameter), or non-central geographic atrophy, AND
• The absence of neovascular maculopathy or central-involving geographic atrophy
After about two years, the Valeda Light Delivery System treatment provides improved mean visual acuity of approximately one line of visual acuity (ETDRS) compared to those not receiving the treatment.
Contraindications for Use
As a precaution, patients have not been tested and should not be treated with Valeda if they have any known photosensitivity to yellow light, red light, or near-infrared radiation (NIR), or if they have a history of light-activated central nervous system disorders (e.g., epilepsy, migraine). In addition, patients should not receive treatment within 30 days of using photosensitizing agents (e.g., topicals, injectables) that are affected by 590, 660, and/or 850 nm light before consulting with their physician.
Precautions
Safety and effectiveness in patient populations and/or conditions excluded from the clinical study has not been established. This includes the following: patients under the age of 50, pregnant or nursing women, current or history of neovascular maculopathy, presence of center involving geographic atrophy (GA) within the central 1mm diameter, media opacities, including cataracts, which might interfere with visual acuity or imaging in the eye, posterior capsule opacification, which might interfere with visual acuity or imaging in the eye, ocular disorder or disease that partially or completely obstructs the pupil, any visually significant disease in any ocular structure apart from dry AMD.
An analysis of the primary effectiveness endpoint (mean BCVA change from baseline for the PBM arm – the mean BCVA change in the Sham arm) showed the following differences between arms for the subgroup of pivotal study patients with early AMD (Beckman Clinical Category Classification):
- At Month 13: +1.90 letters
- At Month 21: -0.10 letters
- At Month 24: +0.29 letters
The eyecare practitioner should consider the observed benefit/risk profile for this sub-population, when contemplating treatment of patients with this classification of Early AMD.
It is possible that treatment benefit may not persist significantly after treatment is stopped. The clinical study provided no significant data concerning the safety and effectiveness of the device should treatments be applied more frequently than described in this manual, or if more than 54 total treatments are delivered per eye.
Twelve (12) eyes (12.9%) in the PBM group and 4 eyes (7.3%) in the Sham group had a fellow eye that had neovascular AMD (nAMD). Of these 5 (41.7%) of 12 eyes in the PBM-treated group converted to nAMD, and 1 (25.0%) of the 4 eyes in the Sham group converted to nAMD. The eye care practitioner should consider the benefit/risk profile in this sub-population and should closely monitor patients whose fellow eye has nAMD.

References: 1. Alcon Data on File, 2025. [REF-27575]

Alcon

THE PIPELINE: TL;DR


Ahh, the pipeline issue. This is the one issue each year we break away from our usual mantra of "make sure everything is clinically relevant!" Of course, the investigational therapeutics and tools highlighted in this issue *may* become clinically relevant, but not quite yet (unless you are an investigator!). Each year, our coverage swells as more therapies move through their investigations and head toward possible FDA approval. Within this issue, our authors mention a whopping 77 therapies for wet or dry AMD, diabetic macular edema, and diabetic retinopathy—and that doesn't even include therapies for inherited retinal diseases, which were covered in our July/August issue (for more on those, see *Further Reading*).

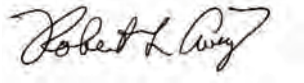
How do you navigate so much information?! Well, for anyone swamped in the clinic and OR with zero time to slog through clinical trial data, here's the short version: Of the therapeutics discussed in this issue, 15 are in phase 3 (Table)—nine of which are tentatively slated to have a primary completion next year. So, if nothing else, keep an eye on KSI-301 and KSI-501 (Kodiak Sciences), EYE103/MK-3000 (Restoret, EyeBio/Merck), OCS-01 (Oculis), vonaprument (ANX007, Annexon), EYP-1901 (EyePoint), ABBV-RGX-314 (Regenxbio/Abbvie), ADVM-022 (Adverum), and OTX-TKI (Ocular Therapeutix).

If you do find yourself with a cup of coffee and a free hour or two to read through the articles, the (very helpful) charts read something like a holiday wish list. Wouldn't it be great to have all these various options to treat our patients? What doesn't work for one might be a life-changing therapy for another. If the anti-VEGF agent isn't maintaining efficacy, maybe a tyrosine kinase inhibitor or a gene therapy will. A patient hates injections? Maybe an oral therapy or eye drop will become a viable alternative.

One day, we will have many more options to choose from to treat our chronic disease patients, and then we can start writing editorials complaining about storage space and overly complicated treatment decision trees.

For now, we wait. This issue always fills us with hope for a future that allows more individualized care for our patients with retinal disease—now that would be a miracle. ■

ALLEN C. HO, MD
CHIEF MEDICAL EDITOR



ROBERT L. AVERY, MD
ASSOCIATE MEDICAL EDITOR

FURTHER READING

THE IRD PIPELINE

More than 30 therapies for inherited retinal disease were highlighted in the July/August issue, which you can read online at retinatoday.com.

READ NOW

TABLE. INVESTIGATIONAL THERAPIES IN PHASE 3

Drug (Company)	Condition	NCT	Trial Status (Estimated Primary Completion)
KSI-301 (tarcocimab tedromer, Kodiak Sciences)	DR, Wet AMD	NCT06270836/ NCT06556368	Active, not recruiting (2026)
KSI-501 (tabirafusp tedromer, Kodiak Sciences)	Wet AMD	NCT06556368	Active, not recruiting (2026)
EYE103/MK-3000 (Restoret, EyeBio/Merck)	DME	NCT06571045	Active, not recruiting (2026)
IBI302 (Innovent Biologics)	Wet AMD	NCT05972473	Active, not recruiting (2027)
OCS-01 (Oculis)	DME	NCT06172257/ NCT05066997	Active, not recruiting (2026)
Vonaprument (ANX007, Annexon)	Dry AMD	NCT06510816	Active, not recruiting (2026)
OTX-TKI (Ocular Therapeutix)	Wet AMD	NCT06223958/ NCT06495918	Active, not recruiting (2026/2027)
EYP-1901 (EyePoint)	Wet AMD	NCT06683742/ NCT06668064	Active, not recruiting (2026)
Elamipretide (Stealth Biotherapeutics)	Dry AMD	NCT06373731	Active, not recruiting (2027)
RC28-E (RemeGen)	Wet AMD	NCT05727397	Recruiting (2025)
ABBV-RGX-314 (Regenxbio/Abbvie)	Wet AMD	NCT04704921/ NCT05407636	Recruiting (2026)
ADVM-022 (Adverum)	Wet AMD	NCT06856577	Recruiting (2026)
Tinlarebant (LBS-008, Belite Bio)	Dry AMD	NCT05949593	Recruiting (2027)
Cemdisiran (Regeneron)	Dry AMD	NCT06541704	Recruiting (2027)
4D-150 (4D Molecular Therapeutics)	Wet AMD	NCT06864988/ NCT07064759	Recruiting (2027/2028)

On the cover: a patient with wet AMD with inactive neovascularization. Image courtesy of Retina Rocks.

4DMT

At the **4FRONT** of wet AMD

4D Molecular Therapeutics (4DMT) is a late-stage biotechnology company focused on unlocking the full potential of genetic medicines. We're advancing durable and disease-targeted therapeutics to transform treatment paradigms.

Our lead retina program, **4D-150**, is a potential backbone therapy designed to provide multi-year sustained delivery of anti-VEGF (aflibercept and anti-VEGF-C) targeted to the retina with a single intravitreal injection. **4D-150** utilizes our retinotropic intravitreal vector, **R100**, which is designed for routine low dose intravitreal delivery to all layers and regions of the retina.

4D-150 is currently being studied in the global **4FRONT** Phase 3 program for the treatment of wet age-related macular degeneration.

Learn more at www.4DMT.com

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GLP-1 RA MEDICATIONS MAY REDUCE RISK OF DRY AMD IN SOME PATIENTS

A study published in *JAMA Ophthalmology* found that the use of glucagon-like peptide-1 receptor agonists (GLP-1 RAs) in patients with obesity without diabetes may lower the risk of developing dry AMD when compared with other weight loss drugs (OWLD).[1]

Data was obtained from the multicenter TriNetX Global Collaborative Network on patients 55 years of age or older who were diagnosed with obesity but not diabetes from January 2004 to July 2025. A total of 91,408 patients were included in the retrospective cohort analysis (45,704 patients in each of the GLP-1 RA and OWLD groups). The results showed that the use of GLP-1 RAs was associated with reduced risk of nonexudative AMD compared with the OWLD group at 5 years ($P < .001$), 7 years ($P < .001$), and 10 years ($P < .001$). No differences were observed in the progression to wet AMD between the two groups for patients who already had dry AMD.[1]

The authors concluded that it may be worthwhile to pursue randomized clinical trials to evaluate the potential ocular benefits of GLP-1 RA use in patients without diabetes.[1]

1. Ahuja AS, Paredes AA 3rd, Young BK. Glucagon-like peptide-1 receptor agonists and age-related macular degeneration. [published online ahead of print October 23, 2025.] *JAMA Ophthalmol*.

OPTOGENETIC THERAPY SHOWS PROMISE FOR RETINITIS PIGMENTOSA

Nanoscope Therapeutics recently reported 3-year data from the REMAIN study, the long-term extension of its phase 2b/3 RESTORE trial evaluating MCO-010, an optogenetic therapy for patients with retinitis pigmentosa (RP). The REMAIN study demonstrated that a single intravitreal injection of MCO-010 produced clinically meaningful and durable vision improvements in patients with RP, sustained through 152 weeks, with a favorable safety and tolerability profile.[1]

The company also released 5-year safety data from its EXTEND study, a follow-up to the phase 1/2a trial of 10 patients with RP. Trial participants who received the higher dose of MCO-010 experienced sustained or enhanced vision-related quality-of-life scores through 5 years, with no serious adverse events or new safety signals over the extended study period.[2]

Nanoscope submitted a rolling Biologics License Application with the FDA for MCO-010 in RP and has reported encouraging data for its use in Stargardt disease.[2]

1. Delany-Gesing A. Nanoscope reports 3-year vision improvements for RP optogenetic therapy. Eyes on Eyecare. October 30, 2025. Accessed November 4, 2025. glance.eyesoneyecare.com/stories/2025-10-30/nanoscope-reports-3-year-vision-improvements-for-rp-optogenetic-therapy
2. Nanoscope reports long-term data for it's optogenetic therapy in retinitis pigmentosa [press release]. Eyewire+. November 4, 2025. Accessed November 11, 2025. eyewire.news/news/nanoscope-reports-long-term-data-for-its-optogenetic-therapy-in-retinitis-pigmentosa

ELI LILLY TO ACQUIRE ADVERUM BIOTECHNOLOGIES

Eli Lilly and Company entered into an agreement to acquire Adverum Biotechnologies, including the latter's lead gene therapy drug candidate, ixo-vec, which is currently being evaluated in the ARTEMIS phase 3 clinical trial. Ixo-vec is a single-administration intravitreal gene therapy for the treatment of wet AMD. The ixo-vec program has been granted Fast Track and Regenerative Medicine Advanced Therapy designations by the FDA, PRIME designation by the European Medicines Agency, and the Innovation Passport from the United Kingdom's Medicines and Healthcare Products Regulatory Agency for the treatment of wet AMD.[1]

The company also entered into an agreement with MeiraGTx to acquire global exclusive rights to MeiraGTx's AAV-AIPL1, a gene therapy program for the treatment of Leber congenital amaurosis type 4. As part of the agreement, Eli Lilly will also obtain exclusive access rights to MeiraGTx's gene therapy platforms for ophthalmology, including its novel intravitreal capsids and AI-generated cell-specific promoters.[2]

1. Lilly to acquire Adverum Biotechnologies [press release]. Eli Lilly and Company. October 24, 2025. Accessed November 4, 2025. investingnews.com/lilly-to-acquire-adverum-biotechnologies
2. Eli Lilly makes another ophthalmic acquisition after gaining rights to MeiraGTx's gene therapy program for LCA4 [press release]. Eyewire+. November 10, 2025. Accessed November 11, 2025. eyewire.news/news/eli-lilly-makes-another-ophthalmic-acquisition-after-gaining-rights-to-meiragtxs-gene-therapy-program-for-lca4

WATCH IT NOW

EyewireTV: Posterior Segment Company Updates
During AAO 2025, experts share updates on the industry pipeline and new products.

REGENERON DELAYS SUBMISSION OF SUPPLEMENTAL BLA FOR HIGH-DOSE AFLIBERCEPT PREFILLED SYRINGE

Following receipt of a complete response letter from the FDA citing an unresolved inspection issue at its manufacturer, Regeneron announced it will delay submission of a supplemental Biologics License Application for its prefilled syringe of 8 mg aflibercept (Eylea HD). Submission is planned for January 2026. The drug remains available through vial administration.[1]

1. Regeneron reports third quarter 2025 financial and operating results [press release]. Regeneron. October 28, 2025. Accessed November 4, 2025. regeneronpharmaceuticalsinc.gcs-web.com/news-releases/news-release-details/regeneron-reports-third-quarter-2025-financial-and-operating

RANIBIZUMAB BIOSIMILAR IN PREFILLED SYRINGE LAUNCHES IN EUROPE

Formycon, Bioeq AG, and Teva Pharmaceutical announced the European launch of FYB201 (Ranivisio), the first ranibizumab biosimilar to become available in a prefilled syringe approved by the European Medicines Agency.[1]

1. Formycon's FYB201/Ranivisio sets innovative standard as Europe's first ranibizumab biosimilar available in pre-filled syringe [press release]. Formycon. October 21, 2025. Accessed November 4, 2025. www.formycon.com/en/blog/press-release/formycons-fyb201-ranivisio-sets-innovative-standard-as-europes-first-ranibizumab-biosimilar-available-in-pre-filled-syringe

TREATMENT WITH AVACINCAPTAD PEGOL DEMONSTRATES LONG-TERM BENEFIT

Astellas recently announced 18-month results from its open-label extension of the phase 3 GATHER2 study, demonstrating that monthly treatment with avacincaptad pegol (Izervay) continued to slow disease progression in patients with geographic atrophy secondary to AMD for up to 3.5 years.[1] The data show that disease progression was reduced by 40.5% compared with projected sham in patients who switched from monthly or every-other-month avacincaptad pegol to monthly treatment at 3.5 years. In addition, there was a 37% slower disease progression compared with projected sham in patients who had previously received sham and then switched to monthly avacincaptad pegol.[1] Patients who initiated treatment earlier experienced greater protection of retinal tissue.[1]

1. Izervay (avacincaptad pegol intravitreal solution) showed increased benefit in reducing geographic atrophy progression over time and consistent long-term safety [press release]. Astellas Pharma. October 19, 2025. Accessed November 4, 2025. www.prnewswire.com/news-releases/izervay-avacincaptad-pegol-intravitreal-solution-showed-increased-benefit-in-reducing-geographic-atrophy-progression-over-time-and-consistent-long-term-safety-302587856.html

QUESTIONNAIRE FOR VITREOUS FLOATERS DEMONSTRATES HIGH RELIABILITY

A study published in *JAMA Ophthalmology* evaluated the reliability of a Vitreous Floaters Functional Questionnaire (VFFQ) for use in cases of vision-degrading myodesopsia due to vitreous floaters, which can lead to reduced quality of life for some patients. To assess reliability, findings from the VFFQ were compared with quantitative measures of vitreous density (via ultrasonography) and visual function (via contrast sensitivity).[1]

Eyewire+ Pharma Update

- **Kodiak Sciences** announced follow-up data from the ongoing APEX phase 1b study evaluating KSI-101 in patients with macular edema secondary to inflammation, including sustained retinal drying through week 20, meaningful visual acuity improvements, and rapid onset of action.
- **4D Molecular Therapeutics** presented positive long-term data from the phase 1/2 PRISM clinical trial evaluating a single intravitreal treatment with 4D-150 in patients with wet AMD who experienced consistent visual acuity maintenance and sustained treatment burden reduction up to 2 years of follow-up.
- **Opus Genetics** announced successful completion of a Type B Regenerative Medicine Advanced Therapy meeting with the FDA regarding OPGx-LCA5, its gene therapy candidate for Leber congenital amaurosis type 5.
- **Bausch + Lomb** reported that its ONE by ONE Recycling Program, developed in collaboration with recycling provider TerraCycle, has collected more than 691,180 pounds—or 114,037,136 units—of used contact lenses and eye and lens care materials in the United States.
- **Ocular Therapeutix** announced that its SOL-R registrational trial of Axpaxli (OTX-TKI) in wet AMD achieved its randomization target of 555 patients, with topline data remaining on track for the first half of 2027.

Want more retina news from *Eyewire+*?

The single-center, cross-sectional study included data from 2017 to 2024. In a group of 169 patients, the researchers used Rasch analysis to identify 23 questions that met acceptable criteria to be used in the VFFQ. Another group of 24 patients completed the 23-item VFFQ three times over 6 months, with results demonstrating high test-retest reliability ($P < .001$). Finally, a comparison of VFFQ results with quantitative metrics in a separate group of 224 patients showed significant correlations between VFFQ scores and both vitreous echodensity on ultrasonography ($P < .001$) and contrast sensitivity ($P < .001$).[1]

Responses to the 23-item VFFQ were highly reliable and significantly correlated with objective measures of vitreous structure and visual function. The authors concluded that the questionnaire may prove useful for evaluating patients, screening, triaging, and assessing treatment responses.[1] ■

1. 1Nguyen JH, Boneva SK, Nguyen-Cuu J, et al. Vitreous floaters functional questionnaire for vision-degrading myodesopsia from vitreous floaters. [published online ahead of print October 2, 2025]. *JAMA Ophthalmol.*

CONGRATULATIONS TO THE 2025 RON MICHELS AWARDEES

The Ronald G. Michels Fellowship Foundation, established in 1991, is a nonprofit organization that supports outstanding 2nd-year vitreoretinal fellows training in the United States.

Each year, the award recipients are honored at the annual Ronald G. Michels Fellowship Foundation meeting. On October 17, the Foundation honored five top-notch retina fellows at the Rosen Centre Hotel in Orlando (Figure). Congratulations to the following fellows!

Figure. Honorees accept their plaques at the annual Ronald G. Michels Fellowship Foundation meeting. From left to right: Drs. Lin, Zafar, Rohowetz, Pan, and Antaki.

Fares Antaki, MDCM, born and raised in Syria, attended medical school at McGill University and residency at the University of Montreal. He trained in artificial medical intelligence at Moorfields Eye Hospital in London before joining the Cleveland Clinic Cole Eye Institute as a vitreoretinal surgery fellow.

> His goal was to do more surgeries than Walter Stark in a day, and he almost beat him a couple of times, which says a lot. That's Fares in a nutshell. Fares is meticulous. Fares goes the extra mile.

Jonathan B. Lin, MD, PhD, attended Emory University for college and received a combined MD/PhD from Washington University in St. Louis. For his PhD, he explored retinal neurodegeneration and the effect of aging and impaired metabolism. He completed his residency at Harvard and is a vitreoretinal surgery fellow at Stanford University.

> I've never received as many compliments about any one fellow as I have about Jon, and I think that just speaks wonders to his ability and kindness as a human.

Warren W. Pan, MD, PhD, MPhil, completed the MD/PhD program at the University of Michigan with a postdoctoral MPhil from the University of Cambridge. He attended the University of Michigan's Kellogg Eye Center for residency and vitreoretinal surgery fellowship.

> "He is that neat combination of surgical primal aptitude and just genuine intellectual curiosity. I really think he instills Ron Michels' spirit."

Landon J. Rohowetz, MD, completed his undergraduate degree at the University of Missouri-Columbia and attended medical school at the University of Missouri-Kansas City. He then attended residency training, vitreoretinal surgery fellowship, and chief residency at Bascom Palmer Eye Institute.

> He's an amazing fellow; he makes every day a joy for us. His accomplishments in terms of academics and clinically and also being the strong family man he is, it's just amazing.

Sidra Zafar, MD, earned her medical degree at the Aga Khan University in Pakistan. She then completed a research fellowship and residency at Wilmer Eye Institute. Dr. Zafar pursued her vitreoretinal fellowship at Wills Eye Hospital and is returning to Wilmer as the Assistant Chief of Service.

> Sidra's got an amazing resume and has written a zillion papers, but there are a few things that separate her. For one, she is unflappable, always focused on the patient, and everyone loves her.

ONE TO WATCH

RT Retina Today

Editorially independent supported by abbvie REGENXBIO

Kirk Hou, MD

Dr. Hou's advice: It is important to follow your passions within your chosen career path. If you have a passion for teaching or research, there are many opportunities to incorporate those activities into your career.

WHERE IT ALL BEGAN

I grew up in Chesterfield, Missouri, and attended Princeton University, where I majored in chemical engineering with a minor in materials science. At the time, I was interested in developing materials for drug delivery. After Princeton, I completed an MD/PhD program at Washington University in St. Louis, where I got my PhD in biophysics. My research focused on the development of nanoparticles for siRNA delivery. In addition to my clinical practice, I am working to start a research lab using this technology to treat macular degeneration. I had incredible mentors during my training who helped me develop a passion for patient care and translational research. Most importantly, my wife, who is a practicing cornea specialist, has always supported me along my journey to becoming a clinician scientist.

MY PATH TO RETINA

As a resident at the University of Califoria Los Angeles (UCLA), I had great exposure to retina from the very first days of my residency. I realized that I wanted to do retina while I was scrubbed in for my first after-hours intraocular foreign body surgery alongside two of our retina fellows, who made a complex case look easy. In addition to working closely with talented fellows, UCLA residents also participate in multimodal imaging rounds with David Sarraf, MD. Learning from him is like drinking from a firehose. As a resident, I did not have time to do any bench work, but he mentored me through a variety of projects that allowed me to present at national conferences. Having the freedom to pursue different areas of research and learn from world-class researchers confirmed my interest in the field of vitreoretinal surgery.

SUPPORT ALONG THE WAY

I was lucky to join the faculty at UCLA Stein Eye Institute, where I get to work with my mentors on a daily basis. It is an honor to continue working with surgical mentors such as Pradeep Prasad, MD, and Hamid Hosseini, MD. I am lucky that I still get to share complex cases with my medical retina mentors Dr. Sarraf and Edmund Tsui, MD. The career of an early clinician scientist can be quite challenging when balancing a busy clinical and surgical practice with teaching responsibilities and research.

It is incredibly important to build a strong network of mentors to guide you through these challenges. Irena Tsui, MD, has been a shining example of how to navigate these challenges, and she has guided me through each step along the way. With the support of the UCLA vitreoretinal faculty, I have started my own research lab investigating new treatments for early macular degeneration.

AN EXPERIENCE TO REMEMBER

Just this past year, a former fellow called me for advice on a complex patient he was taking care of. This experience helped me realize that the relationships I have fostered along the way are a rewarding part of my career as a physician in an academic setting. I look forward to training many fellows over the course of my career. ■

Kirk Hou, MD, is an assistant professor of Ophthalmology with the UCLA Stein and Doheny Eye Institutes. He is also an attending at Olive-View UCLA Medical Center. Dr. Hou is a consultant for Altamira Therapeutics and Abbvie. He can be reached at **khou@mednet.ucla.edu.**

26TH ANNUAL AVTT SYMPOSIUM AND FELLOWS' COURSE: A SUMMARY


Top-notch faculty provided clinical pearls, career and wellness advice, and a wet lab experience.

BY CHRISTOPHER CHUNG, MD, MS, AND JAMES WINEBRAKE, MD

The 26th annual Advanced Vitreoretinal Techniques & Technology (AVTT) Symposium and Fellows' Course, held August 22 – 24, 2025, in Chicago, convened leading vitreoretinal specialists and trainees for 3 days of interactive lectures, debates, surgical case discussions, and hands-on training. The program emphasized practical strategies for both trainees and seasoned retina specialists, advances in imaging and surgery, the evolving therapeutic landscape, and broader professional issues such as advocacy, leadership, and practice management.

BEST PRACTICES AND PROFESSIONAL DEVELOPMENT

The first day, designed for trainees, emphasized career transitions and engagement in the field. To start, course organizer William F. Mieler, MD, analyzed demographic trends in ophthalmology, noting high satisfaction rates but persistent challenges such as reimbursement pressure, regulatory hurdles, and obstacles to launching new practices. He stressed matching training with workforce demands.

Next, R. V. Paul Chan, MD, MSc, MBA, showcased the AAO's Leadership Development Program, which prepares physicians for roles beyond clinical care. With alumni including four AAO presidents, the program has been the catalyst for many international leadership efforts.

Justine Cheng, MD, then emphasized the importance of mastering workflow efficiencies, surgical preparation, and striking a balance between confidence and humility during the early years of practice.

Maria H. Berrocal, MD, urged physicians to avoid the urgency trap, embrace networking, and not fear impermanence in career decisions. She stressed compartmentalizing life's stages and prioritizing relationships and family.

Jennifer I. Lim, MD, outlined the logistical and financial realities of running clinical trials, while Jay Duker, MD, stressed that industry interactions must be grounded in authenticity and aligned with one's values.

Figure. Dr. Mieler moderated an ethics roundtable with experts from across the country.

