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THE RETINA PIPELINE

RIDING THE WAVE OF INNOVATION

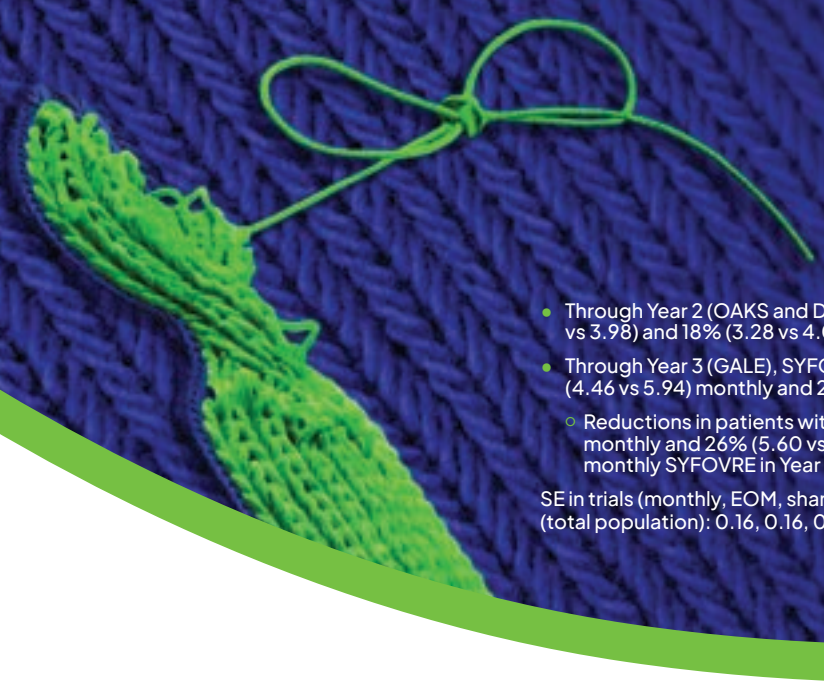
THE THERAPEUTIC LANDSCAPE FOR DR/DME

AN UPDATE ON SUSTAINED DRUG DELIVERY IN RETINA

WET AMD THERAPIES IN THE PIPELINE

SUBSCRIBE FOR FREE

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL



Save more retinal tissue

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

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

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

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

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

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

Discover more at SyfovreECP.com

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

- SYFOVRE is contraindicated in patients with ocular or periocular infections, and in patients with active intraocular inflammation

WARNINGS AND PRECAUTIONS

- **Endophthalmitis and Retinal Detachments**
  - Intravitreal injections, including those with SYFOVRE, may be associated with endophthalmitis and retinal detachments. Proper aseptic injection technique must always be used when administering SYFOVRE to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately.
- **Retinal Vasculitis and/or Retinal Vascular Occlusion**
  - Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.
- **Neovascular AMD**
  - In clinical trials, use of SYFOVRE was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (12% when administered monthly, 7% when administered every other month and 3% in the control group) by Month 24. Patients receiving SYFOVRE should be monitored for signs of neovascular AMD. In case anti-Vascular Endothelial Growth Factor (anti-VEGF) is required, it should be given separately from SYFOVRE administration.
- **Intraocular Inflammation**
  - In clinical trials, use of SYFOVRE was associated with episodes of intraocular inflammation including: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, and anterior chamber flare. After inflammation resolves, patients may resume treatment with SYFOVRE.
- **Increased Intraocular Pressure**
  - Acute increase in IOP may occur within minutes of any intravitreal injection, including with SYFOVRE. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

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

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

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

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

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023. **2.** Data on file. Apellis Pharmaceuticals, Inc. **3.** Sunness JS, Margalit E, Srikumaran D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. *Ophthalmology*. 2007;114(2):271–277. doi:10.1016/j.ophtha.2006.09.016.

Apellis

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Ocular or Periocular Infections

SYFOVRE is contraindicated in patients with ocular or periocular infections.

Active Intraocular Inflammation

SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

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

Retinal Vasculitis and/or Retinal Vascular Occlusion

Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported with the use of SYFOVRE. Cases may occur with the first dose of SYFOVRE and may result in severe vision loss. Discontinue treatment with SYFOVRE in patients who develop these events. Patients should be instructed to report any change in vision without delay.

Neovascular AMD

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

Intraocular Inflammation

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

Increased Intraocular Pressure

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

ADVERSE REACTIONS

Clinical Trials Experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham.

The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

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

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

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:

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

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

Punctate keratitis included: punctate keratitis, keratitis

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

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

Postmarketing Experience

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

There are no adequate and well-controlled studies of SYFOVRE administration in pregnant women to inform a drug-associated risk. The use of SYFOVRE may be considered following an assessment of the risks and benefits.

Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHOD) of SYFOVRE (based on the area under the curve (AUC) systemically measured levels). No adverse maternal or fetal effects were observed in monkeys at systemic exposures approximately 470-fold higher than that observed in humans at the MRHOD.

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

Lactation

Risk Summary

It is not known whether intravitreal administered