Mark Johnson, MD, discussed what he called *compassionomics* and reviewed evidence that physician compassion improves patient outcomes, adherence, and even practice revenue, while also protecting against burnout.

As part of an ethics roundtable, panelists debated real-world dilemmas, including transparency in the delegation of surgical steps, choices in therapy influenced by cost, and handling misinformation on social media (Figure).

Another discussion compared various practice models. The faculty emphasized that professional fulfillment hinges less on setting than on culture, mentorship, and personal alignment. Key considerations in job selection included location, family, partner compatibility, and practice culture.

George A. Williams, MD, tackled physician payments and advocacy; he warned of the growing threats to surgical innovation if payment shifts toward time-based valuation. Dr. Lim urged active engagement in advocacy to safeguard patient care and professional scope.

As part of a discussion on health care disparities, Adrienne Scott, MD, stressed that patient recruitment and diversity of study teams can mitigate disparities in access to clinical trials.

Finally, Dr. Mieler closed out the morning session with his patented photo essay highlighting the importance of mentorship and community to prevent burnout.

The afternoon sessions combined wet lab instruction with medical retina cases. The wet lab offered trainees

direct exposure to advanced equipment and therapeutics in collaboration with the meeting's industry sponsors. The day concluded with dinner and a boat cruise.

IMAGING, SURGICAL INNOVATION, AND MORE

Day 2 began with a focus on advanced imaging and its role in diagnosis and management. Practical pearls for OCT angiography and widefield imaging were emphasized by Amani Fawzi, MD, and SriniVas R. Sadda, MD, including artifact recognition, careful segmentation, and the value of ultra-widefield angiography in diseases such as diabetic retinopathy (DR), retinal vein occlusion, and pachychoroid syndromes. Dr. Cheng highlighted the role of imaging in distinguishing AMD mimickers, and Dr. Johnson described unique OCT features of a potential new class of macular disorders he coined *Müller gliopathies*. Two early debates engaged the audience. Home OCT monitoring shows promise for earlier treatment initiation, according to Dr. Berrocal; however, Dr. Scott argued that it has yet to translate into better visual outcomes at scale. The use of photobiomodulation for dry AMD was debated with humor among close colleagues; while Dr. Sadda cited FDA-approved data showing benefit, Dr. Fawzi cautioned against premature enthusiasm, using Dr. Sadda's own words against him.

Felix Y. Chau, MD, reviewed the classification and treatment options for retinopathy of prematurity, while Robert A. Hyde, MD, PhD, highlighted genetic advances in pediatric retinal degenerations and the role of electrophysiology.

Next, Jennifer J. Kang-Mieler, PhD, reviewed biomarkers and blood flow dynamics in diabetic macular edema. Dr. Sadda noted that leakage, rather than nonperfusion, may better predict DR progression. Dr. Berrocal detailed evolving surgical techniques for diabetic tractional detachments, emphasizing meticulous hyaloid removal.

EMERGING THERAPIES FOR AMD

Sunday's program focused on macular degeneration and inflammation. Dr. Williams explained that the IRIS Registry contains data from nearly one billion encounters, offering opportunities to identify disparities, inform payer negotiations, and personalize care. Next, Dr. Kang-Mieler revealed new drug delivery platforms, including hydrogels and microparticles, that may be able to extend biologic therapy duration, although durability and safety remain under investigation. Dr. Lim summarized novel agents, antifibrotics, tyrosine kinase inhibitors, and gene therapies that could transform wet AMD care, reducing treatment burden.

In addition, Dr. Sadda highlighted OCT features in wet AMD, such as lesion type, pigment epithelial detachments, and fluid fluctuations, that help predict clinical outcomes.

Following Dr. Sadda, Lawrence J. Ulanski, MD, noted that while C3 and C5 inhibitors modestly slow geographic atrophy progression, safety concerns and limited visual benefits are important considerations when deciding if and when to treat a patient. As for wet AMD, Dr. Sadda posited that baseline disease factors drive atrophy more than treatment intensity, challenging the rigid treat-to-dry approach.

The afternoon included three lively debates related to AMD: the utility of biosimilars, complement inhibition for geographic atrophy, and use of OCT angiography when managing choroidal neovascularization.

UVEITIS AND MORE

The closing session addressed challenging inflammatory conditions. Pooja V. Bhat, MD, emphasized systematic evaluation, exclusion of infections, and stepwise use of steroids and immunomodulatory therapy for noninfectious uveitis. Dr. Cheng reviewed the data for cornerstone immunomodulatory treatments, including methotrexate, mycophenolate, and adalimumab (Humira, Abbvie). She also reminded us that, because lymphomas and other neoplastic conditions can mimic uveitis, biopsy and imaging are essential. Dr. Johnson discussed several considerations for uveitis: While surgical intervention can improve vision and reduce traction, postoperative inflammation must be controlled. Dr. Mieler highlighted that prevention of endophthalmitis remains key, and early recognition ensures better outcomes.

LEARN, GROW, AND SHARE

AVTT 2025 underscored the dynamic nature of modern vitreoretinal practice. Across sessions, recurring themes emerged: the need for adaptability in career development, the power of research and collaboration, the integration of compassion into care, and the balance between innovation and evidence. The meeting reaffirmed AVTT's unique role in blending rigorous clinical science with mentorship, practical career guidance, and open debate, ensuring that both trainees and experienced surgeons are equipped for the challenges and opportunities ahead. ■

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MEE VITRECTOMY COURSE: A PRIMER FOR NEW FELLOWS

This popular 2-day meeting provides a hands-on introduction to core concepts in vitreoretinal surgery.

BY MARTA STEVANOVIC, MD, MSC; ELIZABETH J. ROSSIN, MD, PHD; NIMESH A. PATEL, MD; AND JOHN B. MILLER, MD

The 15th annual Mass Eye and Ear (MEE) Vitrectomy Course, held July 11-12, 2025, included a great group of 60 fellows and 50 top faculty from across the country (Figure 1). Uniquely positioned at the beginning of the academic year, this popular course offers a comprehensive overview of core surgical concepts for new surgical fellows.

This course has a long legacy of educational innovations through the leadership of previous directors and co-founders John Loewenstein, MD, and Demetrios Vavvas, MD, and honorary founder Dean Eliott, MD. The course is currently led by John B. Miller, MD; Nimesh A. Patel, MD; and Elizabeth J. Rossin, MD, PhD.

DAY 1: FOUNDATIONS IN KNOWLEDGE

The first day of the course consisted of core lectures and panels focused on the fundamentals of vitreoretinal surgery. The course began with an introduction and welcome by Dr. Miller. The initial set of lectures covered core concepts in procedural and surgical management, including the basics of pneumatic retinopexy, scleral buckling, vitrectomy, and intraocular tamponades. Next, Donald J. D'Amico, MD, led a panel on retinal detachment repair, in which Steve Charles, MD; Raymond Iezzi, MD; John W. Kitchens, MD; Carl D. Regillo, MD; and Christina Y. Weng, MD, discussed their approaches to various types of detachments. A second panel, moderated by María H. Berrocal, MD, discussed surgical

Figure 1. The 15th annual MEE Vitrectomy Course welcomed faculty and fellow attendees from across the country.

management of diabetic retinopathy, including the expertise of Royce W. S. Chen, MD; Gerardo Garcia-Aguirre, MD; Deeba Husain, MD; Thanos Papakostas, MD; and Dimitra Skondra, MD, PhD.

Other notable sessions of the afternoon included insightful discussions on ergonomics in the OR by Robert B. Bhisitkul, MD, PhD; management of endophthalmitis by Yewlin E. Chee, MD; approaches to proliferative vitreoretinopathy by Dr. Regillo; use of IOLs by Dr. Kitchens; surgical approaches to epiretinal membranes and macular holes by Katherine E. Talcott, MD, and Dr. Weng; and the basics of pediatric vitreoretinal surgery by Eric Nudelman, MD, PhD.

A highlight of the afternoon was the Founders Lecture, given by Stanley Chang, MD, who pioneered the use of perfluorocarbon liquids in the surgical management of vitreoretinal pathology. He briefly discussed the development of perfluoro-n-octane (PFO) and then presented a variety of cases highlighting situations in which PFO is particularly helpful.

The day finished with a reception for all attendees, followed by a fellows' mixer at the Liberty Hotel, sponsored by YoungMD Connect, and a faculty dinner at Lucia's Ristorante in the Italian North End.

DAY 2: KNOWLEDGE IN ACTION

The second day of the course took place at MEE and consisted of lectures, wet and dry labs, and small focus groups. The day commenced with a discussion of surgical uveitis basics by Steven Yeh, MD, followed by a talk by Yannek I. Leiderman, MD, PhD, on how to prepare for surgery; finally, a lively panel led by Dr. Kitchens discussed secondary IOLs and featured Mohammad Dahrouj, MD, PhD; Miin (Irene) Roh, MD, PhD; Archana T. Seethala, MD; Andre J. Witkin, MD; Jeremy D. Wolfe, MD; and Thomas Wubben, MD, PhD. After, the fellows divided into smaller groups to attend the wet and dry labs as well as the surgical case discussion and career-mentoring groups.

The wet lab stations, set up in the MEE ORs, offered one-on-one teaching on the basics of vitrectomy (Figure 2), scleral buckling techniques (Figure 3), intraocular foreign body removal, and membrane peeling using both pig and model eyes. These stations allowed fellows to gain essential surgical skills and introduced them to a variety of vitrectomy systems, including the Alcon Unity and Constellation, the Zeiss Eva Nexus, and the Bausch + Lomb Stellaris, as well as different viewing platforms, such as the Bausch + Lomb SeeLuma, the Alcon Ngenuity, and the Oculus Biom with the Zeiss microscope.

The dry lab took place in the state-of-the-art Altschuler surgical training lab. Fellows practiced surgical techniques on several virtual simulators, such as the EyeSi (Haag-Streit) and the Genentech Virtual Simulation system, and were introduced to intravitreal and suprachoroidal injectables,

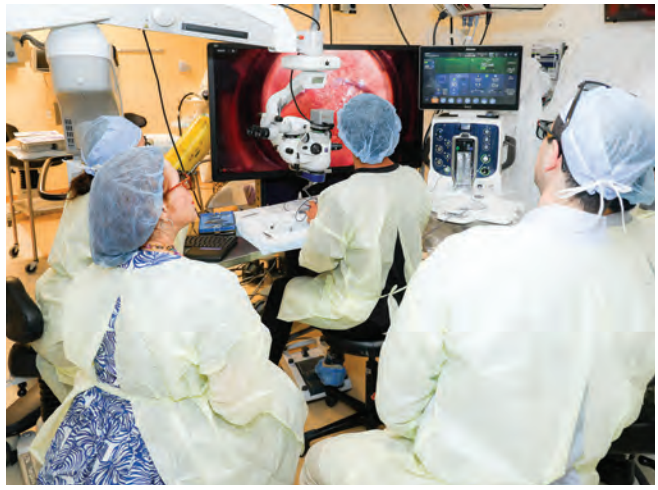

Figure 2. A fellow performed vitrectomy under the guidance of Drs. Maria and Audina Berrocal.

Figure 3. Drs. Chee and Seethala taught scleral buckling techniques.

including the triamcinolone acetonide injectable suspension (Xipere, Bausch + Lomb), the 0.19 mg fluocinolone acetonide intravitreal implant (Iluvien, Ani), and the dexamethasone intravitreal implant (Ozurdex, Abbvie). The newly announced Alcon Unipexy was also featured in the dry lab.

In addition to gaining hands-on experience, fellows attended surgical case discussions where they learned about approaches to complex cases from experienced faculty members. Fellows also participated in small groups led by faculty who offered career mentoring. The small groups provided excellent teaching and mentoring opportunities while also fostering connections between fellows and faculty from across the country.

Several panels were interspersed among the sessions. In addition to Dr. Kitchens' secondary IOL panel, Dr. Eliott moderated a panel on approaches to proliferative vitreoretinopathy, in which Tedi Begaj, MD; Xi Chen, MD, PhD; Dilraj Grewal, MD; Sandra R. Montezuma, MD; Flavio A. Rezende, MD, PhD; and Frances Wu, MD, contributed. Rishi P. Singh, MD, discussed approaches to macular hole repair

(Continued on page 48)

CLINIC EFFICIENCY AS A YOUNG VITREORETINAL SURGEON

Here's how to be efficient while also providing excellent patient care.

BY THEODORE BOWE, MD; ALLEN C. HO, MD; SUNIR J. GARG, MD, FACS; AND OMESH P. GUPTA, MD, MBA

As trainees and young retina specialists, we have the opportunity to learn from many fantastic mentors. One skill many young vitreoretinal surgeons want to improve is balancing clinic efficiency with excellent patient care. Here, I discuss tips, tricks, and advice with some of my mentors at Mid Atlantic Retina, Allen C. Ho, MD; Sunir J. Garg, MD, FACS; and Omesh P. Gupta, MD, MBA.

THEODORE BOWE, MD: HOW DO YOU KEEP YOUR CLINIC FLOWING EFFICIENTLY?

Dr. Ho: There are times when emergencies, new patients, and challenging issues back up the clinic. We tend to think about efficient clinic flow through the lens of the provider, but the key is to think about it from the patient's perspective to make sure their needs are met and their questions are answered. Ensure schedules are streamlined, safety measures are in place, and staff is on the same page about each patient encounter. Having experienced, focused, and engaged team members makes all the difference.

Dr. Garg: One of the most powerful habits you can develop is starting your day on time. Your punctuality—good or bad—sets the tone for your team and patient encounters. It takes time to establish a connection with your patients while doing what we have to do in a timely manner. As you get busier, being direct in an empathetic way is key.

Dr. Gupta: The biggest issue that affects efficiency is doctor distractions. Inevitably, physicians are pulled in many different directions. I try to limit, if not eliminate, distractions completely during clinic hours. The responsibility of running an efficient office does not fall on one person, and the culprit for an inefficient office is usually not one issue. Team effort and a multifactorial solution are both required.

DR. BOWE: WHAT PATIENT COMMUNICATION TACTICS WORK BEST FOR YOU?

Dr. Ho: Optimizing efficient communication with patients is based on trust. I make notes about significant life events in addition to their medical issues. Knowing that a patient just celebrated a milestone birthday with extended family at the beach, for example, creates human interest for me and makes the patient feel more connected to our care team.

Dr. Garg: I tend to use a lot of analogies. Geographic atrophy becomes "there are holes in my old t-shirt, and the edges are fraying and get bigger over time." Blood vessels leaking from diabetic eye disease become "old pipes are starting to leak and ooze, and I have to put a sealant on them to get it to stop." While in training, listen to how attendings describe these concepts to patients. You'll glean useful metaphors and learn what language to avoid.

Dr. Gupta: I describe wet AMD as a weed growing through a crack in the cement sidewalk. The crack in the cement is the break in Bruch membrane, and the weed is the neovascular complex. The weed spray is the anti-VEGF agent. We

IN TODAY'S HEALTH CARE LANDSCAPE, EFFICIENCY IS MORE CRUCIAL THAN EVER FOR THE SUCCESSFUL PRACTICE OF MEDICINE.

spray this weed killer once a month until the weed is dead. Once the weed is dead, we can use the spray less often, but sometimes the weed grows back if the interval between sprays is too long. Also, be consistent in your messaging.

DR. BOWE: HOW DO YOU OPTIMIZE COMMUNICATION WITH PARTNERS AND REFERRING DOCTORS?

Dr. Ho: I try to think about what partners and referring doctors would need and what I would want to know if I was in their shoes. For example, if a patient had surgery with me and has a gas bubble, I will include a note that reflects whether the patient has a long- or short-acting tamponade. If we have an emergency surgery and I need to pass the case to one of my partners, I communicate necessary medical and personal information. Some referring doctors want more frequent communication than others. We have hotline phone numbers for specific referring doctors so their team can reach ours more efficiently.

Dr. Garg: When updating a partner on a case, I stick to the critical pieces of information. For referring doctors, I mostly rely on the examination note from our electronic health record (EHR) that gets sent out. If it's a more unusual case, I'll expand as necessary. If something is time-sensitive, a phone call can be a big time-saver for everyone.

Dr. Gupta: It is paramount to keep the lines of communication open with partners and referring doctors. I would encourage all retina specialists to reach out to referring doctors as often as possible.

DR. BOWE: WHAT ADVICE CAN YOU OFFER ON NOTE WRITING AND EHR USE?

Dr. Ho: Keep notes about each particular patient in a way that helps you better understand them and their visual needs. It makes the experience more meaningful for me, as I enjoy the privilege of being invited into my patients' lives as their retina specialist.

Dr. Garg: I always have a scribe with me. Their level of expertise and engagement can be variable, so make sure to get on the same page from the start.

Dr. Gupta: Spend time getting to know your EHR beyond a superficial level. Customize your profile based on your preferences, edit smart phrases if possible, and eliminate options that you don't find helpful. This can be time-consuming, but the amount of time you save when seeing patients is invaluable. As you become more familiar with your EHR, you will be able to simultaneously talk to patients about one topic and update their chart on another.

DR. BOWE: DO YOU HAVE ANY OTHER PATIENT CARE ADVICE FOR AN EARLY-CAREER RETINA SPECIALISTS?

Dr. Garg: If you're starting off in an office, learn to pace yourself as the patient volume grows. Some techniques can be learned; others come with experience. Don't feel like you need to reinvent the wheel. Try to get all your documentation and patient emails done before you leave the office for the day so you're not taking your work home with you.

Dr. Gupta: Becoming more efficient takes experience and develops over time. Put patient care first, and the rest will fall into place. Those who place a priority on speed often make mistakes or eventually regret their misdirected priorities. In today's health care landscape, efficiency is more crucial than ever for the successful practice of medicine. It is important to take the time to identify any scheduling and efficiency challenges your practice may be facing and then implement the necessary changes to address them. By doing so, you can ensure your practice remains financially successful and on track to provide quality care to your patients. ■

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THE NEED FOR NOVEL INTRAOCULAR TAMPONADE AGENTS

Surgical, diagnostic, and environmental considerations of standard tamponades reveal the potential benefits of a better solution.

BY MARIO ROMANO, MD, PHD; ROBERT L. AVERY, MD; DAVID A. EICHENBAUM, MD; AND ANAT LOEWENSTEIN, MD

Intraocular gases and silicone oil, while instrumental in the evolution of retinal detachment repair, have remained largely unchanged since their introduction in the 1970s; aside from certain refinements in formulation and delivery, no significant innovations in intraocular tamponade agents have emerged.[1-3]

During the Euretina Special Focus Meeting on Ocular Endotamponades, held in Athens on March 15, 2025, international experts gathered to discuss the limitations of current tamponade agents and the critical need for innovation in this space. With evolving surgical techniques, new government restrictions on the use of fluorinated greenhouse gases (F-gases) due to environment concerns, and increasing patient expectations, the call for new tamponade solutions has never been more urgent.

This article reviews the limitations of current agents and explores some of the innovations on the horizon.

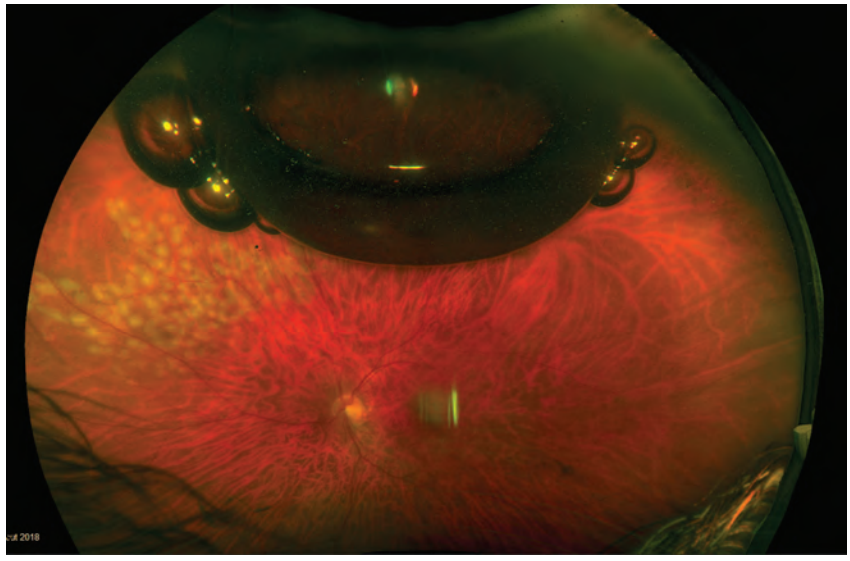

Figure. Imaging of this patient's retina is obscured by a partial gas fill post-vitrectomy.

CHALLENGES WITH CURRENT ENDOTAMPONADE AGENTS

While gases and oils provide mechanical closure of retinal breaks, their clinical drawbacks are significant. With endotamponades, patients are often required to maintain strict, uncomfortable positioning for days or even weeks, depending on the location of the break. Consequently, quality of life can be significantly affected during recovery. For example, for some patients, any preexisting musculoskeletal disease may be exacerbated, leading to inherent compliance challenges and, potentially, reduced surgical success. In addition, air travel and altitude exposure are strictly limited with gas endotamponades, which may present a limitation for certain patients.

Surgeons also experience important diagnostic blind spots during critical phases of follow-up due to the refractive properties of endotamponades, as gas-filled eyes preclude quality OCT imaging and hinder the early identification of complications such as epiretinal membrane formation, macular edema, or incipient retinal redetachment (Figure). Moreover, the concentrated fluid meniscus below the gas bubble creates a stratified

WITH EVOLVING SURGICAL TECHNIQUES, NEW GOVERNMENT RESTRICTIONS ON THE USE OF FLUORINATED GREENHOUSE GASES (F-GASES) DUE TO ENVIRONMENTAL CONCERNS, AND INCREASING PATIENT EXPECTIONS, THE CALL FOR NEW TAMPONADE SOLUTIONS HAS NEVER BEEN MORE URGENT.

environment that may concentrate proinflammatory cytokines and fibrogenic growth factors, such as TGF-β and PDGF, potentially contributing to the development of proliferative vitreoretinopathy.[4] In phakic eyes, gas exposure accelerates cataract progression, hastening the need for cataract surgery.[5]

The use of silicone oil, while it does not require as strict positioning as gas, introduces its own set of potential complications, including emulsification, secondary glaucoma, refractive changes, and the need for a second surgery to remove the oil.[6]

Although gas tamponade is not necessary in all cases of vitrectomy, its common association with retina surgery may deter patients who fear the burdens of postoperative positioning and temporary postoperative vision loss. Such hesitation may compromise patients' long-term visual outcomes and, in some cases, even lead to permanent vision loss.

In this context, the emergence of new agents that can offer direct sealing of retinal breaks without extensive clinical burdens and with a significantly shortened postoperative rest period would represent a meaningful leap forward for both surgeons and patients.

Lack of Environmental Sustainability

Adding to the unmet clinical need for novel endotamponades is pressure to restrict or abolish the use of F-gases for medical purposes in Europe. As part of a broader climate policy, the European Union passed Regulation 2024/573 to address the use of F-gases; the regulation introduces a quota system in 2030 and an outright ban by 2050.[7]

In response, some companies have begun to take a proactive approach in reducing reliance on F-gases in medical technology. One example is the initiation of clinical trials to develop asthma inhalers that eliminate fluorinated propellants in anticipation of these changes.[8]

The proposed regulations on F-gases have raised concern in ophthalmology as well. Euretina has publicly advocated against a complete ban while supporting the overall efforts to minimize the use of F-gases in vitreoretinal surgery and encouraging research on alternative tamponade agents that would minimize greenhouse gas emissions and improve patient outcomes. While patient safety and environmental responsibility are not mutually exclusive, the downstream effects of the stricter F-gas regulations could mean reduced availability and/or rising costs of medical-grade ophthalmic gases, further underscoring the need for viable alternatives.

NEW FRONTIERS IN TAMPONADE SCIENCE

The concept of developing a vitreous substitute or retinal sealant is not new, but such attempts have historically fallen short. Although hydrogel-based materials have demonstrated promise in early animal models, none have successfully translated into the clinic due to issues such as inflammation, poor biocompatibility, complex manufacturing of biomaterials, or surgical impracticality.[9,10]

However, at the Euretina Special Focus Meeting, experts discussed novel approaches to the traditional retinal tamponades. One approach under evaluation by various research groups is the concept of a bioadhesive sealant that would replace gas entirely.[11,12] By adhering directly to the retina and sealing the localized retinal defect, the

FURTHER READING

How to Choose the Right Tamponade

By Lucy V. Cobbs, MD, and Vaidehi S. Dedania, MD

Surgeons have several options, and knowing which one will serve the patient best is the key to a successful surgery.

In *Retina Today*, January/February 2024

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Retina OR Potpourri: Five Questions for Five Top Surgeons

By Steve Charles, MD, FACS, FICS; Charles C. Wykoff, MD, PhD, FASRS, FACS; Audina M. Berrocal, MD; Sengul Ozdek, MD, FEBO; and Edward F. Hall, MD

Experts discuss tough surgical scenarios and controversial topics.

In *Retina Today*, January/February 2025

bioadhesive sealant could potentially allow for earlier visual recovery, reduce or eliminate strict positioning, and reduce the risk of proliferative vitreoretinopathy by minimizing concentration of potential pathologic cytokines inferiorly and cellular ingress through retinal breaks. It may also decrease the rate of cataract formation.

If the development of such an approach continues, it could represent a paradigm shift in how we manage retinal detachments. It is also worth mentioning that surgeons have used Tisseel glue with some success in the past,[13] while others hve explored a gel-based sealant.[14]

LET'S GET TO WORK

As clinical and regulatory pressures mount and our tools for diagnosis and intervention continue to grow more refined, we must match that progress with equally thoughtful innovation in how we manage retinal breaks. The future of surgical success in the retina OR will be defined not only by anatomic improvement, but also by our patients' access to care, recovery experience, and long-term visual outcomes. It's time to evolve "beyond the bubble" and seek a new solution to the problem of standard gas and oil tamponades. ■

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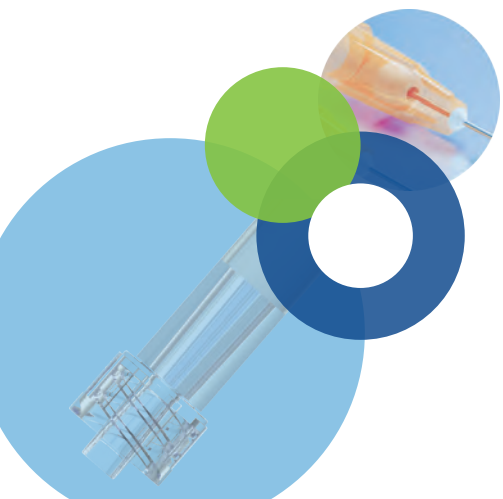

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ADVANCES IN THERAPY FOR DIABETIC EYE DISEASE

The pipeline is rich with therapies that promise reduced treatment burden and improved efficacy.

By Alicia H. Chen, MD; Jacob Holland, BS; and Sally S. Ong, MD



Diabetic retinopathy (DR) and diabetic macular edema (DME) are leading causes of vision loss in working-age individuals.[1] Current treatments include anti-VEGF injections and panretinal photocoagulation. However, many patients experience treatment-resistant disease and significant injection burden (Figure). Recent clinical trials have examined novel drugs that target pathways other than VEGF or use alternative delivery methods to improve outcomes and extend treatment intervals. Here, we review the many therapies making their way through the clinical trial pipeline for DR and DME (Table).

INTRAVITREAL INJECTION

KSI-301 (tarcocimab tedromer, Kodiak Sciences) is an anti-VEGF antibody biopolymer conjugate that inhibits all VEGF-A isoforms. In the phase 3 GLOW1 trial (NCT05066230), 41.1% of patients with DR treated with KSI-301 achieved a ≥ 2-step Diabetic Retinopathy Severity Scale improvement at 48 weeks compared with 1.4% in the sham group. The phase 3 GLOW2 trial (NCT06270836) design closely follows the successful GLOW1 study but includes three monthly loading doses instead of two.[2]

EYE103/MK-3000 (Restoret, EyeBio/Merck) is a tetravalent, tri-specific antibody that activates the Wnt signaling pathway. The phase 2b/3 BRUNELLO study (NCT06571045) is comparing EYE103 with ranibizumab (Lucentis, Genentech/Roche) in patients with DME. The primary outcome measures are safety and mean change in visual acuity from baseline to week 52.[3]

AT A GLANCE

- Three therapies are in phase 3 trials for diabetic retinopathy (DR) and diabetic macular edema (DME): KSI-301 (tarcocimab tedromer, Kodiak Sciences), OCS-01 (Oculis), and EYE103/MK-3000 (Restoret, EyeBio/Merck).
- Companies are also exploring novel delivery methods, including topical, oral, subcutaneous, intravitreal implants, suprachoroidal, periocular, and subretinal.
- Gene therapies for DR/DME, including ABBV-RGX-314 (Abbvie/Regenxbio) and 4D-150 (4D Molecular Therapeutics), are showing promise.

AG-73305 (Allgenesis Biotherapeutics) is an Fc-fusion protein that blocks both VEGF and integrin pathways. In the phase 2a trial for DME (NCT05301751), AG-73305 led to a statistically significant increase in visual acuity of 6.4 ETDRS letters and a mean central subfield thickness (CST) reduction of 100 µm at 4 weeks following a single injection. By week 24, more than 50% of patients did not require any supplemental injections.[4] The company is pursuing a phase 2b trial.[5]

Vamikibart (Genentech/Roche) is a monoclonal antibody that inhibits interleukin-6. The phase 2 trial (NCT05151744) revealed that combining vamikibart with ranibizumab did not provide significantly greater improvements in visual acuity compared with ranibizumab alone in patients with DME.[6] A second completed phase 2 trial (NCT05151731) evaluated the safety and efficacy of vamikibart alone compared with ranibizumab; results are pending.

RO7446603 (Genentech/Roche) is being tested for the treatment of DME. Part 1 of the phase 1/2 THAMES study (NCT06850922), focused on safety, is complete with results pending. Part 2 is recruiting and will evaluate the efficacy of RO7446603 in combination with faricimab (Vabysmo, Genentech/Roche) administered as a single injection.

EYE201 (tiespectus, EyeBio/Merck) is a proprietary intravitreal injection under investigation for the treatment of DME, branch retinal vein occlusion (BRVO), and wet AMD. Part 1 of the phase 1/2a study (NCT06664502) is evaluating the safety of multiple ascending doses in patients with BRVO. Part 2 will assess the safety and effectiveness of two doses of EYE201 in patients with DME and wet AMD.

INTRAVITREAL IMPLANTS

EYP-1901 (Duravyu, EyePoint) is a sustained-release intravitreal implant that delivers vorolanib, a selective tyrosine kinase inhibitor. The phase 2 VERONA trial (NCT06099184) achieved its primary outcome by demonstrating that both doses of EYP-1901 (1.3 mg and 2.7 mg) significantly delayed the need for a supplemental injection compared with the 2 mg aflibercept (Eylea, Regeneron) control in patients with DME.[7] The 2.7 mg dose demonstrated an early and sustained 7.1 letter gain at 24 weeks with a 76 µm reduction in CST.[7] The company is planning a phase 3 trial, expected to begin by the end of 2025 or early 2026.[7]

PER-001 (Perfuse Therapeutics) is an endothelin receptor antagonist in a sustained-release intravitreal implant for DR. In the phase 2a trial (NCT06003751), PER-001 showed improvements in contrast sensitivity, peripheral vision, and retinal structure, including reduced macular ischemia, leakage, and microaneurysm burden, compared with sham.[8,9] The company is pursuing a phase 2b trial.[8]

EC-104 (Eclipse Life Sciences) is an extended release fluocinolone acetonide implant intended to treat DR and center-involving DME. The phase 2 BETTIS-1 trial (NCT06536491) is comparing two doses of EC-104 with the dexamethasone implant (Ozurdex, Abbvie) in patients who previously showed a suboptimal response to anti-VEGF therapy and have a history of local corticosteroid treatment without significant increases in IOP.

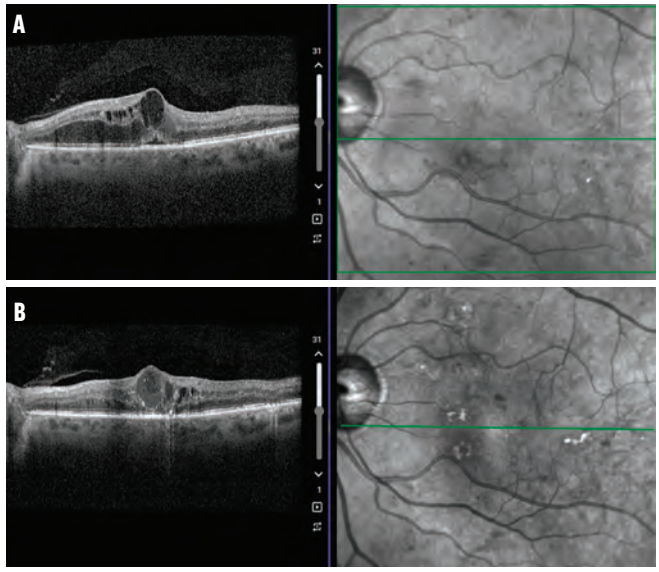

Figure. This patient presented with center-involving DME and a baseline VA of 20/40 (A). Three years later (B), his VA is 20/50 after 11 anti-VEGF injections, eight dexamethasone implants, and focal laser treatment. He continues receiving treatment due to persistent center-involving DME, highlighting the need for more durable treatment options.

SUPRACHOROIDAL DELIVERY

OXU-001 (Dexaspheres, Regeneron) is a sustained-release formulation of dexamethasone delivered with the suprachoroidal Oxulumis device (Regeneron). The phase 2 trial (NCT05697809) aimed to assess two different doses in patients with DME in part A, and then compare it with the dexamethasone implant (Ozurdex, Abbvie) in part B. Recruitment was halted for non-safety reasons after three patients were treated in part A; part B was not initiated. No serious adverse events or device effects were reported.

The phase 2 CAPE study (NCT05512962) evaluated the Oxulumis device in its delivery of triamcinolone acetonide (Triesence, Harrow) in patients with DME. None of the 25 patients experienced serious ocular or systemic adverse events or adverse device effects by week 24. Patients who received 2.4 mg and 4.0 mg doses experienced CST reductions of 62.5 µm and 127.7 µm, respectively, and improvements of 4.8 ETDRS and 11.0 ETDRS letters at 24 weeks.[10]

TOPICAL DRUGS

OCS-01 (Oculis) is a 15 mg/ml dexamethasone ophthalmic solution intended for the treatment of DME. In the phase 2/3 DIAMOND-1 trial (NCT05066997), participants received OCS-01 or placebo eye drops six times daily during a 6-week loading phase, followed by three times daily during a 6-week maintenance phase. Stage 1 of the trial met its

TABLE. INVESTIGATIONAL THERAPIES FOR DIABETIC EYE DISEASE

Drug (Company)	Condition	Mechanism	Delivery	NCT	Trial Status
Phase 3					
KSI-301 (tarcocimab tedromer, Kodiak Sciences)	DR	Anti-VEGF-A antibody biopolymer conjugate	Intravitreal injection	NCT06270836	Active, not recruiting
OCS-01 (Oculis)	DME	Dexamethasone	Topical	NCT06172257 NCT05066997	Active, not recruiting
EYE103/MK-3000 (Restoret, EyeBio/Merck)	DME	Wnt signaling agonist	Intravitreal injection	NCT06571045	Active, not recruiting
Phase 2					
UBX1325 (foselutoclax, Unity Biotechnology)	DME	BCL-XL inhibitor	Intravitreal injection	NCT06011798	Complete
Vamikibart (Genentech/Roche)	DME	IL-6 inhibitor	Intravitreal injection	NCT05151731 NCT05151744	Complete Complete
BAY 1101042 (runcaciguat, Bayer)	NPDR	Guanylate cyclase activator	Oral	NCT04722991	Complete
OPL-0401 (Valo Health)	DR	Rho kinase 1 and 2 inhibitor	Oral	NCT05393284	Complete
CU06-1004 (Curacle)	DME	Endothelial dysfunction blocker	Oral	NCT05573100	Complete
AG-73305 (Allgenesis Biotherapeutics)	DME	Anti-VEGF and anti-integrin Fc-fusion protein	Intravitreal injection	NCT05301751	Complete
EYP-1901 (Duravyu, EyePoint Pharmaceuticals)	DME	Tyrosine kinase inhibitor	Intravitreal implant	NCT06099184	Complete
OXU-001 (Dexaspheres, Regeneron)	DME	Dexamethasone	Suprachoroidal	NCT05512962 NCT05697809	Complete Complete
ABBV-RGX-314 (Abbvie/Regenxbio)	DR, DME	Gene therapy	Suprachoroidal Subretinal	NCT04567550 NCT06942520	Active, not recruiting Recruiting
4D-150 (4D Molecular Therapeutics)	DME	Gene therapy	Intravitreal injection	NCT05930561	Active, not recruiting
PER-001 (Perfuse Therapeutics)	DR	Endothelin receptor antagonist	Intravitreal implant	NCT06003751	Active, not recruiting
Tonabersat (Jaeb Center for Health Research)	DME	Connexin43 hemichannel inhibitor	Oral	NCT05727891	Active, not recruiting
INV-102 (Invirsa)	DME	Unknown	Topical	NCT06599684	Recruiting
EC-104 (Eclipse Life Sciences)	DR, DME	Fluocinolone acetonide	Intravitreal implant	NCT06536491	Recruiting
EYE201 (tiespectus, EyeBio/Merck)	DME, BRVO, AMD	Unknown	Intravitreal injection	NCT06664502	Recruiting
VX-01 (Vantage Biosciences)	NPDR	Amine oxidase copper-containing 3 inhibitor	Oral	NCT06770933	Recruiting
EC-104 (Eclipse Life Sciences)	DR, DME	Fluocinolone acetonide	Intravitreal implant	NCT06536491	Recruiting
RO7446603 (Genentech/Roche)	DME	Unknown	Intravitreal injection	NCT06850922	Recruiting
Phase 1					
AIV007 (AiViva BioPharma)	DME	Tyrosine kinase inhibitor	Periocular injection	NCT05698329	Active, not recruiting
OCU200 (Ocugen)	DME	Fusion protein	Intravitreal injection	NCT05802329	Recruiting
RO7497372 (Genentech/Roche)	DME	Unknown	Intravitreal injection	NCT06847854	Recruiting
K9 (Inflammasome Therapeutics)	DME	Inflammasome inhibitor	Oral	NCT06781255	Recruiting
Octreotide (University of Alabama at Birmingham)	PDR, DME	Somatostatin analog	Intranasal	NCT06881888	Not yet recruiting

Abbreviations: DME, diabetic macular edema; DR, diabetic retinopathy; NPDR, nonproliferative DR; PDR, proliferative DR; BRVO, branch retinal vein occlusion.

primary and secondary outcomes, with the treatment group experiencing significant improvements in BCVA and reductions in CST compared with placebo at week 12.[11] Stage 2 of the trial is evaluating treatment out to 52 weeks. The phase 3 DIAMOND-2 trial (NCT06172257) is also evaluating patients over a 52-week period with results expected in 2026.[12]

INV-102 (Invirsa) is a topical ophthalmic solution used for DME associated with nonproliferative DR (NPDR). The phase 2 clinical trial (NCT06599684) is assessing the efficacy of INV-102 in patients with both non-center-involving and center-involving DME over 8 and 12 weeks, respectively. INV-102 will be given three times daily for a 2-week loading period, followed by twice daily.

ORAL OPTIONS

Tonabersat (Jaeb Center for Health Research), an orally administered connexin43 hemichannel inhibitor originally used for neurological conditions, is now under investigation for DME. The phase 2 Protocol AN (NCT05727891) trial is evaluating the effect of tonabersat (80 mg twice daily) on CST in patients with center-involving DME who have good visual acuity compared with placebo over a 6-month period.

CU06-1004 (Curacle) is an endothelial dysfunction blocker that inhibits retinal vascular leakage induced by VEGF and angiopoietin-2.[13] In the completed phase 2a trial (NCT05573100), dose-dependent improvements in BCVA were observed in patients with DME, with the highest dose group (300 mg) achieving a gain of 5.8 letters. CST remained stable for all dose cohorts at 12 weeks. The company is planning for phase 2b and 3 studies.[14]

VX-01 (Vantage Biosciences) is an orally administered small-molecule therapy designed to target amine oxidase copper-containing 3, which drives neovascular inflammation in NPDR.[15] The phase 2 trial (NCT06770933) is evaluating the efficacy of daily doses of VX-01 versus placebo after 52 weeks.

GENE THERAPIES

ABBV-RGX-314 (Abbvie/Regenxbio) is a one-time gene therapy that uses a transgene to produce an anti-VEGF antibody fragment. Two phase 2 trials—ALTITUDE (NCT04567550) and ELAAVATE (NCT06942520)—are evaluating suprachoroidal and subretinal administration, respectively, in patients with DR and DME. Preliminary 1-year results from ALTITUDE show that the treatment was well tolerated, slowed disease progression, and reduced vision-threatening events in patients with NPDR.[16]

4D-150 (4D Molecular Therapeutics) is an intravitreal injection that delivers two transgenes encoding aflibercept and an miRNA sequence targeting VEGF-C.[17] In the phase 2 SPECTRA trial (NCT05930561), patients who received the 3E10 vg/eye dose gained a BCVA of 9.7 letters and had a reduction in CST of 174 µm at 60 weeks. These patients also required fewer supplemental injections compared with those who received lower doses of 4D-150 or aflibercept injections.[18] The FDA and European Medicines Agency agreed that a single phase 3 trial, based on data from the SPECTRA, PRISM, and upcoming 4FRONT trials, is sufficient for submitting a Biologics License Application and a Marketing Authorization Application, respectively, for 4D-150 in DME.[18]

A DIVERSE PIPELINE TO WATCH

Beyond the therapies highlighted here, several novel drugs are in phase 1, including: RO7497372 (Genentech/Roche), OCU200 (Ocugen), AIV007 (AiViva BioPharma), K9 (Inflammasome Therapeutics), and octreotide.

With so many therapeutics under investigation with varying mechanisms of action and delivery approaches, we are hopeful that there will soon be many more treatment options to offer our patients. Reducing the treatment burden and improving therapeutic efficacy are keys to preserving vision in this vulnerable patient population. ■

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TRIALS AND INNOVATIONS IN GEOGRAPHIC ATROPHY THERAPY

Novel mechanisms of action and delivery methods hold promise for patients with dry AMD.

By James M. Harris, MD, PhD, and Eleonora M. Lad, MD, PhD


This year has been busy for the geographic atrophy (GA) pipeline. The Valeda light delivery system (LumiThera/Alcon) gained approval for the treatment of early and intermediate dry AMD, joining the two complement inhibitors, pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izervay, Astellas), as FDA-approved treatments for dry AMD. Additionally, post-hoc analysis of the AREDS and AREDS2 studies showed a 33% and 30% slower progression of noncentral GA to the foveal center point, respectively, for patients taking supplements compared with placebo for a mean follow-up period of 3 years.[1]

However, these therapies and supplements are just the tip of the iceberg when it comes to potential treatments for dry AMD. The current pipeline, some of which is highlighted below, contains many exciting therapies that target a diverse range of mechanisms with novel delivery strategies (Table).

PHASE 3 TRIALS

Elamipretide (Stealth Biotherapeutics) targets mitochondrial dysfunction by blocking cardiolipin from interacting with cytochrome c, preventing its conversion from an electron carrier into a peroxidase, which has been shown to reduce reactive oxygen species generation while boosting ATP generation.[2] ReNEW (NCT06373731) is investigating the effect of a once-daily subcutaneous injection of 40 mg elamipretide on the change in macular photoreceptor loss area after 48 weeks.[3] While the ReCLAIM-2 phase 2 trial (NCT03891875) failed to meet its primary endpoints of change in low-luminance BCVA (LLBCVA) and change in GA area growth, it did reduce

AT A GLANCE

- Four investigational therapies are in phase 3 trials for the treatment of geographic atrophy: elamipretide (Stealth Biotherapeutics), tinlarebant (LBS-008, Belite Bio), vonaprument (ANX007, Annexon), and Cemdisiran (Regeneron).
- Novel approaches such as sialic acid-coated nanoparticles, phospholipid modulators, Fas inhibitors, and gene and stem cell therapies are in phase 2 trials.
- At least two retinal implants hold promise for restoring some vision in patients with late-stage disease.

TABLE. INVESTIGATIONAL THERAPIES FOR DRY AMD

Study Drug (Company)	Mechanism	Delivery	Trial NCT	Trial Status	Completion	Last Update
Phase 3						
Vonaprument (ANX007, Annexon)	C1q inhibitor	Intravitreal	NCT06510816	Active, not recruiting	October 2026	November 2025
Elamipretide (Stealth Biotherapeutics)	Mitochondrial enhancer/ cardiolipin blocker	Subcutaneous	NCT06373731	Active, not recruiting	August 2027	November 2025
Tinlarebant (LBS-008, Belite Bio)	RBP4 antagonist	Oral	NCT05949593	Recruiting	August 2027	February 2025
Cemdisiran (Regeneron)	siRNA/C5 inhibitor	Subcutaneous	NCT06541704	Recruiting	November 2027	November 2025
Phase 2						
Eyecyte-RPE (Eyestem Research)	RPE cell replacement	Subretinal	NCT06394232	Recruiting	April 2025	September 2024
AVD-104 (Aviceda Therapeutics)	Siglec binding	Intravitreal	NCT05839041	Active, not recruiting	September 2025	December 2024
JNJ-1887 (JNJ-81201887; AAVCAGsCD59; Janssen)	sCD59 overexpression/ membrane attack complex inhibition	Intravitreal	NCT05811351	Active, not recruiting	February 2026	November 2025
OCU-410 (Ocugen)	Gene therapy (*RORA* overexpression)	Subretinal	NCT06018558	Active, not recruiting	February 2026	June 2025
BI 771716 (Boehringer Ingelheim/CDR-Life)	Proprietary antibody fragment	Oral	NCT06722157	Active, not recruiting	October 2026	October 2025
RPESC-RPE-4W (Luxa Biotechnology)	RPE cell replacement	Subretinal	NCT04627428	Recruiting	December 2026	October 2025
BI 1584862 (Boehringer Ingelheim)	Phospholipid modulator	Oral	NCT06769048	Recruiting	February 2027	October 2025
GAL-101 (Galimedix Therapeutics/Théa Open Innovation)	Amyloid-beta aggregation inhibitor	Topical	NCT06659549	Recruiting	March 2027	June 2025
CPCB-RPE1 (Regenerative Patch Technologies)	RPE cell replacement	Subretinal	NCT06557460	Recruiting	December 2027	August 2025
ONL1204 (ONL Therapeutics)	FasR inhibitor	Intravitreal	NCT06659445	Recruiting	November 2028	October 2025
OpRegen (RG6501, Lineage Cell Therapeutics, Genentech/Roche)	RPE cell replacement	Subretinal	NCT05626114	Recruiting	March 2031	October 2025
Iptacopan (LNP023, Novartis)	Complement factor B inhibitor	Oral	NCT05230537	Active, not recruiting	October 2026	July 2025
Phase 1 and 1/2						
VOY-101 (Perceive Biotherapeutics)	Gene therapy (complement factor H)	Intravitreal	NCT05380492 NCT06087458	Active, not recruiting Recruiting	November 2025 June 2027	April 2024 October 2025
PST-611 (Eyevensys)	Gene therapy (transferrin)	Ciliary muscle injection	NCT07024732	Not yet recruiting	December 2025	June 2025
ASP7317 (Astellas)	RPE cell replacement	Subretinal	NCT03178149	Recruiting	June 2026	October 2025
K8 (Inflammasome Therapeutics)	Inflammasome inhibition	Intraocular implant	NCT06164587	Recruiting	August 2026	August 2025
KRIYA-825 (Kriya Therapeutics)	Gene therapy (anti-C3 and C5)	Suprachoroidal	NCT06765980	Recruiting	December 2027	September 2025
National Eye Institute	RPE cell replacement	Subretinal	NCT04339764	Recruiting	May 2029	September 2025

Abbreviation: RPE, retinal pigment epithelium.

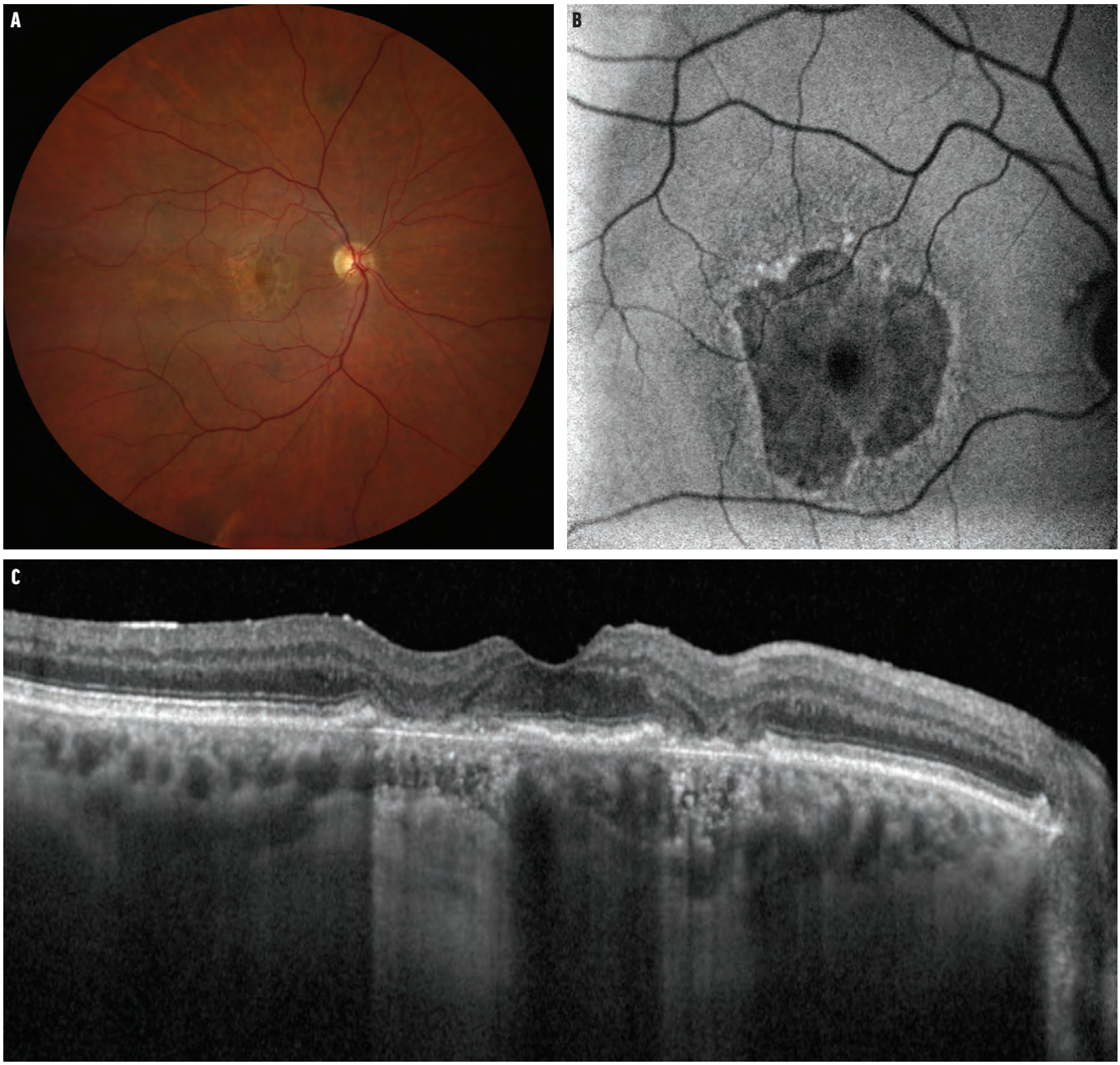
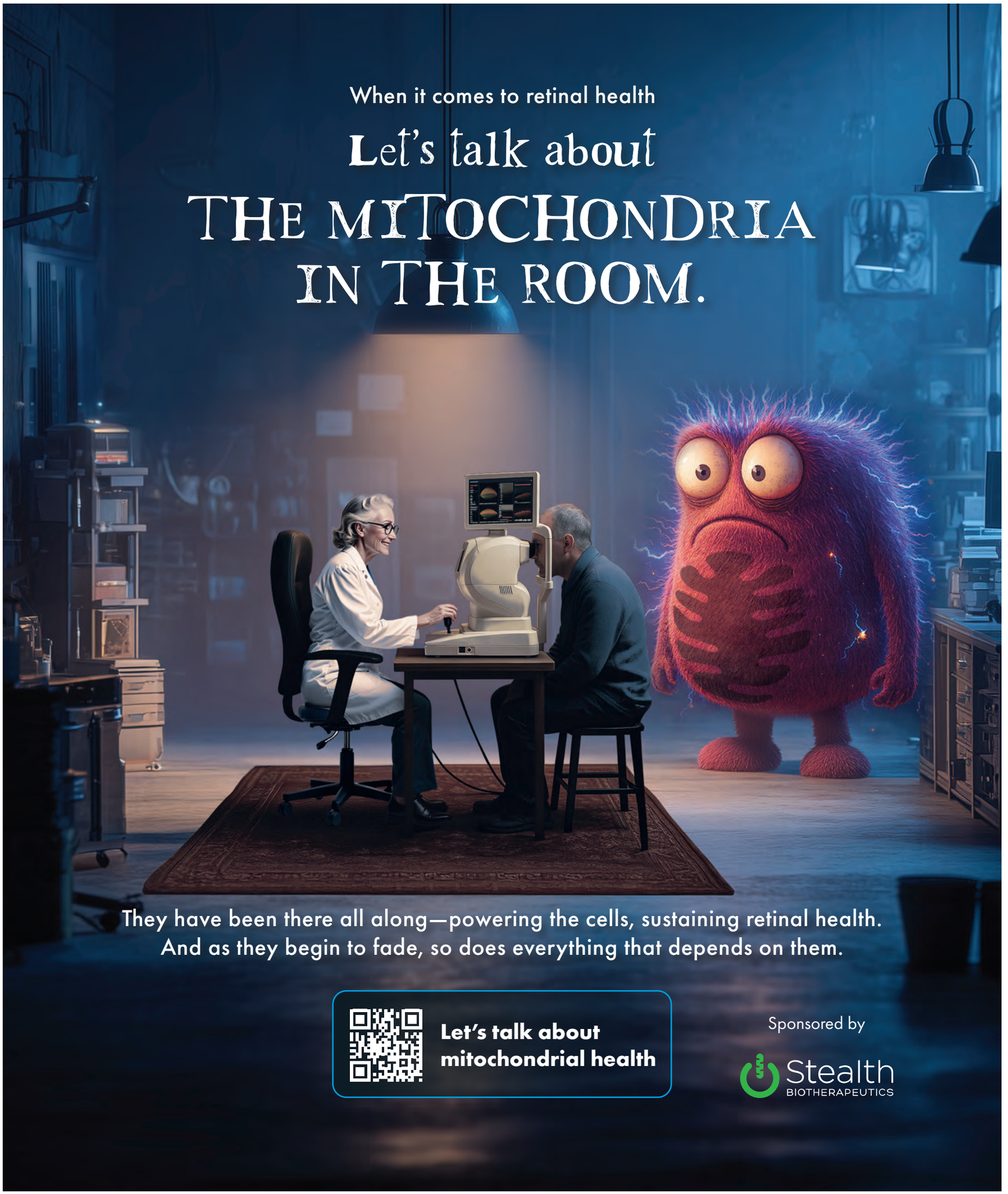


Figure. Fundus photography of a patient with GA that is threatening, but not yet involving, the fovea (A). The color photograph shows RPE loss with a central island. Fundus autofluoresence reveals hypoautofluoresence corresponding to the areas of RPE atrophy with a border of hyperautofluoresence and sparing of the foveal island (B). OCT confirms perifoveal loss of outer retinal layers (EZ and RPE), while the central foveal island's outer retinal layers are preserved (C).

progression of total ellipsoid zone (EZ) attenuation by 43% compared with baseline (P = .0034) and partial EZ attenuation by 47% compared with placebo (P = .0034) after 48 weeks (n = 176).[4]

Tinlarebant (LBS-008, Belite Bio) is a small molecule aimed at reducing the accumulation of the visual cycle pathway metabolite A2E, a toxic component of lipofuscin, by inhibiting retinal binding protein 4. The PHOENIX trial (NCT05949593) is investigating the effect of 5 mg daily oral tinlarebant with a primary endpoint of the rate of change in GA lesion size after promising phase 2 results in Stargardt disease.[5]

Vonaprument (ANX007, Annexon) is a Fab antibody fragment targeting C1q dosed monthly or every other month via intravitreal injection. The fully-enrolled ARCHER II study (NCT06510816) has a primary endpoint of prevention of ≥ 15-letter loss.[6] The phase 2 ARCHER study did not meet its primary endpoint of GA area reduction but found that treatment reduced the rates of ≥ 15-letter loss in BCVA to 5.6% and 9.8% in patients treated monthly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STALLED PROGRAM

ALK-001 (gildeuretinol, Alkeus Pharmaceuticals), an oral therapy designed to reduce the dimerization of vitamin A, did not meet its primary endpoint in the phase 3 SAGA trial, although treatment led to a 15.3% reduction in GA lesion growth rate from 6 to 24 months.[1] ALK-001 is currently under investigation for the treatment of Stargardt disease in the phase 2 TEASE trial (NCT02402660).

1. Topline results from Alkeus Pharmaceuticals' study of oral gildeuretinol demonstrate significant trend in slowing GA progression and visual function improvement [press release]. Alkeus Pharmaceuticals. October 23, 2024. Accessed September 24, 2024. tinyurl.com/r72eyjnz

and every other month, respectively, compared with 21.3% in sham patients.[7] Pooled analysis showed reduced EZ loss in the central 2.0 mm by 48% and central 1.5 mm by 50% after 1 year.[8]

Cemdisiran (Regeneron), an siRNA that reduces complement factor 5 (C5), is under investigation in the SIENNA phase 3 trial as a subcutaneous monotherapy or in combination with pozelimab, a C5 antibody, to treat GA (NCT06541704) with a primary endpoint of GA lesion area growth on fundus autofluorescence. In a phase 3 trial for myasthenia gravis, treatment with the combination therapy led to nearly 99% inhibition of complement activity.[9]

PHASE 2 STUDIES

AVD-104 (Aviceda Therapeutics) is a sialic acid-coated nanoparticle that helps recruit complement factor H to cell membranes and binds siglec receptors on macrophages, which is believed to reduce phagocytic and inflammatory activity.[10] The phase 2 SIGLEC trial (NCT05839041) is measuring the rate of GA area growth after monthly intravitreal injections of low- or high-dose AVD-104 compared with 2 mg avacincaptad pegol over 1 year. Preliminary results from part 1 of the trial (n = 30) showed a 48% reduction in GA lesion growth rate compared with fellow eyes and a 4.8- to 6.5-letter dose-dependent improvement compared with baseline at 3 months following a single injection.[11]

BI 1584862 (Boehringer Ingelheim) is a phospholipid modulator with daily oral dosing that is being studied in the dose-escalation JADE study (NCT06769048) comparing this drug with placebo, measuring the rate of change in GA area after 50 weeks.[12]

BI 771716 (Boehringer Ingelheim/CDR-Life) is an antibody fragment under investigation in the VERDANT study (NCT06722157) comparing the rate of change in GA area after 56 weeks of intravitreal BI 771716 versus pegcetacoplan. Safety endpoints were met in a prior phase 1 study (NCT06006585).[12]

Gal-101 (Galimedix Therapeutics/Théa Open Innovation) is a small-molecule inhibitor of toxic amyloid beta monomer aggregation under investigation for the treatment of Alzheimer disease, GA, and glaucoma. Following a successful phase 1 safety trial,[13] the eDREAM trial (NCT06659549) is testing GAL-101 eye drops versus placebo over 48 to 96 weeks, with a primary outcome of change in GA area.

ONL1204 (ONL Therapeutics) inhibits the Fas receptor, which triggers cells to undergo apoptosis. The GALAXY trial (NCT06659445) is comparing a dose escalation of every 12- or 24-week intravitreal dosing with placebo or monthly avacincaptad pegol, with a primary endpoint of GA lesion area change. Preliminary phase 1b data showed a 42% to 50% reduction in this metric after two injections 3 months apart.[14]

Iptacopan (LNP023, Novartis) is an oral complement factor B inhibitor under investigation to potentially prevent conversion from early or intermediate AMD to late-stage disease. The phase 2 trial (NCT05230537) enrolled 170 patients who were randomly assigned oral iptacopan or placebo and are being followed for 2 years.

Gene Therapies

JNJ-1887 (AAVCAGsCD59, Janssen) is an intravitreal gene therapy overexpressing soluble CD59, an endogenous protein that inhibits the formation of the membrane attack complex. The PARASOL study (NCT05811351) is comparing high and low doses administered with prophylactic steroids in 305 patients, with a primary outcome of the difference in GA lesion area after 18 months.[15]

OCU-410 (AAV-hRORA, Ocugen), a one-time gene therapy overexpressing the *RORA* gene delivered through subretinal injection, showed a 2-line improvement in LLBCVA and a 44% decrease in GA lesion growth at 9 months compared with controls in part 1 of the ArMaDa trial (NCT06018558).[16] *RORA* is a nuclear hormone receptor believed to regulate lipid metabolism, oxidative stress, and inflammation, including complement signaling.[17]

Stem Cell Therapies

CPCB-RPE1 (Regenerative Patch Technologies) is a subretinal implant consisting of 100,000 human embryonic stem cell-derived retinal pigment epithelium (RPE) cells grown on a synthetic Bruch membrane. In the phase 1 study, several patients showed improved BCVA after 1 year.[18] A phase 2b trial (NCT06557460) is comparing CPCB-RPE1 with sham using the change in retinal sensitivity by microperimetry after 1 year as the primary endpoint.

OpRegen (RG6501, Lineage Cell Therapeutics/Genentech/Roche) is a suspension of 200,000 allogeneic RPE cells delivered subretinally. In phase 1 of the GAlette trial (NCT02286089), 10 patients had a mean increase of

6.2 letters in BVCA after 36 months and durable increases in the external limiting membrane and RPE drusen complex on OCT. Phase 2a of the trial (NCT05626114) is investigating successful surgical delivery of OpRegen to the subretinal space and adverse events 3 months after treatment, with a secondary outcome measure of qualitative improvement in retinal structure by OCT.[19]

RPESC-RPE-4W (Luxa Biotechnology) is a single subretinal dose of 50,000, 150,00, or 250,000 RPE cells derived from human RPE stem cells. Preliminary data from six patients treated with 50,000 cells showed a good safety profile and a BCVA gain of 21.67 letters in a worse-seeing group after 1 year and a more modest 3.3 letter gain after 3 months in a better-seeing group (NCT04627428).[20]

RETINAL PROSTHETICS

The PRIMA implant (Science Corporation) is designed to mimic photoreceptor function by sending visual information and power from a pair of glasses to a subretinal implant that electrically activates inner retinal neurons. The PRIMAvera European study (NCT04676854) showed a mean improvement of 23 letters after 12 months of device implantation in 38 patients, with a feasibility study ongoing in the United States.[21]

The Smaller-Incision New-Generation Implantable Miniature Telescope (SING IMT, Samsara Vision) is under investigation in the CONCERTO study (NCT05438732) for patients with late-stage AMD.[22] Intermediate-term visual and safety outcomes 6 months postoperatively showed that 97.1%, 68.6%, and 51.4% of operated eyes achieved at least 1, 2, and 3 lines in best-corrected distance VA, respectively. In addition, 97.1% of patients were able to read at near distance compared with 28.6% at baseline.[23] The device received a CE mark for the European Union in 2020.[22]

LOOKING AHEAD

In addition to the therapies discussed here, several other phase 1 and phase 1/2 drug candidates use induced pluripotent stem cell-derived RPE; gene therapies targeting complement factor H, C3, and C5; an intraocular implant that elutes kamuvudines, which inhibit inflammasomes; and others. See the Table for more information.

We are excited by the diverse mechanisms of action under investigation. The underlying pathobiology driving GA is likely multifactorial, and therapies targeting multiple mechanisms may be required to fully control the disease (Figure). We are also encouraged by the advances in stem cell and gene therapy technologies and novel delivery systems, which hold great potential as future GA treatments. ■

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

Moments like this deserve your protection.

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

Dr. Arshad Khanani is a compensated physician.

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

IZERVAY is contraindicated in patients with ocular or periocular infections and in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

- Intravitreal injections, including those with IZERVAY, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.

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

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

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

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

Consistent real-world safety across more than 400k vials distributed.[2,4*]

izervay™ (avacincaptad pegol intravitreal solution) 2 mg

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

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

*As of 08/25. Based on samples and commercially distributed vials.
†Based on Symphony data from 3/24-7/25. May not represent entire population.

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

Neovascular AMD

- In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Over 24 months, the rate of neovascular (wet) AMD or choroidal neovascularization in the GATHER2 trial was 12% in the IZERVAY group and 9% in the sham group. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

Increase in Intraocular Pressure

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

ADVERSE REACTIONS

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

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

MAT-US-IZE-2025-00619 10/25

astellas

IZERVAY™ (avacincaptad pegol intravitreal solution)
Rx only
Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 800-707-4479.

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

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
IZERVAY must be administered by a qualified physician.
2.2 Recommended Dosage
The recommended 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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ANTI-VEGF AND BEYOND:

EXPANDING THERAPEUTIC OPTIONS FOR WET AMD

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

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



After 20 years of therapy with anti-VEGF agents, the landscape for wet AMD management is now transforming from anti-VEGF monotherapy to a diverse pipeline of novel disease targets and innovative delivery technologies. In this article, we summarize the spectrum of emerging therapies for wet AMD (Table), including biosimilars, gene therapy, tyrosine kinase inhibitors (TKIs), and other novel drug targets.

GENE THERAPIES

Current investigational gene therapies for wet AMD employ a one-time administration (intravitreal, subretinal, or suprachoroidal) of an adeno-associated viral (AAV) vector carrying non-integrating transgenes encoding anti-VEGF proteins or multitarget constructs. By enabling continuous intraocular production of these therapeutics, gene therapy may greatly reduce or eliminate anti-VEGF injection burden in patients with wet AMD.

4D-150 (4D Molecular Therapeutics) is an intravitreally delivered AAV R100 vector containing an aflibercept/anti-VEGF-C miRNA transgene. In the phase 1/2 PRISM trial (NCT05197270) 4D-150 reduced the injection burden by 83% and eliminated injections entirely in 57% of patients, compared with aflibercept (Eylea, Regeneron) every 8 weeks.[1] The phase 3 4FRONT-1 (NCT06864988) and 4FRONT-2 (NCT07064759) trials are enrolling.[2]

ABBV-RGX-314 (sura-vec, Regenxbio/Abbvie) contains a

AT A GLANCE

- By enabling continuous intraocular production of anti-VEGF proteins, gene therapy may greatly reduce or eliminate anti-VEGF intravitreal injection burden in patients with wet AMD.
- Tyrosine kinase inhibitors, which block receptor-mediated (ie, VEGFR) signaling by decreasing receptor phosphorylation, may have the potential to augment and replace existing therapies.
- Novel drug delivery methods include suprachoroidal, subretinal, topical, and even subcutaneous routes.

THE RETINA PIPELINE

TABLE. SUMMARY OF WET AMD THERAPIES IN DEVELOPMENT (AS OF NOVEMBER 2025)					
Therapy (Company)	**Drug Type/Mechanism**	**Delivery Method**	**Trial Identifier**	**Trial Status**	**Primary Completion**
Phase 3					
4D-150 (4D Molecular Therapeutics)	Gene therapy	Intravitreal	NCT06864988 NCT07064759	Recruiting	June 2027 November 2028
ABBV-RGX-314 (Regenxbio/Abbvie)	Gene therapy	Subretinal	NCT05407636 NCT04704921	Recruiting	October 2026 December 2026
ADVM-022 (Adverum)	Gene therapy	Intravitreal	NCT06856577	Recruiting	December 2026
EYP-1901 (EyePoint)	Tyrosine kinase inhibitor	Implant	NCT06668064 NCT06683742	Active, not recruiting	August 2026 October 2026
IBI302 (Innovent Biologics)	Fusion protein	Intravitreal	NCT05972473	Active, not recruiting	February 2027
KSI-301/KSI-501 (Kodiak Sciences)	Anti-VEGF-A/fusion protein	Intravitreal	NCT06556368	Active, not recruiting	August 2026
OTX-TKI (Ocular Therapeutix)	Tyrosine kinase inhibitor	Implant	NCT06223958 NCT06495918	Active, not recruiting	April 2026 January 2027
RC28-E (RemeGen)	Anti-VEGF/fibroblast growth factor 2	Intravitreal	NCT05727397	Recruiting	November 2025
Phase 2					
CLS-AX (Clearside Biomedical)	Tyrosine kinase inhibitor	Suprachoroidal	NCT05891548	Complete	
D-4517.2 (Ashvattha Therapeutics)	Tyrosine kinase inhibitor	Subcutaneous	NCT05387837	Active, not recruiting	May 2025
ISTH0036 (Isarna)	Antisense oligonucleotide	Intravitreal	EudraCT 2021-001213-36	Complete	
RBM-007 (Ribomic)	Anti-fibroblast growth factor 2	Intravitreal	NCT04200248	Complete	
SYL1801 (Sylentis)	siRNA	Topical	NCT05637255	Complete	
TO-0-1002 (Theratocular Biotek)	Tyrosine kinase inhibitor	Topical	NCT05390840	Unknown status	March 2024
Phase 1 and 1/2					
AM712 (AffaMed)	Anti-VEGF/angiopoietin-2	Intravitreal	NCT05345769	Complete	
AR-14034 (Alcon)	Tyrosine kinase inhibitor	Implant	NCT05769153	Recruiting	September 2027
AXT107 (AsclepiX Therapeutics)	VEGF-A/C inhibiting and Tie2 activating	Suprachoroidal	NCT05859776	Active, not recruiting	March 2025
CG-P5 (Caregen)	VEGFR2-inhibitor	Topical	NCT06132035	Recruiting	May 2025
Episcleral brachytherapy	Focal radiation	Episcleral	NCT02988895	Unknown status	May 2023
EXG102-031 (Exegenesis Bio)	Gene therapy	Subretinal	NCT05903794	Active, not recruiting	February 2026
FT-003 (Frontera Therapeutics)	Gene therapy	Intravitreal	NCT06492863	Recruiting	October 2024
HG202 (HuidaGene Therapeutics)	Gene therapy	Subretinal	NCT06031727 NCT06623279	Recruiting Not yet recruiting	June 2025 February 2027
KH631 (Chengdu Origen/Vanotech)	Gene therapy	Subretinal	NCT05657301	Recruiting	September 2026
KH658 (Chengdu Origen/Vanotech)	Gene therapy	Suprachoroidal	NCT06458595 NCT06825858	Recruiting Not yet recruiting	March 2026 Unknown
Lenvatinib (AiViva BioPharma)	Tyrosine kinase inhibitor	Periocular gel	NCT05698329	Active, not recruiting	March 2025
MK-3000 (EyeBio/Merck)	Anti-FZD4, LRP5, and TSPAN12 Wnt agonist	Intravitreal	NCT05919693	Complete	
OLX10212 (OliX Pharmaceuticals)	siRNA	Intravitreal	NCT05643118	Recruiting	November 2024
PAN 90806 (PanOptica/Zhaoke)	Tyrosine kinase inhibitor	Topical	NCT03479372	Complete	
Recently Discontinued Programs					
AR-13503 (Aerie/Alcon)	Rho kinase and protein kinase C inhibitor	Implant	NCT03835884	Complete	
AKST4290 (Alkahest)	CCR3 inhibitor	Oral	NCT04331730	Complete	
OPT-302 (Opthea)	Anti-VEGF-C/D	Intravitreal	NCT04757610 NCT04757636	Terminated	
UBX1325 (Unity Biotechnology)	B-cell lymphoma-extra-large inhibitor	Intravitreal	NCT05275205	Complete	

Image courtesy of Lejla Vajzovic, MD

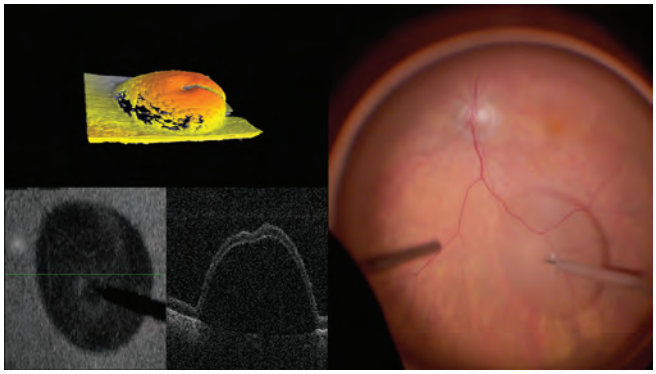

Figure. Intraoperative OCT can help clinicians ensure proper subretinal bleb formation during treatment with gene therapy.

ranibizumab-like protein transgene delivered subretinally or suprachoroidally via an AAV8 vector (Figure). The phase 2b/3 ATMOSPHERE (NCT04704921) and phase 3 ASCENT (NCT05407636) trials are assessing noninferiority of subretinal ABBV-RGX-314 to monthly ranibizumab (Lucentis, Genentech/Roche) and bimonthly aflibercept, respectively. In the phase 2 AAVIATE trial (NCT04514653), suprachoroidal delivery of ABBV-RGX-314 led to a reduction or elimination of supplemental anti-VEGF injections in 80% and 50% of patients, respectively, over 6 months compared with monthly ranibizumab.[3]

ADVM-022 (ixo-vec, Adverum) contains an aflibercept transgene delivered intravitreally using the AAV2.7m8 vector. In the phase 2 LUNA trial (NCT05536973), ADVM-022 led to an 80% reduction in supplemental anti-VEGF injections over 52 weeks compared with patients' prior injection burden. Additionally, 50% of patients remained injection free.[4] The phase 3 ARTEMIS trial (NCT06856577) is enrolling.

FT-003 (Frontera Therapeutics) is an intravitreally delivered AAV2.7m8 vector containing an aflibercept transgene. Interim data from a phase 1/2 trial (NCT06492863) demonstrated an 80% reduction in the need for supplemental aflibercept injections, along with improvements in BCVA and retinal structure.[5]

Several gene therapies are in phase 1 trials, including EXG102-031 (Exegenesis Bio; NCT05903794), HG202 (HuidaGene Therapeutics; NCT06031727 and NCT06623279), KH631 (Chengdu Origen/Vanotech; NCT05657301), and KH658 (Chengdu Origen/Vanotech; NCT06825858 and NCT06458595).

BISPECIFIC AND TRISPECIFIC DRUGS

Anti-VEGF therapy coupled with alternative pathway targeting is a promising strategy to improve efficacy of wet AMD therapies; this approach was recently validated with the approval of faricimab (Vabysmo, Genentech/Roche), a bispecific VEGF-A/angiopoietin-2 antibody. Others are under investigation, including the following:

KSI-301 (tarcocimab tedromer, Kodiak Sciences) is an intravitreally delivered anti-VEGF-A antibody, which did not meet its primary endpoint of noninferiority to 8-week dosing of aflibercept based on BCVA in the phase 2b/3 DAZZLE trial (NCT04049266).[6] The phase 3 DAYBREAK trial (NCT06556368) is assessing adjusted dosing and trial design with a primary endpoint of noninferiority to aflibercept based on BCVA.

KSI-501 (tabirafusp tedromer, Kodiak Sciences) is also under investigation as part of the DAYBREAK trial. This therapy is an intravitreal bispecific VEGF trap/anti-interleukin-6 fusion protein.

IBI302 (efdamrofusp alfa, Innovent Biologics) is an intravitreal recombinant fusion protein containing decoy VEGFR and a complement receptor 1 domain to reduce VEGF and C3b/C4b activation. In a phase 2 trial (NCT05403749), IBI302 showed noninferiority to every-8-week aflibercept based on BCVA.[7] The phase 3 STAR trial (NCT05972473) is ongoing.

RC28-E (RemeGen) is an intravitreally delivered decoy receptor trap fusion protein that binds soluble VEGF and fibroblast growth factor 2. An open-label phase 1 clinical trial showed evidence of improvements in BCVA and retinal anatomic parameters.[8] A phase 3 trial (NCT05727397) is assessing noninferiority of RC28-E with aflibercept based on BCVA.

AXT107 (AsclepiX Therapeutics) is a suprachoroidally injected, integrin-regulating peptide that inhibits VEGF-A/C and activates Tie2 signaling and has completed recruitment in phase 1/2 testing in the DISCOVER trial (NCT05859776).

AM712 (AffaMed) is a recombinant humanized monoclonal antibody targeting VEGF and angiopoietin-2 that showed improvements in BCVA, central subfield thickness (CST), and anti-VEGF dosing frequency in the phase 1 CONQUER trial (NCT05345769).[9]

TYROSINE KINASE INHIBITORS

TKIs block receptor-mediated (ie, VEGFR) signaling by decreasing receptor phosphorylation. These drugs may have the potential to augment or replace existing anti-VEGF or multitarget therapies.

EYP-1901 (Duravyu, EyePoint Pharmaceuticals) is a semiannually administered intravitreal implant containing the TKI vorolanib. In the phase 2 DAVIO2 trial, EYP-1901 demonstrated noninferiority to aflibercept and reduced supplemental anti-VEGF injection burden by approximately 80%.[10] The phase 3 LUCIA (NCT06683742) and LUGANO (NCT06668064) trials are fully enrolled.

OTX-TKI (Axpaxli, Ocular Therapeutix) is an intravitreal hydrogel implant containing axitinib. In a phase 1 trial (NCT04989699), treatment with OTX-TKI showed noninferiority to aflibercept and led to an 89% reduction in anti-VEGF injection burden.[11] The phase 3 SOL-1 (NCT06223958) and SOL-R (NCT06495918) trials are ongoing.

ANTI-VEGF BIOSIMILARS

Two ranibizumab (Lucentis, Genentech/Roche) and six aflibercept (Eylea, Regeneron) biosimilars are FDA approved in the United States and several others have been approved in the European Union (Table). The bevacizumab (Avastin, Genentech/Roche) biosimilar Lytenava (ONS-5010, Outlook Therapeutics) is approved for intravitreal use by the European Medicines Agency, and the company was recently issued a complete response letter by the FDA in August 2025.

TABLE. FDA- AND EMA-APPROVED ANTI-VEGF BIOSIMILARS

Drug Name (Biologic, Company)	FDA Approved	EMA Approved
Aflibercept Biosimilars		
Afqlir/Enzeevu (aflibercept-abzv, Sandoz)	✓	✓
Afiveg (Stada)	X	✓
Ahzantive/Baiama (aflibercept-mrbb, Formycon/Klinge)	✓	✓
Eiyzey/Vgenfli (Polpharma/Sandoz)	X	✓
Eydenzelt (aflibercept-boav, Celltrion)	✓	✓
Eyluxvi (Alteogen)	X	✓
Mynzepli (aflibercept-tvnh, Alvotech)	X	✓
Opuviz (aflibercept-yszy, Samsung Bioepis/Biogen)	✓	✓
Pavblu (aflibercept-ayyh, Amgen)	✓	✓
Yesafili (aflibercept-jbvf, Biocon Biologics)	✓	✓
Ranibizumab Biosimilars		
Byooviz (ranibizumab-nuna, Samsung Bioepis/Biogen)	✓	✓
Cimerli (ranibizumab-eqrn, Sandoz)	✓	X
Epruvy (Midas Pharma)	X	✓
Ranivisio (Bioeq)	X	✓
Rimmyrah (Qilu Pharma)	X	✓
Ximluci (Stada/Xbrane Biopharma)	X (Received CRL)	✓
Bevacizumab Biosimilars		
Lytenava (bevacizumab-vikg, Outlook Therapeutics)	X (Received CRL)	✓

Abbreviations: EMA, European Medicines Agency; CRL, complete response letter.

CLS-AX (axitinib, Clearside Biomedical) is a suprachoroidally delivered TKI. In the phase 2b ODYSSEY trial (NCT05891548), treatment with CLS-AX was noninferior to aflibercept every 8 weeks based on BCVA and led to an 84% reduction in anti-VEGF injections.[12]

D-4517.2 (migaldendranib, Ashvattha Therapeutics) is a subcutaneously administered TKI that bioaccumulates within choroidal neovascularization. In a phase 2 trial (NCT05387837), treatment with D-4517.2 led to a 69% reduction in supplemental aflibercept injections compared with patients' injection history, with stable BCVA and CST.[13]

TO-O-1002 (MG-O-1002, Theratocular Biotek) is a TKI delivered as a topical eye drop three times a day. In a phase 2a study (NCT05390840), TO-O-1002 was shown to reduce the need for supplemental anti-VEGF injections by 86% compared with a placebo drop.[14]

KHK4951 (tivozanib, Kyowa Kirin Group) is another topical TKI in a phase 2 trial (NCT06116890) evaluating high, middle, and low doses. The primary outcome is the reduction of 15 or more letters in BCVA at week 44; secondary

outcomes include the need for intravitreal aflibercept and OCT and fluorescein angiography changes.

Other TKIs in early-phase investigations include AR-14034 (axitinib, Alcon; NCT05769153), PAN-90806 (PanOptica/Zhaoke; NCT03479372), and lenvatinib (AIV-007, AiViva BioPharma; NCT05698329).

NOVEL DRUG TARGETS AND DELIVERY MODALITIES

Innovation continues for novel drug targets, offering the opportunity to expand the therapeutic repertoire outside of mainstay anti-VEGF therapy.

ISTH0036 (Isarna) is an intravitreally administered antisense oligonucleotide that reduces expression of TGF-β2 to reduce profibrotic signaling. In a recent phase 2a trial (EudraCT 2021-001213-36), ISTH0036 led to a 70% decrease in subretinal hyperreflective material, stable or improved BCVA, and decreased CST relative to baseline.[15]

RBM-007 (umedaptanib pegol, Ribomic) is an intravitreally delivered pegylated anti-FGF-2 RNA aptamer with antifibrotic activity. In the phase 2 TOFU (NCT04200248) and RAMEN (NCT04640272) trials, RBM-007 did not show a benefit over aflibercept alone. The TEMPURA open-label extension study (NCT04895293) showed BCVA and CST stabilization or improvements compared with baseline in anti-VEGF-naïve patients.[16]

SYL1801 (Sylentis) is a daily eye drop containing an anti-NRARP siRNA that modulates notch-Wnt crosstalk to reduce angiogenesis; the phase 2a trial (NCT05637255) showed stabilization or improvements in BCVA compared with baseline.[17]

MK-3000 (Restoret, EyeBio/Merck) is an intravitreal anti-FZD4/ LRP5/TSPAN12 antibody that activates canonical Wnt signaling. In the phase 1/2 AMARONE trial (NCT05919693), MK-3000 in combination with monthly aflibercept resulted in improved BCVA and decreased CST.[18]

OLX10212 (OliX Pharmaceuticals) is an intravitreally delivered siRNA targeting an undisclosed target involved in inflammation, which is currently undergoing phase 1 testing (NCT05643118).

CG-P5 (Caregen) is a once-daily eye drop containing a VEGFR2-inhibiting peptide. A phase 1 study (NCT06132035) is assessing the safety of CG-P5 compared with a placebo drop or monthly aflibercept.

Episcleral brachytherapy (Salutaris Medical Devices) involves the delivery of transscleral radiation to reduce actively proliferating, pathological cells within areas of choroidal neovascularization. In the phase 1 NEAMES trial (NCT02988895), this focal radiation treatment reduced anti-VEGF injection burden compared with patient history.[19]

LOOKING AHEAD

The wet AMD treatment landscape is rapidly shifting toward highly durable, targeted, and potentially curative approaches. As we enter 2026, key phase 3 readouts and potential regulatory approvals could mark the beginning of a new era, one in which anti-VEGF monotherapy is augmented by an armamentarium of complementary therapies that can be tailored to the needs of an individual patient. ■

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TREATING UVEITIS TODAY AND TOMORROW

Many novel therapies are under investigation to treat noninfectious uveitis and uveitic macular edema.

By Yesde Esther Son, MD, PhD, and Tedi Begaj, MD


Noninfectious uveitis (NIU) comprises a heterogeneous group of inflammatory disorders in which therapy is shaped by anatomic phenotype, systemic associations, and relapse risk. Local corticosteroid options, conventional antimetabolites, and anti-tumor necrosis factor (anti-TNF) therapy anchor current practice. Nonetheless, steroid-related ocular adverse events and systemic treatment constraints have motivated a pipeline focused on cytokine-specific biologics and oral pathway inhibitors, together with steroid-sparing topical and local candidates for anterior disease and uveitic macular edema (UME).

This article focuses on agents under investigation for the treatment of NIU/UME. To help you navigate the robust list, each therapy is tagged with a color-coordinated clinical readiness tier (CRT), defined as the following:

- **CRT-5:** on-label standard
- **CRT-4:** off-label standard with prospective evidence/broad use
- **CRT-3:** promising, late-phase
- **CRT-2:** early/uncertain
- **CRT-1:** negative/not recommended
- **CRT-0:** perioperative only

CORTICOSTEROIDS

Long-acting intravitreal corticosteroid implants remain foundational therapeutic choices for chronic NIU of the posterior segment (NIU-PS). The FDA-approved options include the 0.7 mg dexamethasone biodegradable intravitreal

AT A GLANCE

- Long-acting intravitreal corticosteroid implants remain foundational therapeutic choices for chronic noninfectious uveitis of the posterior segment.
- For steroid-sparing therapy, systemic antimetabolites and adalimumab are well-established, while infliximab is used off-label for refractory cases.
- Near-term readouts most likely to alter practice include intraocular non-steroidal cytokine therapy for uveitic macular edema, oral precision immunology, and topical steroid-sparing therapy for anterior disease.

implant (Ozurdex, Abbvie; Figure), the 0.59 mg fluocinolone acetonide implant (Retisert, Bausch + Lomb), the 0.18 mg fluocinolone acetonide insert (Yutiq, Ani)—which will effectively be replaced by the 0.19 mg implant (Illuvien, Ani)—and suprachoroidal triamcinolone acetonide (Xipere, Clearside Biomedical/Bausch + Lomb).

Two perioperative depots—9% dexamethasone intraocular suspension (Dexycu, EyePoint) and the 0.4 mg dexamethasone intracanalicular insert (Dextenza, Ocular Therapeutix)—are used during cataract surgery but are not chronic NIU therapies. Dexamethasone nanoparticle eye drops (OCS-01, Oculis) are under investigation for uveitis-related/post-surgical macular edema (NCT05608837).

ANTIMETABOLITES

Systemic methotrexate (MTX; generic) and mycophenolate mofetil (CellCept, Genentech/Roche) are guideline-concordant, first-line steroid-sparing agents. In the FAST randomized trial, overall efficacy was similar; exploratory analyses favored methotrexate in intermediate/posterior/panuveitis phenotypes.[1]

Intravitreal MTX (generic) has advanced beyond case series. In the MERIT trial, the dexamethasone implant outperformed intravitreal MTX and ranibizumab (Lucentis, Genentech/Roche) at 12 to 24 weeks based on OCT outcomes in UME; however, intravitreal MTX remains a pragmatic option when steroid-induced IOP or systemic issues dominate.[2]

ANTI-TNF-α AGENTS

Adalimumab (Humira, Abbvie) is the established systemic biologic for NIU. The VISUAL 1 and 2 randomized trials reduced time to treatment failure versus placebo.[3,4] In juvenile idiopathic arthritis–associated uveitis (JIA-U), adalimumab plus MTX improved control in two randomized studies.[5-8]

Infliximab (Remicade, Janssen) is widely used off-label for severe Behçet/NIU-PS and cases refractory to antimetabolites and/or adalimumab; however, the evidence comes from prospective and retrospective series rather than modern phase 3 randomized controlled trials.[9,10] Additional systemic TNF inhibitors are employed off-label when adalimumab is inadequate or not tolerated. Golimumab (Simponi, Janssen) has supportive cohort data in refractory JIA-U,[11] and certolizumab pegol (Cimzia, UCB) reduced acute anterior uveitis (AAU) flares in axial spondyloarthritis in the open-label phase 4 C-VIEW study.[12]

Local anti-TNF agents remain investigational. Intravitreal adalimumab is under investigation compared with systemic dosing (NCT02706704). Intravitreal infliximab shows mixed outcomes and safety signals in small studies (eg, for Behçet posterior uveitis) and is not recommended as a substitute for systemic therapy.[9,10] Etanercept (Enbrel, Amgen) is not favored in uveitis based on neutral/negative trials and reports of paradoxical worsening of uveitis.[13-16]

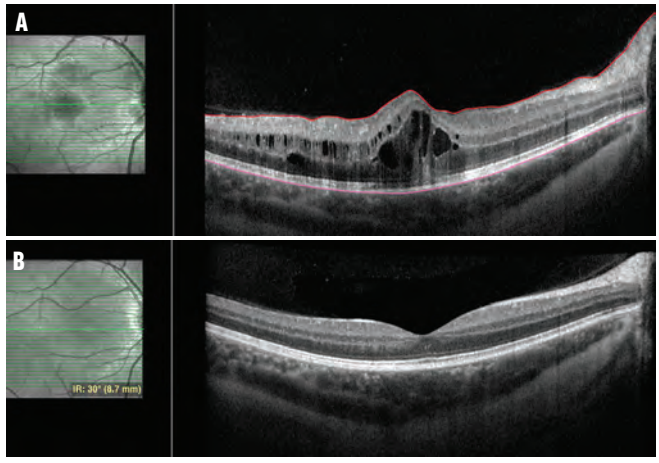

Figure. OCT imaging shows significant cystoid macular edema in a patient with sarcoid anterior/intermediate uveitis (A). One month after treatment with a dexamethasone intravitreal implant, the edema has resolved (B).

ANTI-CYTOKINE ANTIBODIES (NON-TNF)

Systemic IL-6 inhibition with tocilizumab (Actemra, Genentech/Roche) shows bioactivity in a prospective NIU study (NCT01717170) and is used in refractory UME, particularly after anti-TNF failure.[17] In pediatric JIA-U, the phase 2 APTITUDE trial did not meet its primary endpoint; signals of benefit were most evident in eyes with persistent UME (greater central subfield thickness reduction and visual acuity trend) and in patients requiring anti-TNF rescue, with subsequent observational data suggesting more rapid edema resolution with intravenous versus subcutaneous dosing in some series.[18-20] Intravitreal tocilizumab for UME is limited to small/early reports; most evidence reflects systemic administration.[21-23]

Vamikibart (RO7200220/RG6179, Genentech/Roche) is an investigational human monoclonal antibody against IL-6; it is injected intravitreally and is under investigation in the phase 3 MEERKAT and SANDCAT trials for UME (NCT05642312 and NCT05642325). MEERKAT recently met its primary endpoint (the proportion of patients with a 15-letter or more improvement from baseline in BCVA at week 16), and while SANDCAT showed similar vision gains, it did not meet the primary endpoint.[24]

Targeting IL-12/23 with ustekinumab (Stelara, Janssen) has supportive observational signals in a phase 2 trial (NCT02911116) for NIU/Behçet but no phase 3 program. However, targeting IL-17A has produced divergent results. Ixekizumab (Taltz, Eli Lilly) is recruiting an open-label proof-of-concept study in refractory NIU (NCT06085079). Secukinumab (Cosentyx, Novartis) failed to meet the primary endpoints across three phase 3 subcutaneous

trials[25]; however, small open-label data suggested activity with intravenous dosing in uveitis.[26] Finally, the high-affinity, small-protein IL-17A blocker izokibep (Acelyrin/Affibody) did not meet the primary endpoint in a phase 2b/3 NIU study (NCT05384249).

JAK/STAT AND TYK2 PATHWAY INHIBITORS

Oral small-molecule inhibitors are another significant innovation in the uveitis space. Brepocitinib (Priovant Therapeutics), a dual JAK1/TYK2 inhibitor, completed a positive phase 2 NIU study (NCT05523765) and is in phase 3 (NCT06431373). The selective TYK2 inhibitor ESK-001 (Alumis) is in a randomized phase 2 proof-of-concept study for non-anterior NIU (NCT05953688).

Baricitinib (Olumiant, Eli Lilly), a JAK1/2 inhibitor, is under study in pediatric JIA-U (NCT04088409).[27] Upadacitinib (Rinvoq, Abbvie) is being evaluated prospectively to reduce AAU flares in axial spondyloarthritis (NCT07018206), addressing prevention rather than treatment of NIU. Tofacitinib (Xeljanz, Pfizer) has encouraging adult and pediatric case series data (including for Blau syndrome and JIA-U) but no dedicated phase 3 NIU program.[28-30] Although filgotinib (Gilead), a preferential JAK1 inhibitor, showed efficacious signals in randomized testing, the NIU program (NCT03207815) was terminated.[31]

NOVEL MECHANISMS

Dazdotuftide (TRS01, Tarsier Pharma) is a first-in-class topical non-steroidal immunomodulatory eye drop for NIU; a phase 3 trial is completed, and a Special Protocol Assessment has been granted for the next registrational trial (NCT05042609). Sirolimus (DE-109, Santen), a novel mammalian target of rapamycin inhibitor, showed dose-related bioactivity but missed its primary endpoint in the phase 3 SAKURA trial (NCT01358266).[32,33]

TREATING UVEITIS IN YOUR CLINIC TODAY AND TOMORROW

Near-term readouts most likely to alter practice include: (1) intraocular non-steroidal cytokine therapy for UME (vamikibart); (2) oral precision immunology for non-anterior NIU (brepocitinib and ESK-001); and (3) topical steroid-sparing therapy for anterior disease (dazdotuftide).

Until then, local corticosteroids (ie, Ozurdex and Illuvien), systemic antimetabolites (methotrexate and mycophenolate), and adalimumab remain anchors, while infliximab is valuable for select cases that require higher dose modulation or are refractory to previous therapy. ■

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SETTING EXPECTATIONS FOR GEOGRAPHIC ATROPHY TREATMENT

From early- to late-stage disease, tailored conversations emphasize preservation, proactive care, and supportive strategies.

By Sonia Mehta, MD

Now that treatment options are clinically available for geographic atrophy (GA) secondary to age-related macular degeneration (AMD), managing patients' expectations for outcomes remains paramount.

In clinical trials, complement inhibition therapy has been shown to slow the progression of atrophy by 25% to 34%.[1,2] Importantly, however, neither available agent has been shown to reverse existing atrophy, nor to restore vision. Therefore, the goal of treatment is to stabilize the disease to every extent possible, and thereby, maintain visual function for as long as possible.

Navigating Patient Communication

Patients with GA typically arrive in my clinic complaining of visual symptoms—metamorphopsia, blind spots, or scotomas—that have been progressive over time. Yet, because vision loss typically does not occur until late in the disease process, these patients often have preserved functional vision and good visual acuity. This scenario presents a unique challenge for clinicians: while these are the patients who will benefit the most from complement inhibition therapy, the relative lack of symptoms can lead to hesitancy about starting treatment.

Whenever possible, I like to use results from OCT and fundus autofluorescence imaging to demonstrate where their blind spots are. If I have follow-up data, I will also show patients their disease progression over time. Using imaging in this way, as an educational tool, can help facilitate a discussion about starting treatment.

Furthermore, although GA is a progressive disease, the presentation is heterogenous, and the rate of progression is highly individualized. As such, I tailor the conversation about the goal of treatment based on the presenting anatomy and the prognosis for future lesion growth. With patients whose GA has not yet entered the foveal region, we will discuss how to preserve functional vision for as long as possible. When the fovea has already been affected, the conversation shifts to how we will work together to limit the size of the blind spot.

Establishing Rapport: Setting Expectations and Discussing Risks

One thing we have learned from longer-term follow-up from the pivotal trials of the two complement inhibitors is that there appears to be greater benefit the longer patients are on therapy.[3,4] As a result, having patients involved in the decision making to initiate treatment, and, ultimately, having them adhere to treatment when they will not appreciate any positive change in their visual acuity, is critical for long-term success.

In my experience, getting patients to commit to long-term complement inhibition therapy starts by setting realistic expectations for outcomes. It is vitally important that patients understand that managing GA is like dealing with a speeding train: complement inhibition therapy can slow its progress, but it will not stop it entirely. Patients should also be aware of the risks associated with these medications. Although rare, injection-related complications, such as bleeding, infections of the eye, retinal tears, and detachments, have been reported. There is a risk of conversion to wet AMD, which occurs in about 2% of patients, as well.

Another aspect of the treatment conversation that bears mentioning relates to being honest with patients who would not benefit from therapy for whatever reason. It's difficult to tell patients they have end-stage disease, and, from a medical standpoint, there is not much we can do. However, I try to direct these discussions toward positive developments in this space, as it is a very active area of research. There are numerous active clinical trials available for this patient population, including stem cell therapy and gene therapy. I also suggest using low vision aids to help them function with their remaining vision. Above all, I make sure to reinforce the value of supportive care, monitoring disease progression, and working together to maintain independence as long as possible.

Final Pearls

My advice to fellow practitioners would be, if you have patients in your clinic who are complaining of progressive vision loss from dry AMD with GA, to start the discussion about potential treatment options. Prior to the availability of treatment, we could not be proactive about treating dry AMD. Now with the advent of complement inhibition therapy, we can at least slow the progression. Our goal is to remind patients they are not alone in this fight against GA, and we are here to help them maintain independence and remain comfortable for as long as possible. ■

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OPTOGENETICS:

BRINGING LIGHT TO THE BLIND

A primer on the mechanism of action and what's in the pipeline.

An interview with Vinit B. Mahajan, MD, PhD

***RETINA TODAY (RT)*: CAN YOU EXPLAIN THE CONCEPT OF OPTOGENETICS?**

Vinit B. Mahajan, MD, PhD: Optogenetics began as a lab technique where light (opto-) was used to control genetically modified cells (-genetics) that were engineered to respond to specific wavelengths of light.[1] This technology has now been translated into novel therapeutics to potentially treat patients who have lost sight due to the degeneration of photoreceptor cells.[2]

Photoreceptors sense light using opsin proteins. In nature, there are thousands of different opsin proteins used by bacteria, algae, fish, reptiles, animals, and even fungi to sense light. Humans have three opsin proteins for color and one for dim light. When photoreceptors die, as in retinitis pigmentosa, there are no opsins left to turn light into an electrical signal.

For human optogenetic therapy, scientists engineer a single new opsin protein to sense light and trigger an electrical signal.[2] Each optogenetic company has made its own uniquely engineered opsin protein (Table).

The trick is to turn the surviving retinal cells that normally don't sense light into light-sensitive cells. The two target cells being used so far are retinal ganglion cells and bipolar cells (Figure). To deliver the engineered opsin, customized gene therapy vectors target these cells, and special cell-specific DNA promoters restrict protein expression to the target cell.

Although retinal ganglion cells were the first cells to be targeted, bipolar cells may have some advantages.[3] The number and density of bipolar cells is much higher than retinal ganglion cells, so the theoretical resolution is higher. As for retinal circuitry, bipolar cells are closer to photoreceptors and remain connected and modulated by amacrine cells, so bipolar cells may generate more nuanced signals.

AT A GLANCE

- For optogenetic therapy, scientists engineer a single new opsin protein to sense light and trigger an electrical signal. This technology has been translated into novel therapeutics to potentially treat patients who have lost sight due to the degeneration of photoreceptor cells.
- At least five companies have created opsin proteins and have started human clinical trials. Each uses its own opsin protein and some type of adeno-associated viral vector, and two require extraocular devices.
- So far, local immunosuppression with corticosteroids has been sufficient to address any immune reactions to the opsin and gene therapy vector.

TABLE. OPTOGENETIC THERAPY PIPELINE

Therapy (Company)	Opsin	Cell Target	Clinical Trial Stage	Delivery, Vector, Device
MCO-010 (Nanoscope Therapeutics)	Multicharacteristic opsin; broad light sensitivity	Bipolar	Phase 2b/3 RESTORE (NCT04945772); rolling FDA BLA in progress	Intravitreal, AVV2, no extraocular device
RST-001 (RetroSense/ Abbvie)	Channelrhodopsin-2; high-intensity blue light	RGC	Phase 1/2a (NCT02556736)	Intravitreal, AAV2, no extraocular device
GS030 (GenSight Biologics)	ChrimsonR (red-shifted opsin)	RGC	Phase 1/2a PIONEER (NCT03326336)	Intravitreal, AAV2, requires light-amplifying goggles
BS01 (Bionic Sight)	ChronosFP	RGC	Phase 1/2 (NCT04278131); Regenerative Medicine Advanced Therapy designation	Intravitreal, AAV2, requires wearable neuroprosthetic
RTx-015 (Ray Therapeutics)	ChRown	RGC	Phase 1 ENVISION (NCT06460844)	Intravitreal, AAV2.7m8, no extraocular device

Abbreviations: RGC, retinal ganglion cells; BLA, Biologics License Application; AAV2, adeno-associated viral vector-2.

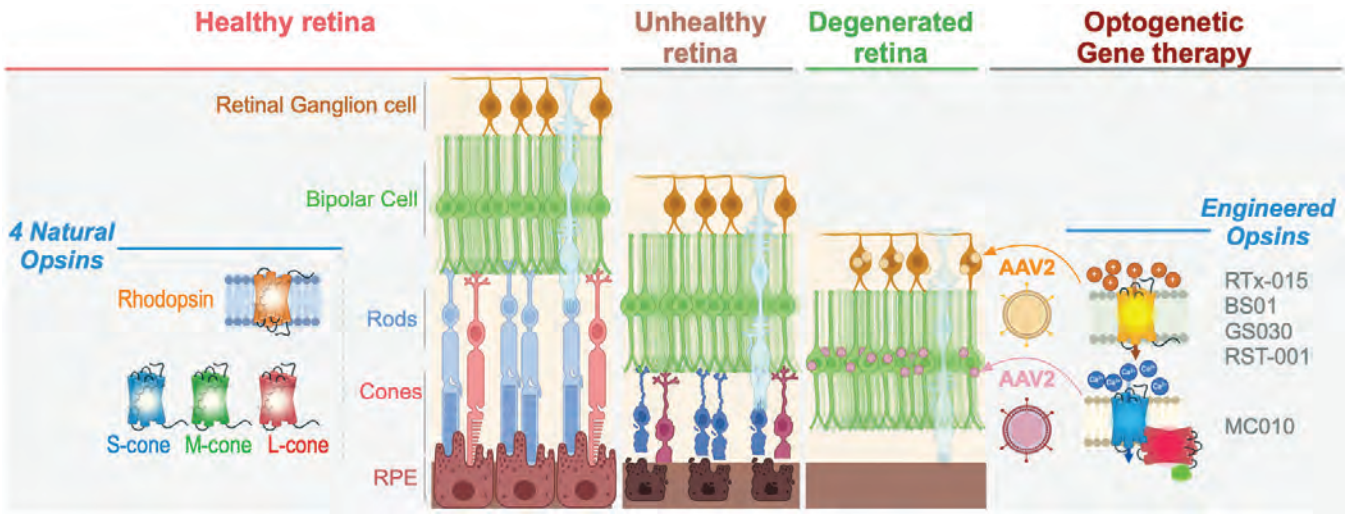

Figure. A healthy retina has four light-sensing opsin proteins expressed by rod and cone photoreceptors. Patients lose vision when retinal photoreceptors degenerate and opsin proteins are lost. Optogenetics uses gene therapy vectors to deliver single engineered opsins to either retinal ganglion or bipolar cells to make these cells light sensitive and restore sight.

RT: WHAT THERAPIES ARE IN THE PIPELINE AND HOW ARE THEY DIFFERENT FROM ONE ANOTHER?

Dr. Mahajan: At least five companies have created opsin proteins and have started human clinical trials (Table). Each uses its own opsin protein with some type of adeno-associated viral vector delivered by an intravitreal injection, and two require extraocular devices, such as goggles, to focus light and amplify the opsin signal.

Most have targeted retinal ganglion cells, but I expect we will hear more about bipolar cell targeting. In addition, newer engineered opsin proteins that have not yet entered human clinical trials are in development.

RT: HOW IS OPTOGENETIC GENE THERAPY DIFFERENT FROM OTHER GENE THERAPIES?

Dr. Mahajan: There are a lot of similarities between optogenetics and more traditional gene therapy, like injecting a viral vector to deliver a new gene. The main difference is that optogenetics doesn't replace a defective gene. Optogenetics doesn't care which gene is not working; it's agnostic. Instead, optogenetics inserts a new protein (opsin) into retina cells. I think it's one of the most amazing things happening in medicine today. We are reengineering our tissues with synthetic proteins to restore our most important sense—sight!

RT: WHICH PATIENTS COULD BENEFIT FROM OPTOGENETICS?

Dr. Mahajan: We all have patients in our clinics with advanced retinal degeneration and very low vision—even light perception—where vision loss is caused by photoreceptor cell loss, but the inner retina is preserved. While clinical trials have focused on patients with genetic eye disease, advanced AMD patients with geographic atrophy may also benefit from optogenetics.

RT: WHAT CAN PATIENTS SEE AFTER OPTOGENETIC THERAPY?

Dr. Mahajan: In the first reported case, a patient underwent optogenetic therapy, and when trained to use goggles, they could better identify close objects in front of them (such as a plate or mug) and navigate better (eg, identifying crosswalks).[4] In other studies, patients demonstrated statistically significant visual acuity gains, visual field expansion, and functional improvements such as avoiding obstacles and identifying differently shaped objects in low light. Anecdotal patient reports include improved face recognition, room navigation, and large object recognition.[5,6]

RT: WHAT ARE THE POTENTIAL RISKS WITH OPTOGENETICS AS A THERAPEUTIC APPROACH?

Dr. Mahajan: Although a lot could go wrong, the clinical trials are promising from a safety perspective. Because a nonhuman protein is being put into the body, there is a concern for immune reactions that reject the opsin and immune reactions against the gene therapy vector. So far, local immunosuppression with corticosteroids has been sufficient to address this complication.

Another question is, what happens when atypical cells start sending light signals to the brain? What will the brain see? Will it all be random noise? The recent clinical trials for inherited retinal degeneration and anecdotal patient feedback point to a clinical and functional benefit without visual confusion. As more clinical data comes in, we will gain a better understanding. ■

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MASS EYE AND EAR

(Continued from page 17)

with Audina M. Berrocal, MD; Jonathan S. Chang, MD; Jose R. Davila, MD; Dan A. Gong, MD; Mrinali Gupta, MD; and Ines Maria De Carvalho Lains, MD, PhD.

The day concluded with a reception and dinner at the Hampshire House in the Back Bay. During the event, Robert C. Gentile, MD, delivered the final talk, "Top 10 Things to Keep Your Attending AND YOU Happy!"—a humorous reminder of common pet peeves and useful advice to fellows on developing good habits in the clinic and the OR.

FELLOWS READY TO SUCCEED

The 15th annual MEE Vitrectomy Course was a resounding success. It gave the fellows a comprehensive introduction to vitreoretinal surgery by focusing on core concepts and offering hands-on lab sessions to build surgical skills. This course equipped fellows with the foundational knowledge and tools necessary to begin their training with success, while also encouraging meaningful connections with faculty and peers across different institutions.

We look forward to next year's top-notch educational offerings at the 16th annual MEE Vitrectomy Course, set for July 10-11, 2026! ■

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

David Shieh, MD

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

I had an inkling that I would end up pursuing a career in retina after rotating in ophthalmology as a medical student. The first time I saw the retina, I was captivated by its beauty. Since then, the retina has never failed to inspire a sense of awe.

I formally decided to become a retina specialist about halfway through residency. I was fascinated by the sophistication of the techniques we have at our disposal to treat one of the most delicate tissues in the human body. I was struck by how incredibly thankful our retina patients were, even if their visual acuity was objectively poor. Retina specialists have the chance to make a profound effect on saving a patient's vision, and that is the most beautiful thing to me.

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

I was fortunate to have many great mentors throughout my training. While in residency, I learned to appreciate the complexity and the art of retina from Warren Sobol, MD; Shree Kurup, MD; Jose J. Echegaray, MD; and Daniel Weidenthal, MD. I will always strive to emulate their skill, knowledge, and humility.

In fellowship, I had the privilege of training under Yu-Guang He, MD; Rafael Ufret-Vincenty, MD; J. William Harbour, MD; Judy Kim, MD; Rand Spencer, MD; Zachary Robertson, MD; Angeline Wang, MD; Jennifer Cao, MD; Noy Ashkenazy, MD; Kishan Patel, MD; Mary Kansora, MD; and Ilyse Kornblau, MD. They taught me how to make tough decisions in surgery, approach difficult medical cases, and treat patients with thoughtfulness and kindness.

I will always remember the collegiality and insightful discussions of our weekly retina journal clubs. I also want to mention my senior fellows, Jason Chien, MD, and Sami Kabbara, MD, who provided much of the knowledge and skills I needed to thrive.

***RT:* What was one of the most memorable experiences of your fellowship?**

I spent 6 months at Parkland, the county hospital of Dallas, during my second year of fellowship. On that rotation, I was the primary retina surgeon for most of the hospital system's patients, from their initial presentation to their postoperative follow-ups. My decisions will forever be a part of those patients' medical journeys, especially in cases where I coached junior fellows. It was a heavy responsibility, and I will always remember each success story and surgical failure. Those patients' stories will stay with me forever.

***RT:* What are you hoping to accomplish now that you are in practice?**

In my early years, I will focus on refining my craft, and my main priority will be taking care of my patients. I am also interested in teaching and research and hope to give back to the retina community.

As I mature in my practice, I plan to pass on my knowledge to residents and fellows and participate in various clinical trials.

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

Take each case as a learning opportunity and always look for ways to improve upon your last experience. The retina can humble you in endless ways, and each case will be a new challenge. It is incredibly satisfying to see your own growth through residency, fellowship, and beyond; remember that the challenges will make each success sweeter. ■

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ROBOTICS IN RETINAL SURGERY:

RECENT ADVANCES AND APPLICATIONS

Researchers are making strides to integrate new tools to help surgeons in the OR.

By Shima Dehghani, MD; Anahita Zabihi, MD; and Eileen S. Hwang, MD, PhD



Robotic technology is reshaping the landscape of vitreoretinal surgery, driven by the need for micrometer-scale precision and stability that often exceed the limits of human dexterity.[1,2] The retina's fragile anatomy and the technical demands of vitreoretinal procedures such as membrane peeling, subretinal injection, and vascular cannulation have led to the development of specialized robotic platforms.[3-8]

Advances in robotic control, intraoperative imaging, and microsurgical instrumentation have begun to redefine what is possible in retinal surgery.[5,9] In this article, we highlight several innovations that mark a transition from proof-of-concept engineering to clinical tools, offering stability, precision, and safety for the most delicate retinal procedures.

PRECEYES SURGICAL SYSTEM: FIRST-IN-HUMAN EXPERIENCE

One of the earliest robots to enter the retinal space, the Preceyes Surgical System (Carl Zeiss Meditec), demonstrated precision better than 20 µm and tremor-free control, proving robotic microsurgery feasible and safe.[6,7,10,11] In 2018, this system became the first remotely controlled robotic platform to successfully perform surgery inside the human eye.[6] The device has received CE marking in Europe,[12] and New York Eye and Ear is collaborating with Preceyes/Carl Zeiss Meditec to pursue FDA approval.[13]

In practice, the surgeon is positioned at the usual surgical site and operates from a console equipped with a joystick-style controller, which translates hand movements to the robotic arm holding the intraocular instruments positioned at the ocular entry site through standard 23-, 25-, or 27-gauge sclerotomies (Figure 1).[12]

Randomized and first-in-human trials demonstrated successful robot-assisted membrane peeling and subretinal injections, achieving anatomic and functional outcomes comparable with manual surgery.[3,6-8,14,15]

AT A GLANCE

- Advances in robotic control, intraoperative imaging, and microsurgical instrumentation have begun to redefine what is possible in retinal surgery.
- The Preceyes Surgical System (Carl Zeiss Meditec), OQrimo (Riverfield), ORYOM (Forsight Robotics), and others have shown promise for automating membrane peeling, subretinal injection, and vascular cannulation.
- Limitations to the adoption of robotics in retina include high upfront and ongoing costs, limited commercial availability, and lack of differentiated reimbursement.

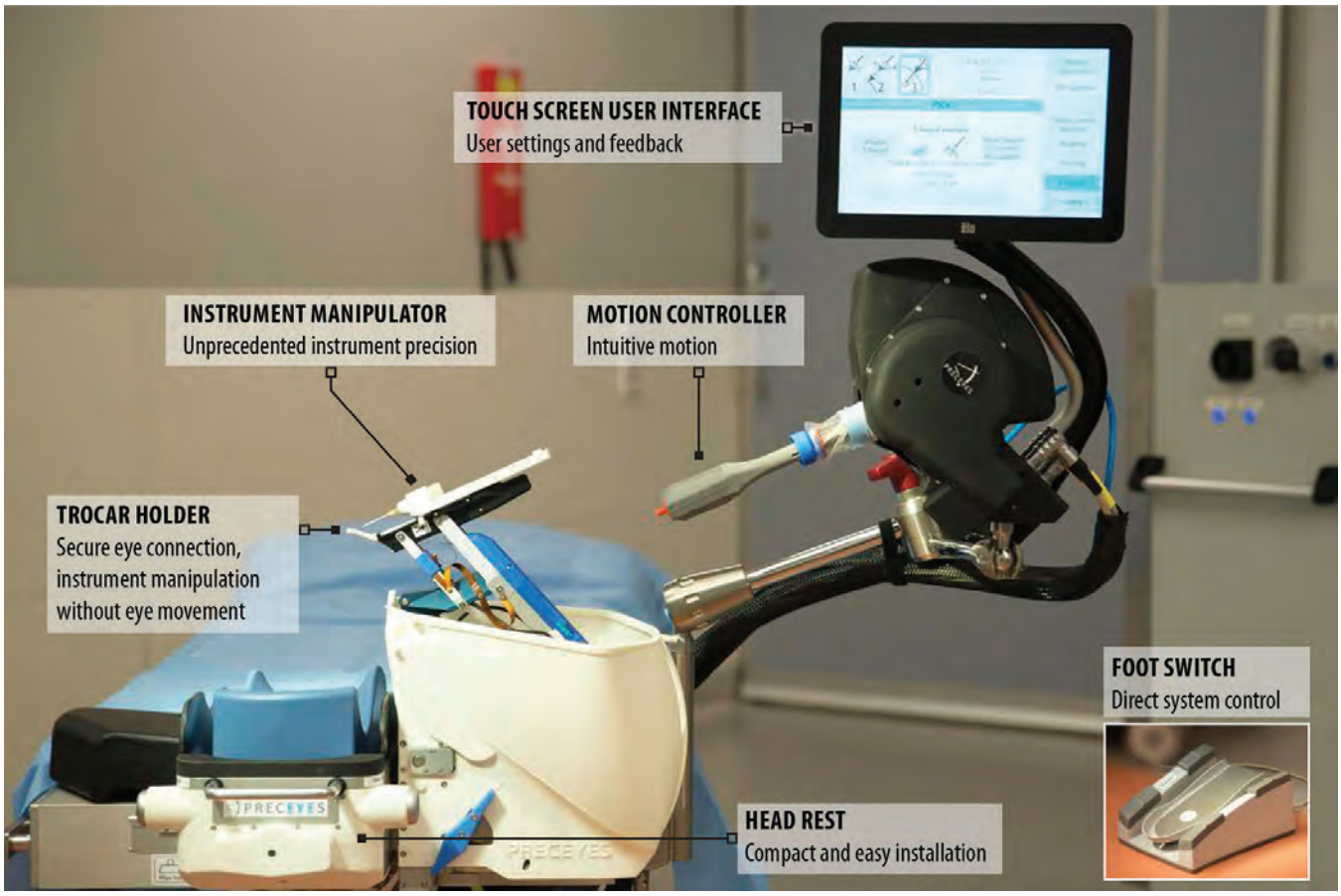

Image courtesy of Carl Zeiss Meditec.

Figure 1. The Preceyes Surgical System, a telemanipulation robotic platform designed for intraocular microsurgery, includes a robotic arm that holds intraocular instruments.

Robot assistance also enabled stable cannulation and controlled subretinal drug delivery without increasing microtrauma or adverse events.[6,7,14] Integration of intraoperative OCT-based distance sensors further enhanced depth control and safety.[14] Experimental animal studies showed consistent retinal vein cannulation and targeted delivery of agents such as ocriplasmin for retinal vein occlusion.[10] Surgeons reported reduced fatigue and improved precision with experience, although procedures took longer during the learning phase.[16]

OQRIMO: A ROBOTIC ENDOSCOPE HOLDER

Visualization challenges, particularly in eyes with corneal opacity, small pupils, or intraocular tumors, have long limited surgical efficiency. In 2021, researchers in Japan created the Eye Explorer robotic system to stabilize and manipulate an endoscope, allowing for bimanual surgery. The device balances its own weight to prevent accidental drops and provides a wide intraocular field of view (horizontal 118°, vertical 97°). By reducing external force on the eye by more than 15% compared with manual handling, the Eye Explorer may also reduce the risk of iatrogenic injury.[17]

Building on this success, OQrimo (Riverfield) became the first clinically approved ophthalmic endoscope-holding robot in Japan in 2023 (Figure 2).[5] OQrimo is designed to enhance stability through a gimballed structure that allows the endoscope to pivot smoothly while remaining steady and properly oriented. The endoscope can be positioned at the desired surgical site using a foot pedal control, and it comes with automatic safety withdrawal.[5,18]

In a prospective study of seven eyes undergoing vitrectomy, the OQrimo endoscope-holding robot assisted trocar placement in eyes with long axial lengths. Two trocars were placed 3.5 mm to 4.0 mm from the limbus at the 2 and 8 clock positions.[19] The OQrimo-stabilized endoscope, inserted through the 2 clock hour port, allowed direct visualization of the contralateral pars plana for precise third trocar insertion near the ora serrata. No clinically significant complications occurred, supporting the system's short-term safety for intraocular use.[19] Ongoing work in Japan is exploring its integration into complex vitreoretinal procedures.[5]

HEAD-MOUNTED ROBOT FOR SUBRETINAL INJECTION

A 2025 study by Posselli et al introduced a head-mounted robot designed to improve the safety and precision of subretinal injections. The lightweight device

Image courtesy of Riverfield

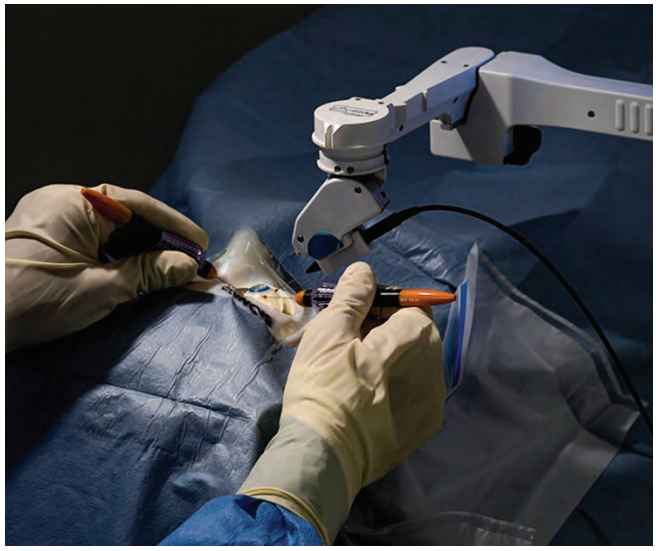

Figure 2. OQrimo, approved for use in Japan in 2023, uses a robotic arm to maneuver and stabilize an endoscope, allowing for bimanual surgery.

Image courtesy of Acusurgical

Figure 3. Dr. Nerinchkx uses the Luca robot during retinal surgery at the Ghent University Hospital in Belgium.

(0.8 kg) attaches to a custom-fitted headpiece that moves with the patient's head to keep the eye and robot perfectly aligned during small movements or breathing.[20]

Using a hybrid ex vivo/in situ model with enucleated porcine eyes mounted on human volunteers, investigators demonstrated < 1 µm positioning accuracy and consistent cannula placement even with simulated head motion. In 21 subretinal injections performed at a low flow rate (0.18 mL/min), the system achieved 100% bleb formation success, compared with an approximately 64% success rate with manual techniques.[20,21] These results suggest head-mounted robotic assistance could enable safer, more reproducible subretinal injections under conscious sedation.[20,21]

OTHER PLATFORMS ON THE HORIZON

The ORYOM system (Forsight Robotics) introduces a remote, 3D-based control to ophthalmic surgery. Surgeons operate through a console while the robot performs precise, tremor-free maneuvers. Although its first target is cataract surgery, its core technology could migrate to vitreoretinal procedures requiring similar precision.[22,23]

The Intraocular Robotic Interventional and Surgical System, designed by researchers at the University of California Los Angeles, uses dual robotic arms that handle standard microsurgical instruments for anterior and posterior segment procedures. The system, which uses joystick bimanual control and integrates OCT for semiautomated precision, is designed to allow quick instrument exchange using conventional intraocular tools.[24] Early studies demonstrated successful performance of capsulorhexis, lens removal, and retinal vein cannulation in ex vivo porcine eyes.[25,26] Notably, it was the first robot to complete an entire cataract surgery mechanically.[24]

Ophthorobotics is a company targeting one of the most common retinal interventions: intravitreal injections. The device mounts on the patient's head, identifies the pupil, and performs automated pars plana injections under supervision. Animal studies demonstrated accurate placement, suggesting automation may one day feasibly reduce clinician workload in high-volume injection clinics.[5,24,27]

Weighing just 306 g, RAM!S (Technical University of Munich) is a palm-sized robot that is designed to deliver 5 µm positional accuracy and has successfully executed subretinal injections in experimental models.[5,24,28] Its compact design could make robotic assistance practical even in small surgical suites.

Unlike the mechanical actuation used for most robots, OctoMag (ETH) employs magnetic fields to steer a wireless microrobot inside the eye, which has achieved vein cannulation in animal models.[29,30]

The Acusurgical Luca robot uses two robotic arms controlled by the surgeon from a pilot station (Figure 3). The system is designed to provide precision up to 10 µm for full vitreoretinal surgeries such as vitrectomy.

At the 2025 Retina World Congress, Fanny Nerinckx, MD, presented early results from six patients who underwent robotic surgery for macular pathology. The procedures—vitrectomy with the induction of a posterior vitreous detachment—were successful with no device-related adverse events.[31] A European trial (NCT06294613) is recruiting up to 15 patients undergoing vitreoretinal surgery for macular pucker.

LIMITATIONS OF CURRENT ROBOTIC PLATFORMS

The costs, limited commercial availability, and lack of differentiated reimbursement make adoption of robotic

systems financially challenging. If reimbursement remains equivalent to manual surgery, robotic procedures are not currently cost-effective. Existing cost-utility analyses in retinal surgery still focus solely on traditional procedures such as pars plana vitrectomy, scleral buckle, and pneumatic retinopexy, excluding robotic platforms.[32-34]

In addition, technical and workflow challenges hinder integration. Robotic systems often introduce longer operative times and require a steep learning curve.[6,15,35,36] The need for specialized training, standardized credentialing, and integration into the workflow adds logistical complexity.[9,37-39] Space constraints in the OR are also a consideration; the Preceyes system, for instance, requires an additional foot pedal, adding to the existing microscope, laser, and vitrector pedals.

Ergonomically, the surgeon's hand position is offset while maintaining visualization through the microscope, which may be less intuitive than conventional manipulation. Many surgeons are accustomed to tactile feedback and may be reluctant to adopt robotic systems that alter hand-eye coordination.

Institutional investment decisions likely depend on cost savings, safety benefits, and clear workflow compatibility.

THE ROAD AHEAD

Ophthalmic robotics have moved rapidly from experimentation to real-world feasibility. The next phase will require addressing economic and logistical hurdles, including workflow integration, training, and cost. As technology continues to miniaturize and integrate with intraoperative OCT and imaging guidance, robotic platforms may soon extend the limits of human dexterity, enabling safer, more reproducible procedures for complex vitreoretinal and subretinal therapies. The promise of the coming decade is not to replace the surgeon, but to enhance the surgeon's precision, endurance, and confidence in the most delicate corners of the eye. ■

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DIFFERENTIATING RD TYPES: A CASE FOR OCULAR IMAGING



OCT helped us identify and manage a case of exudative retinal detachment.

BY ZHUOJUN GUO, MD, PHD; AHMED SHAKARCHI, MD, MPH; AND SAMI UWAYDAT, MD

Retinal detachment (RD), in which the neurosensory retina is separated from the retinal pigment epithelium (RPE), can be classified as rhegmatogenous, exudative, or tractional.[1] Rhegmatogenous RD is caused by a retinal break, exudative (or serous) RD is caused by excessive fluid accumulation in the subretinal space from inflammation or a tumor, and tractional RD is caused by preretinal membrane contraction. Distinguishing among the three types of RD is crucial for appropriate management, as each has a distinct pathophysiology and management approach (Figure 1). Differentiating between rhegmatogenous RD and exudative RD can be challenging when media opacities, bullous RD, or an uncooperative patient preclude an adequate fundus examination of the peripheral retina to identify a retinal break. A recent article describes OCT features that can help differentiate the three types of RD.[2] Here, we present a case in which OCT helped guide diagnosis and treatment.

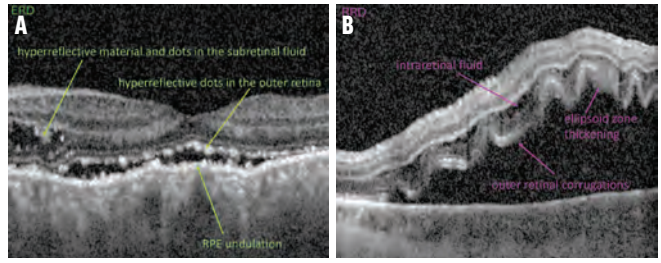


Figure 1. OCT images of an exudative (A) and rhegmatogenous RD (B) reveal distinct features.

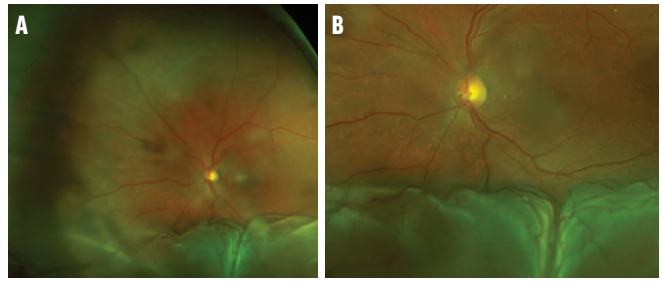


Figure 2. Fundus photography revealed an inferior exudative RD in the left eye (A). Note the fluid shift under the inferior arcade on head tilt (B).

CASE REPORT

A 72-year-old man presented with 7 days of blurry vision in the left eye. He had an ocular history of mild nonproliferative diabetic retinopathy in each eye and a medical history of post-traumatic stress disorder, type 2 diabetes, hypertension, and hyperlipidemia. His VA was 20/20 OD and 20/70 OS. Confrontational visual fields were full in the right eye but restricted in the superior quadrants of the left eye. Anterior segment examination was normal in the right eye but showed 2+ nuclear sclerosis in the left eye.

Dilated fundoscopy revealed several dot-blot hemorrhages in the right eye with an attached retina and inferior RD in the left eye. No visible retinal breaks were found in the left eye. B-scan ultrasonography demonstrated diffuse choroidal thickening in each eye. There was no intraocular mass noted. The axial length of the right eye measured 23.26 mm, and the left eye measured 22.81 mm.

Sequential pseudocolor fundus photography of the left eye demonstrated shifting subretinal fluid with head tilt (Figure 2). OCT of the left eye showed a macula-off RD, hyperreflective dots in the outer retina, and RPE undulation (Figure 3A). Systemic lab work was nonrevealing, except for a borderline T-spot tuberculosis test. MRI of the brainand orbits with and without contrast showed circumferential smooth enhancement of the left globe, suggestive of scleritis.

The patient was initially managed with 60 mg prednisone

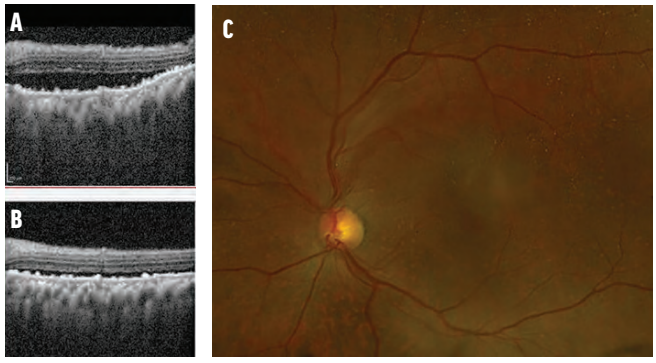


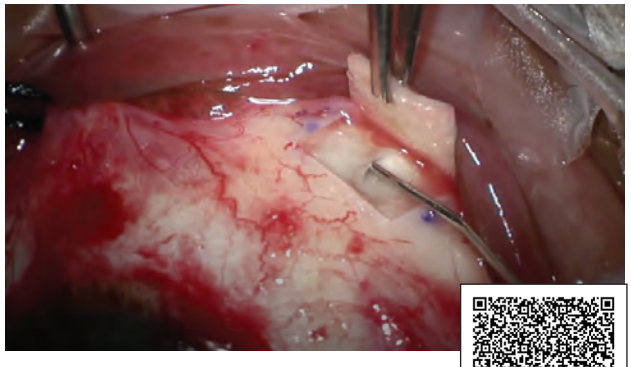
Figure 3. OCT documented the exudative RD (A). One week after scleral window surgery, the subretinal and intraretinal fluid had resolved (B). A 3 months, the retina had reattached (C).

daily. There was some improvement in the subretinal fluid and visual acuity of the left eye, but the prednisone had to be tapered due to high and uncontrolled blood glucose. After the cessation of prednisone, his VA worsened to 20/400 OS. The diagnosis of uveal effusion syndrome was entertained. The decision was made to proceed with surgery to create scleral windows (Video). A 4 mm x 4 mm, 90% depth scleral window was created in each quadrant, 8 mm from the limbus. A Kelly Descemet punch was used to create a full-thickness hole in the bed of the scleral window. OCT of the left eye 1 week later showed improved subretinal and intraretinal fluid (Figure 3B). Subretinal fluid under the fovea had resolved by the 3-month postoperative visit, and his VA had improved to 20/200 OS (Figure 3C).

DISCUSSION

When managing RD, it is vital to differentiate among the three types. Dilated fundus examination provides information on the RD location, the presence or absence of retinal tears, and the appearance of the detached retina. A corrugated inner surface of a detached retina is consistent with rhegmatogenous RD, while a smooth inner retinal surface with shifting subretinal fluid is indicative of exudative RD.[3]

WATCH IT NOW



Video. Surgical Management of Exudative Retinal Detachment With a Scleral Window

OCT is a valuable diagnostic tool for differentiating between rhegmatogenous and exudative RD.[2] According to a recent study, OCT of the macula is likely to show intraretinal fluid, ellipsoid zone thickening, and outer retinal corrugations in rhegmatogenous RD and hyperreflective material and dots in the subretinal fluid, hyperreflective dots in the outer retina, and RPE undulation in exudative RD.[2]

Exudative RD occurs when there is accumulation of fluid between the photoreceptors and RPE in the absence of a retinal break. The inner and outer blood-retinal barrier and the RPE keep the potential space between the photoreceptors and RPE free of fluid. Inflammation, infections, neoplasms, and other etiologies can cause exudative RD.[4] Nanophathlmic exudative RD is seen in patients with a short axial length (20 mm or less) in the absence of an infection or inflammatory etiology.[5] Management options for nanophthalmic-related exudative RD include focal laser photocoagulation or scleral window surgery.[5] Management of exudative RD in an eye with average axial length consists of medical management of the underlying infectious or inflammatory condition. In the event of a normophalmic eye with exudative RD and no identifiable etiology, surgical intervention with a scleral window should be considered.[6]

GUIDE THE WAY

Characteristic features on macular OCT can help differentiate exudative RD from rhegmatogenous RD. Exudative RD that is unresponsive to medical treatments may be successfully managed with scleral window surgery. ■

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A CASE OF PEHCR

Considerations for managing this rare chorioretinal degenerative disease.

BY SURAJ D. DESAI, BS; RISHABH GUPTA, MD; FRED G. CRAWFORD, MD; AND MATHEW W. MACCUMBER, MD, PHD

Peripheral exudative hemorrhagic chorioretinopathy (PEHCR) is a rare, degenerative disease of the choroid and retina characterized by subretinal or sub-retinal pigmented epithelium (RPE) hemorrhage and an exudative mass outside the macula, usually near the periphery. It predominantly affects elderly (ie, mean age of 80 years of age) female patients and can be unilateral or bilateral.[1] Because of the far peripheral location of these lesions and their variable presentations, diagnosis may be difficult; consequently, PEHCR is sometimes mistaken for other ocular conditions, such as choroidal melanoma or retinal detachment (RD). Although the exact etiology is unknown, systemic hypertension has been found in approximately 51% of patients.[1] Additionally, research has suggested possible associations with AMD and polypoidal choroidal vasculopathy, given their similar hemorrhagic and exudative properties.[2]

This article details a case example of PEHCR and provides an overview of the pertinent literature on various management approaches.

CASE REPORT

An 81-year-old man presented on an emergency basis with cloudy, obscured vision in his left eye for 1 to 2 days. His past medical history included type 2 diabetes, and his ocular history included chronic subtotal RD and vitreous syneresis in his right eye, epiretinal membrane that was worse in his right eye than his left, and nuclear sclerosis in each eye. He denied symptoms of RD. His BCVA at presentation was 20/30 OD and 20/40 OS with no improvement with pinhole. A dilated examination revealed a new posterior vitreous detachment in his left eye.

Four days after presentation, fundus photography revealed an inferotemporal and inferonasal opaque elevation in his left eye with a white exudative pattern, appearing yellow and green on pseudocolor widefield imaging (Figure 1). Early-frame widefield fluorescein angiography (FA) of his left eye demonstrated appropriate filling times but with limited visualization of the inferotemporal area and a blocking defect (Figure 2). Late-frame widefield FA of the left eye showed central leakage consistent with cystoid macular edema (CME) and peripheral subretinal vascular leakage inferotemporally, likely due to hemorrhage (Figure 3). A diagnosis of PEHCR was subsequently made.

Because of his relatively preserved vision, the patient was initially observed and scheduled for a follow-up appointment 4 days later. Given findings consistent with

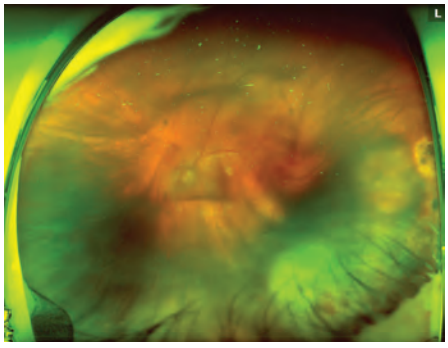

Figure 1. Fundus photography of the patient's left eye 4 days after presentation showed an inferotemporal and inferonasal opaque elevation with a white exudative pattern, appearing yellow and green in the pseudocolor imaging.

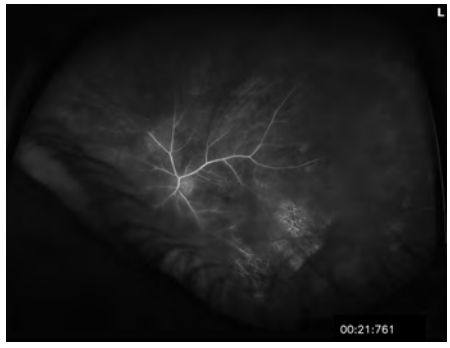

Figure 2. Early-frame widefield FA of his left eye at 21.8 seconds demonstrated appropriate filling times but with limited visualization of the area inferotemporally and a blocking defect.

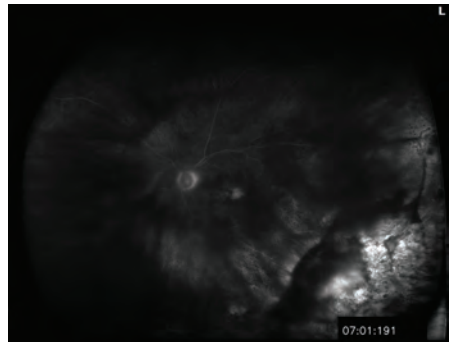

Figure 3. Late-frame FA of his left eye at 7 minutes and 1 second showed central leakage consistent with CME, along with inferotemporal peripheral subretinal vascular leakage, likely due to hemorrhage.

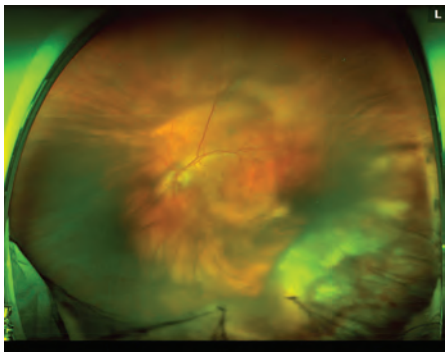

Figure 4. Fundus photography of his left eye 141 days after presentation showed lesion regression and partial resorption of blood with increasing fibrosis.

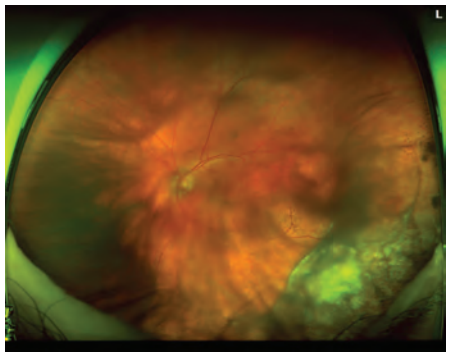

Figure 5. Fundus imaging of his left eye 417 days after presentation showed marked regression of the hemorrhage and subretinal fibrosis.

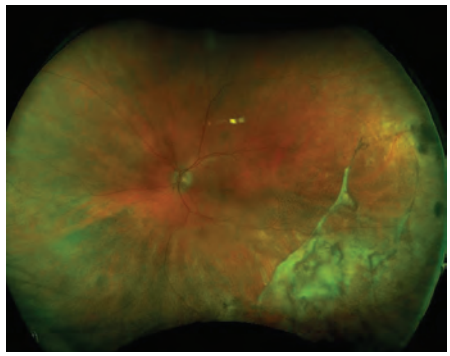

Figure 6. Fundus photography of the left eye 1,166 days after initial presentation showed resolution of the subretinal hemorrhage with fibrosis.

active exudative choroidal neovascularization (CNV) in his left eye, intravitreal anti-VEGF therapy with bevacizumab (Avastin, Genentech/Roche) was initiated to decrease exudation.

At follow-up 141 days after initial presentation and after four bevacizumab injections, his BCVA was 20/60 OS, improving to 20/50 OS with pinhole. The lesion appeared improved and more fibrotic (Figure 4). At 417 days after presentation, following eight bevacizumab injections, his BCVA was 20/70 OS with no improvement on pinhole. Fundus photography showed marked regression of the hemorrhage and atrophic fibrosis (Figure 5). At 1,166 days, following nine bevacizumab injections, six aflibercept injections (Eylea, Regeneron), and four high-dose aflibercept injections (Eylea HD, Regeneron), fundus photography showed resolution of the subretinal hemorrhage with fibrosis (Figure 6).

DIAGNOSTIC AND MANAGEMENT PEARLS

PEHCR is often difficult to diagnose due to its far peripheral location, low incidence, and frequently asymptomatic presentation.[1] In the largest case series to date, involving 173 patients, Shields et al reported that 42% of patients were asymptomatic.[1] Among symptomatic individuals, decreased visual acuity, flashes, and floaters were the most common symptoms.[1] In a separate case series of 46 patients, Mantel et al noted that some patients may less commonly experience metamorphopsia, scotomas, and pain.[2]

About 21% of eyes have decreased visual acuity secondary to PEHCR due to vitreous hemorrhage (14%), subretinal hemorrhage (5%), or subretinal fluid extending into the macula (2%).[1] Lesions are typically located temporally (77%) or inferiorly (43%), with nasal (20%) and superior (20%) involvement being less frequent. Some eyes demonstrate multi-quadrant involvement. The average visual acuity in affected patients can range from 20/20 to 20/40.[1-3]

Shields et al also found that macular findings such as drusen, RPE changes, and CNV were present in 48% of ipsilateral eyes and 56% of contralateral eyes.[1] Although the exact etiology of PEHCR remains unclear, CNV is believed to play a significant role in its pathogenesis.[4] Mantel et al suggested some macular changes may be age-related rather than disease-specific and that PEHCR may occur independently of AMD.[2] Drusen, a hallmark feature of AMD, are often absent in PEHCR lesions; however, Mantel et al's case series demonstrated a higher prevalence of AMD (68.9%), likely due to the older average age of their cohort.[2]

Multimodal imaging is critical for diagnosing and monitoring PEHCR. Shields et al described key features that can help distinguish it from choroidal melanoma.[1] OCT is useful for assessing the amount of exudation into the peripheral choroidal thickness. Ultrasound typically reveals a dome-shaped or plateau-shaped lesion with an average thickness of 3 mm and low-to-moderate internal echogenicity. Widefield FA can show blocking defects in the presence of subretinal or sub-RPE hemorrhage, hypofluorescence due to RPE atrophy or hyperplasia, and CNV. In contrast, choroidal melanoma often has low internal echogenicity but may show high internal echogenicity of intrinsic vascular components.

Management Strategies

Most PEHCR lesions can be observed, as they tend to regress on their own over time. However, several treatment modalities have been explored for vision-threatening lesions, including anti-VEGF therapy, cryotherapy, and laser photoablation.[5,6] Vandefonteyne et al conducted a large case series (84 eyes) involving ranibizumab (Lucentis, Genentech/Roche), aflibercept, and bevacizumab, in addition to laser photocoagulation, photodynamic therapy (PDT), vitrectomy, and cryotherapy.[7] In this study, vitrectomy was indicated for persistent vitreous hemorrhage and the only intervention associated with

MOST PEHCR LESIONS CAN BE OBSERVED, AS THEY TEND TO REGRESS ON THEIR OWN OVER TIME. HOWEVER, SEVERAL TREATMENT MODALITIES HAVE BEEN EXPLORED FOR VISION-THREATENING LESIONS, INCLUDING ANTI-VEGF THERAPY, CRYOTHERAPY, AND LASER PHOTOABLATION.

significant improvement in visual acuity. This likely reflects the benefit of clearing the vitreous cavity, while other therapies treated peripheral lesions that had less involvement with the macula.[7] Another study showed favorable results with ranibizumab, suggesting it is comparable in efficacy with bevacizumab.[8]

Safir et al observed significant disease regression with repeat bevacizumab injections, but there was no statistically significant difference in visual acuity compared with untreated groups.[5] Zicarelli et al reported that among 50 eyes, 18 were observed, 18 received combined anti-VEGF and PDT, 13 received anti-VEGF only, and one underwent PDT.[3] No significant difference in macular involvement was found between treatment groups.[3] However, four of the 18 eyes that were observed developed vitreous hemorrhage or macular involvement, suggesting anti-VEGF therapy may reduce the risk of posterior extension and be useful in treating macular- or vision-threatening disease.[3]

Photocoagulation may be beneficial for polypoidal lesions but is generally ineffective against the underlying choroidal vascular network.[3] Alforja et al caution that photocoagulation can exacerbate subretinal hemorrhage,[9] while others have noted its potential to induce CME.[10] Cryopexy may also worsen subretinal hemorrhage and lead to fibrosis.[9]

Overall, while these treatments are useful for lesion regression, they have demonstrated limited efficacy in improving visual outcomes.

CONSIDER PEHCR WHEN PERIPHERAL LESIONS ARE PRESENT

PEHCR should be included in the differential diagnosis when peripheral lesions are noted, as accurate diagnosis and appropriate management are essential to avoid unnecessary interventions. While the prognosis for PEHCR is generally good, with 89% of lesions stabilizing or regressing over a 15-month observation period,[1] anti-VEGF therapy should be considered when exudative or hemorrhagic properties involve the macula and threaten vision. ■

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CHOROIDAL METASTASIS FROM LUNG ADENOCARCINOMA

Diagnosis of choroidal malignancy should prompt a workup for systemic disease in patients with no known history of cancer.

BY WEILIN SONG, MD; JULIE K. KWON, MD; BASIL K. WILLIAMS JR, MD; AND JAYANTH SRIDHAR, MD

Choroidal metastasis is the most common intraocular malignancy and the first sign of systemic malignancy in up to a third of patients with cancer.[1,2] The two most common primary tumor sites are breast and lung, which are found in 40% to 53% and 20% to 29% of cases, respectively.[1] The choroid's rich vascular supply makes it the most common site of uveal metastases.[3] Due to the predominance of metastases involving the post-equatorial region and its frequent association with subretinal fluid, patients typically present with blurred vision and, less commonly, flashes, floaters, and ocular pain.[3-5] However, 9% to 11% of patients are asymptomatic at presentation, and lesions may be found on routine ocular examination.[3]

The diagnosis of ocular metastasis is based on clinical examination and ocular imaging and, in patients without a known history of cancer, can prompt expedited evaluation and treatment of the primary cancer. While choroidal metastases frequently occur in the later stages of disseminated disease and are generally considered a poor prognostic sign, recent advances in systemic therapies have significantly improved survival rates.[1]

Here, we present a case of choroidal metastasis from lung adenocarcinoma, with improvement of visual function and near complete resolution of the metastatic lesion and subretinal fluid after initiation of systemic chemotherapy and immunotherapy.

OCULAR MANIFESTATION AS AN EARLY SIGN

A 59-year-old woman presented for evaluation of acute onset blurry vision and photopsia in her right eye. Her past medical history was significant for tobacco use (10 pack-years) and chronic obstructive pulmonary disease. Of note, she was also undergoing workup of a lung mass and multiple pulmonary nodules, which were detected incidentally on imaging for persistent pain after trauma to the right chest. She had recently undergone bronchoscopy and biopsy, with nondiagnostic pathology showing rare, atypical cells.

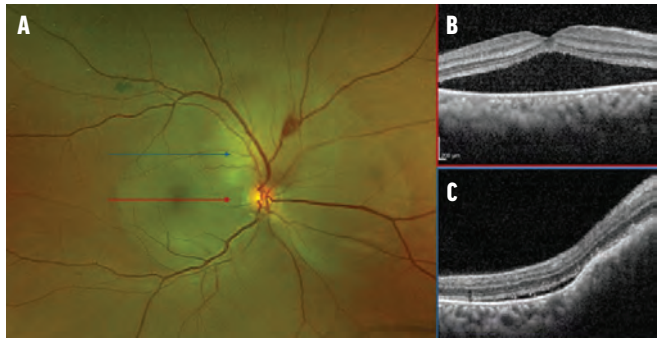

Figure 1. Color fundus photography illustrated a choroidal mass superior to the optic nerve with associated subretinal fluid extending to the macula and nasally to the nerve, a superonasal flame hemorrhage, and a superotemporal pigmented choroidal lesion along the superior arcades (A). OCT through the central macula showed subfoveal subretinal fluid (B). OCT through the superior macula showed a large choroidal mass with an irregular surface and shallow subretinal fluid (C).

On initial ophthalmic examination, her VA was 20/200 OD and 20/25 OS. The anterior segment was unremarkable bilaterally. Dilated fundus examination of her right eye was notable for a choroidal mass superior to the nerve with associated macula-involving subretinal fluid and a flame hemorrhage lesion (Figure 1A and B); her left eye was unremarkable. The choroidal mass had moderate echo-density on B-scan ultrasound and an irregular

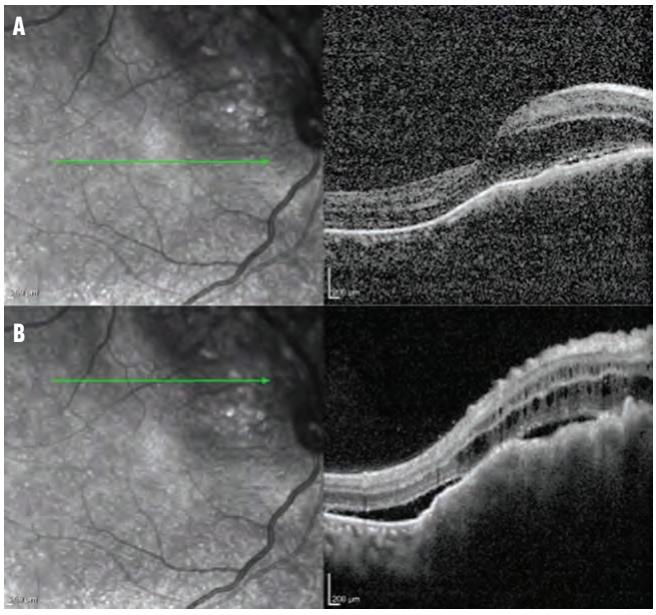

Figure 2. OCT through the central macula showed subfoveal extension of the choroidal mass and shallow subretinal fluid (A). OCT through the superior macula showed increased surface irregularity and intraretinal and subretinal fluid (B).

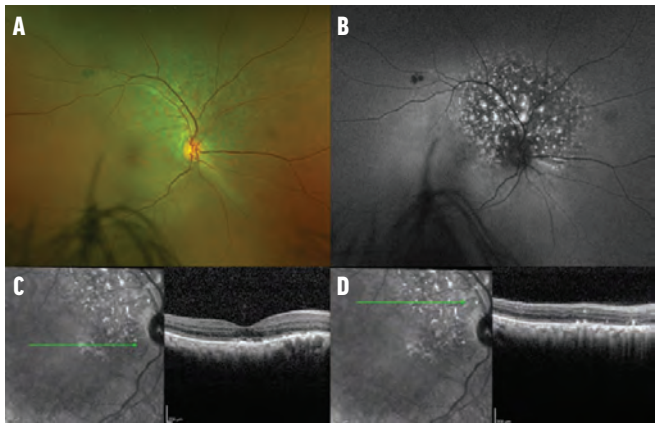

Figure 3. Fundus photography showed regression of the choroidal mass and resolution of the subretinal fluid and flame hemorrhage after treatment (A). FAF showed hyperautofluorescent and hypoautofluorescent regions corresponding to the prior choroidal mass (B). OCT through the central macula showed regression of the choroidal mass and resolution of the subretinal fluid (C). OCT through the superior macula similarly showed regression of the choroidal mass, resolution of the subretinal and intraretinal fluid, and hyperintense areas of lipofuscin primarily in the outer retina corresponding to the hyperautofluorescent regions on FAF (D).

surface on OCT (Figure 1C).

Based on a strong suspicion for metastatic disease, the patient received MRI of the brain and orbits, which did not show any other lesions. On follow-up 6 weeks later, the patient was pending repeat lung biopsy with interventional radiology. The subretinal fluid had improved, but there appeared to be progression of the choroidal mass toward the fovea, along with increased peripapillary intraretinal fluid (Figure 2).

The patient was diagnosed with stage IV metastatic non-small cell lung cancer (NSCLC), with fine-needle aspiration sample of a supraclavicular lymph node consistent with lung adenocarcinoma. She was initiated on systemic chemotherapy with carboplatin and pemetrexed, and immunotherapy with pembrolizumab was added during the fourth cycle. Maintenance therapy with pemetrexed and pembrolizumab was initiated on the seventh cycle.

Three months after initiating therapy, the patient's VA had improved to 20/50 OD, the subretinal fluid had resolved, and the choroidal metastasis had significantly regressed (Figure 3). On OCT and fundus autofluorescence (FAF), there was ellipsoid zone attenuation and multiple small hyperreflective areas consistent with lipofuscin in the prior area of choroidal metastasis. The patient's oncologist also noted improvement of systemic disease burden on subsequent CT imaging.

IS IT METASTASIS, OR SOMETHING ELSE?

As demonstrated in this patient, choroidal metastases generally appear as creamy white or pale-yellow masses that are flat or plateau-shaped, although color and morphology can vary depending on the primary tumor site.[1,2] The most common associated feature is subretinal fluid, which is present in up to 73% of cases and is usually perilesional.[2,3] The differential diagnosis of choroidal metastases includes choroidal melanoma, hemangioma, granuloma, osteoma, and sclerochoroidal calcification.[5]

Certain imaging features can help differentiate choroidal metastases from other intraocular masses. On ultrasonography, choroidal metastases are generally flat or slightly dome-shaped and are characterized by a medium to high nonhomogeneous reflectivity. In contrast, choroidal melanomas have low-to-medium reflectivity and grow in a nodular configuration, sometimes leading to rupture of the Bruch membrane and appearing in a classic mushroom shape. On OCT, the most prominent feature of choroidal metastases is an irregular or lumpy anterior surface, as was seen in this case, as opposed to a smooth mound or dome of a nevus or melanoma.[6,7] Hyperreflective areas of lipofuscin have been previously described in the literature and are thought to be the shed outer segments of photoreceptors.[7,8]

MANAGEMENT

While most patients have known or suspected systemic cancer at the time of choroidal metastasis detection, those without a history of cancer should undergo prompt, thorough investigation for systemic malignancy. In cases of an unidentified primary source, fine-needle aspiration biopsy can assist in providing cytological information to help differentiate between metastasis versus primary lesion.[9,10]

WHILE CHOROIDAL METASTASES FREQUENTLY OCCUR IN THE LATE STAGES OF KNOWN DISSEMINATED DISEASE, UP TO A THIRD OF PATIENTS HAVE NO KNOWN HISTORY OF CANCER AT THE TIME OF CHOROIDAL METASTASIS DIAGNOSIS.

The treatment approach depends on multiple considerations, including the patient's life expectancy, presence of other metastases, and location and number of choroidal tumors. Systemic chemotherapy, immunotherapy, targeted therapy, or hormone therapy are preferred initial options for patients who can begin treatment quickly, especially for those with bilateral, multifocal choroidal metastases or systemic metastases.

In patients with metastatic NSCLC, platinum-based chemotherapy is the standard first-line treatment. The addition of immunotherapy with pembrolizumab may provide additional therapeutic effect by restoring the antitumor immunity mediated by T cells and is associated with significantly longer progression-free and overall survival with fewer adverse effects.[11]

There have been two reported cases of choroidal metastases from NSCLC treated with pembrolizumab and cytotoxic chemotherapy leading to regression, although one noted recurrence after the patient was continued on pembrolizumab alone as maintenance therapy.[11,12]

Focal therapy is advised in choroidal tumors that are causing visual loss if there is a delay in or minimal response to systemic therapy or if the primary tumor cannot be identified. This includes whole eye radiotherapy for bilateral or multifocal metastases and plaque radiotherapy, transpupillary radiotherapy, or photodynamic therapy for solitary metastasis.[5]

KEEP YOUR SKILLS SHARP

While choroidal metastases frequently occur in the late stages of known disseminated disease, up to a third of patients have no known history of cancer at the time of choroidal metastasis diagnosis.[1,2] Therefore, ophthalmologists should be familiar with the diagnostic features and workup to allow for prompt diagnosis and treatment of the primary cancer. ■

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UPDATE ON SICKLE CELL RETINOPATHY MANAGEMENT

Here's where we are—and where my research shows we could be going.

BY JENNIFER I. LIM, MD, FARVO, FASRS

Ischemia and infarction inherent in sickle cell disease result in myriad ocular manifestations, the most important of which are the retinal manifestations.[1] Sickle cell retinopathy (SCR) findings can be divided into five stages.[2] Nonproliferative SCR is comprised of stage 1, characterized by arteriolar narrowing, and stage 2, characterized by arteriovenous anastomosis. Proliferative sickle cell retinopathy (PSR) is comprised of stage 3, characterized by peripheral retinal neovascularization (in a classic seafan configuration); stage 4, characterized by vitreous hemorrhage; and stage 5, characterized by retinal detachment (RD).

SCR SIGNS AND SYMPTOMS

The progression of SCR from nonproliferative to proliferative has been closely studied. In one study, only 10% of the eyes of patients with sickle cell disease experienced a VA loss of 20/60 or worse.[3] The proliferative stage is responsible for the majority of vision loss from SCR, with an incidence of vision loss of 31 per 1,000 eye-years of observation among eyes affected by PSR compared with 1.4 per 1,000 eye-years among eyes experiencing nonproliferative changes.[4]

In addition to the well-defined clinical spectrum, there are also subclinical findings of SCR. My research team has shown that patients without visual symptoms with good visual acuity can have significant thinning on macular OCT imaging.[5,6] Moreover, this macular thinning has been associated with decreased sensitivity on microperimetry testing.[7] OCT angiography (OCTA) reveals flow voids associated with macular thinning in both pediatric and adult patients.[8] In addition, AI analysis of OCTA images can be used to classify the stage of PSR.[9,10]

MANAGEMENT OF SCR

Patients with sickle cell disease should receive a screening examination at least yearly.[11] Typically, this should start at 8 to 10 years of age. Unfortunately, most patients with sickle cell disease are not screened.[12] Although there is no treatment for nonproliferative SCR, my research team has shown hydroxyurea is associated with lower rates of macular thinning.[13]

Stage 3

Management for stage 3 SCR includes observation, laser photocoagulation, and intravitreal anti-VEGF injections. With a 30% rate of spontaneous regression of retinal neovascularization, some question whether treatment is necessary.[3] A prospective laser trial showed the efficacy of laser treatment, which was well-tolerated. Laser resulted in a lower rate of prolonged visual acuity loss (1% vs 6.7%) and a lower incidence of vitreous hemorrhage (11% vs 18.7%) compared with observation.[14] The laser treatment included laser application to an area extending one disc diameter beyond the anterior and posterior seafan borders and one clock hour to each side of the seafan. However, the rates of complete seafan closure and new seafan formation were the same for the treated and observation arms.[14]

Subsequently, postmortem studies have shown increased VEGF and HIF-1α staining in the 2 mm area around the retinal neovascularization. The authors suggest that a more generous application of laser surrounding the seafan of two disc diameters could ablate the regions that contribute to HIF-1α and VEGF production and result in better, more successful outcomes.[15]

More recently, anti-VEGF treatment has been used in the management of both stage 3 and stage 4 PSR.[16-19] Isolated case reports have shown regression of seafans soon after intravitreal anti-VEGF injection. In most cases, laser photocoagulation is applied, so there are no data using anti-VEGF alone for the management of stage 3 PSR.

To compare anti-VEGF therapy with laser for stage 3 or 4 PSR, I created the Anti-VEGF vs. Laser Photocoagulation for PSR Study (ALPS). In preparation for this prospective study, the ALPS collaborators performed a retrospective study to collect preliminary evidence of efficacy

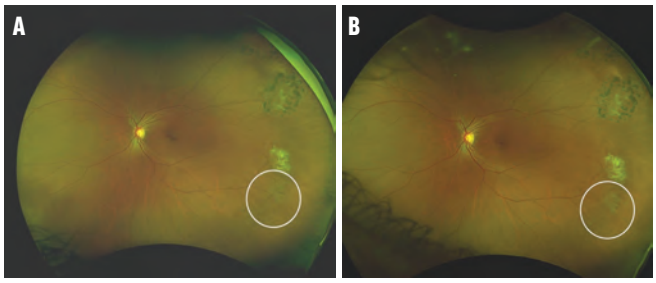

Figure. Color fundus photography of the left eye of a patient with stage 3 PSR shows an active seafan (A, white circle). Five weeks after treatment with an anti-VEGF agent, the seafan is inactive (B, white circle).

for the use of intravitreal anti-VEGF injections for stage 3 and 4 PSR. We found that anti-VEGF therapy for stage 3 eyes may result in seafan regression (Figure). We did not encounter any cases of endophthalmitis. However, seafans recurred in one-third of patients with complete regression. In addition, some of the treating physicians combined anti-VEGF with laser photocoagulation after seafan regression occurred. The ALPS study will help refine the treatment and determine the efficacy and safety of anti-VEGF for PSR.[19,20]

Stage 4

For stage 4 PSR, treatment options include observation and pars plana vitrectomy (PPV). If the vitreous hemorrhage is mild and there is no associated tractional RD, consider using laser photocoagulation or anti-VEGF injection.[16-19] Otherwise, for more significant vitreous hemorrhage, perform either anti-VEGF injection or PPV for non-clearing vitreous hemorrhage. In the retrospective anti-VEGF study by the ALPS investigators, anti-VEGF injections for stage 4 resulted in three or more lines of visual acuity improvement in all eyes with vitreous hemorrhage; this improvement usually occurred within 1 month of treatment.[19] Some investigators added laser photocoagulation after the hemorrhage cleared, and others used additional anti-VEGF injections as needed. The prospective ALPS study will determine whether intravitreal anti-VEGF injections can result in a significantly lowered rate of PPV versus observation.

Stage 5

Treatment for eyes with stage 5 PSR typically requires PPV, although consideration can be given to pneumatic retinopexy for rhegmatogenous RD without tractional RD and scleral buckling procedures with or without PPV. Concerns related to PPV in patients with sickle cell disease include the risk of inducing a sickle cell crisis, iatrogenic retinal breaks, optic and retinal ischemia, and postoperative anterior segment ischemia. As such, it is important to avoid systemic hypotension and keep the patient well-hydrated and warm during surgery.

In the first report of surgery for PSR in 1971, scleral buckling was used to repair RDs, which led to high rates of postoperative anterior segment ischemia.[21] Consequently, to mitigate the risk of this complication, preoperative exchange blood transfusion, local anesthesia without epinephrine, and supplemental oxygen were recommended. The authors strongly recommended avoiding compression of the long posterior ciliary vessels, meticulously controlling IOP, and using cryopexy sparingly. These recommendations reflected the prevalent surgical techniques of that era before the widespread adoption of PPV. In general, I agree that scleral buckling, particularly high buckles, should be avoided.

In 1982, Jampol et al introduced PPV with or without scleral buckling for treating PSR complications.[22] The series had a 30% rate of iatrogenic retinal tears. The rate of reattachment was low at 60%, and only 50% of eyes had improved postoperative visual acuity. Since then, with improvements in PPV techniques and instrumentation, better anatomic and visual outcomes have been achieved. However, the rates of recurrent RD remain high at 29% to 50%, as compared with non-PSR-related RDs.[23-27]

At my institution, modified techniques using delamination over segmentation and careful vitreous base shaving with release of all anterior-posterior traction and circumferential traction have resulted in improved anatomic and visual acuity outcomes. I often use a lighted pick and internal limiting membrane forceps to segment the seafans free of the vitreous adhesions and adjacent retinal tissue. To avoid bleeding and retinal tear formation, I do not attempt to delaminate adherent seafans. In addition, I ensure the IOP is kept at a low, normal range to avoid optic nerve infarction.

Using this modified 25-gauge technique, my colleagues and I achieved a 100% reattachment rate for PSR-related RDs.[28] Over a median follow-up of 42 months, BCVA stabilized or improved by 3 or more lines in 96% of eyes. Median VA improved from 20/400 preoperatively to 20/40 postoperatively.[28] Our study highlights the importance of early intervention in macula-on RD cases to maximize the postoperative visual outcomes.

MANAGEMENT QUICK HITS

When managing stage 3 PSR, consider intravitreal anti-VEGF injection with close follow-up versus laser photocoagulation. Use more generous laser photocoagulation (two disc diameters around the seafan).

For stage 4 PSR, use anti-VEGF injection with or without laser versus PPV with laser.

For stage 5, small-gauge PPV with modified techniques may achieve anatomic reattachment while minimizing risks of intraoperative complications.

The ALPS prospective study will help decipher the efficacy and safety of anti-VEGF therapy for PSR. Overall,

long-term stability of visual and anatomic outcomes after surgical intervention in PSR cases is possible with continued monitoring and treatment of ischemic-related complications and management of postoperative cataracts that occur with time. ■

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RETINECTOMY FOR TRD/RRD WITH PDR AND CATARACT

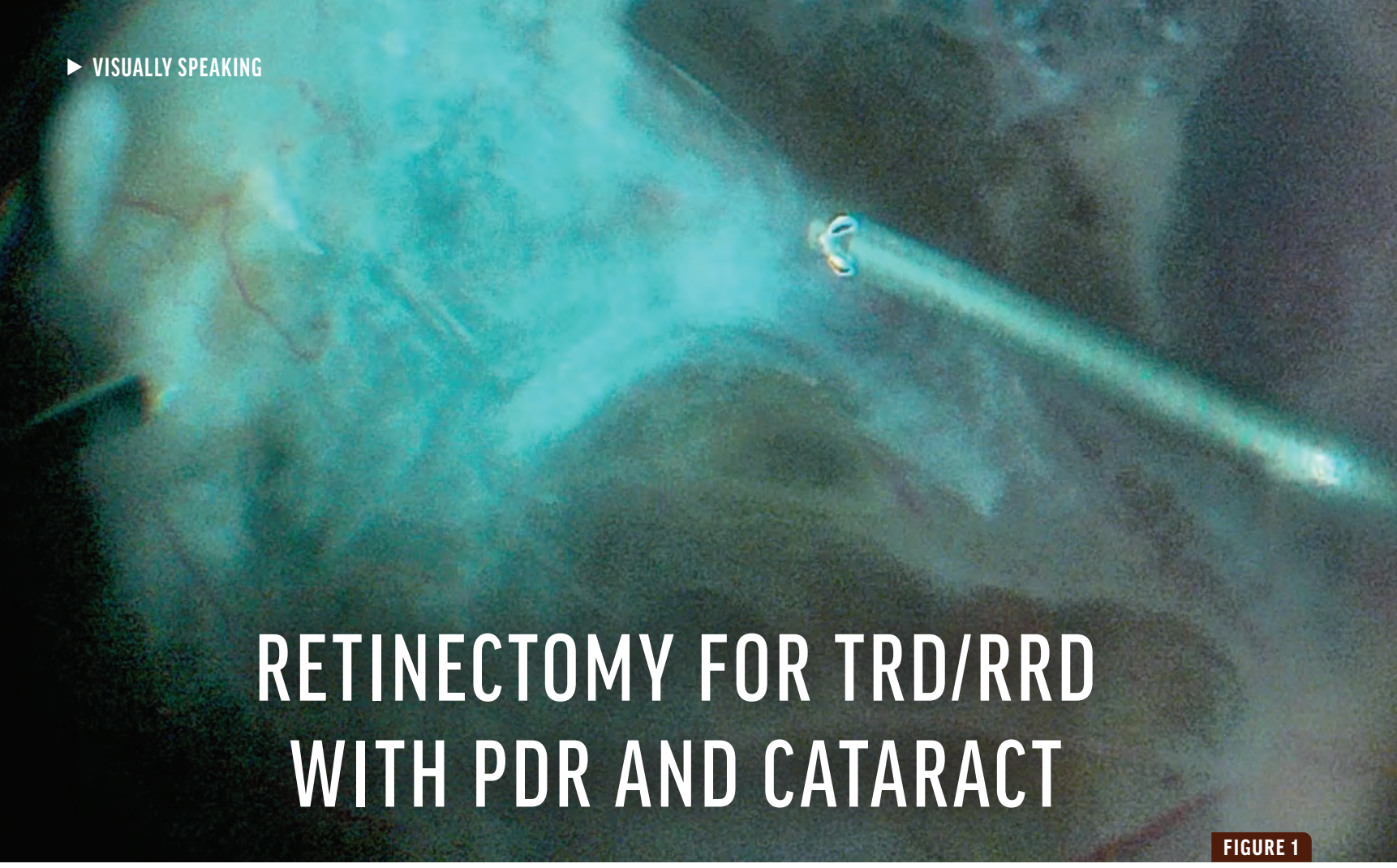


FIGURE 1


Remain adaptable in your surgical planning for such highly complex cases.

BY ADRIANA P. PÉREZ NEGRÓN, BS, AND MARÍA H. BERROCAL, MD

The management of combined tractional and rhegmatogenous retinal detachment (TRD/RRD) in the setting of diabetic retinopathy (DR) is particularly challenging, and visual outcomes are often poor.[1]

In eyes with longstanding RD, such as in the following case, features such as retinal stiffness and foreshortening, subretinal membranes, and extensive fibrous proliferation are often present; in these cases, retinectomy is often required to relieve traction and achieve retinal reattachment.[2]

CASE REPORT

A 54-year-old man with a 20-year history of poorly controlled type 2 diabetes and various systemic comorbidities—including hypertension, obesity, dyslipidemia, and a prior cerebrovascular accident—presented with several months of progressive vision loss in his left eye. His BCVA was 20/30 OD and hand motion OS. He had not previously received ophthalmic care.

Fundoscopic examination of his right eye revealed signs of proliferative DR, for which panretinal photocoagulation was promptly performed. His left eye exhibited dense vitreous hemorrhage and a cortical cataract that precluded adequate fundus visualization; B-scan ultrasonography was used to confirm a TRD/RRD.

A combined surgical procedure was pursued, including phacoemulsification with IOL implantation and 27-gauge pars plana vitrectomy. Intraoperatively, extensive fibrovascular proliferation was noted, extending from the inferior optic nerve to the vitreous base (Figure 1).

Additional findings included subretinal membranes and a partially adherent posterior hyaloid, consistent with a combined TRD/RRD. Thus, membrane dissection and posterior hyaloid removal were performed, and the subretinal membranes were extracted through strategically placed retinotomies.

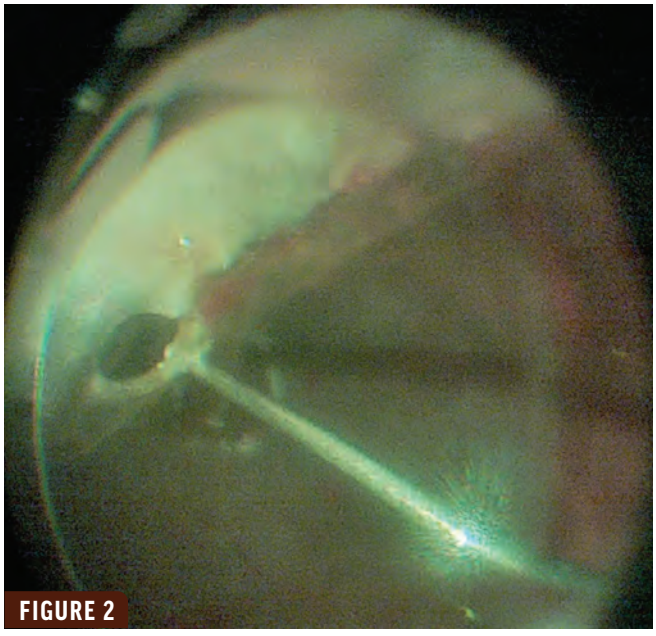


FIGURE 2

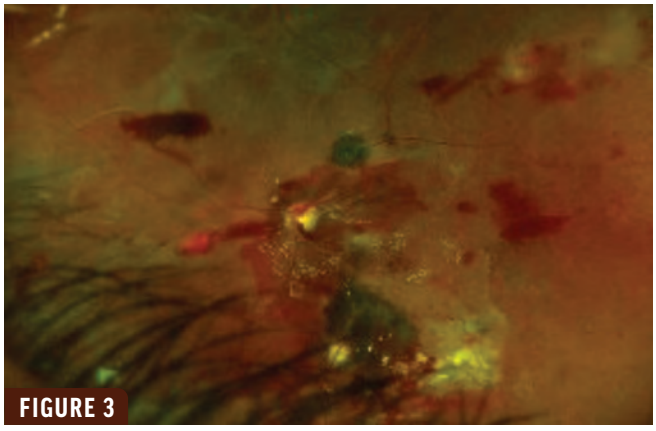


FIGURE 3

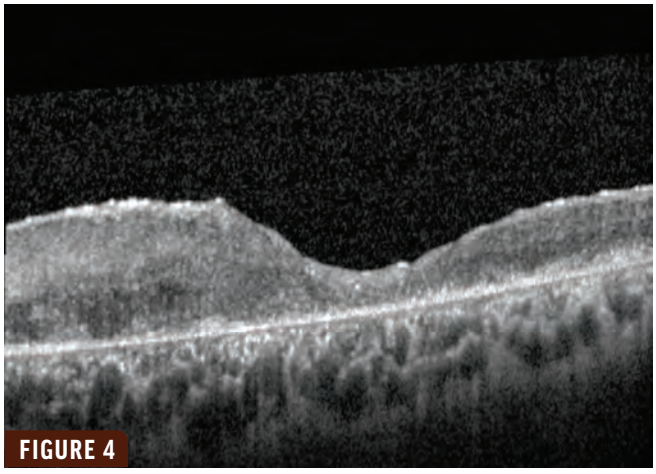
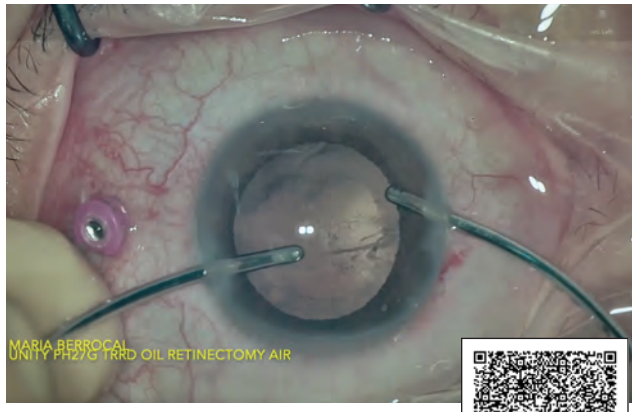


FIGURE 4

Despite these efforts, significant tenting of the inferior retina toward the dense peripheral fibrovascular tissue persisted, precluding reattachment and necessitating a retinectomy under air to relieve residual traction (Figure 2). This approach allowed real-time visualization of retinal flattening and minimized the extent of necessary retinal excision. Silicone oil was used as a long-term tamponade (Video).

Postoperatively, the retina remained attached (Figures 3 and 4), and VA improved to counting fingers at 4 ft OS. The patient is scheduled for silicone oil removal.

WATCH IT NOW



Video. Surgical Management of Combined Tractional and Rhegmatogenous Retinal Detachment and Cataract

BALANCING MULTIPLE SURGICAL GOALS

Retinectomy under air provided enhanced intraoperative visualization and control, particularly in the setting of complex combined TRD/RRD. By integrating cataract extraction and advanced vitreoretinal techniques in a single procedure, we were able to optimize both anatomic and functional outcomes in a highly challenging clinical scenario. ■

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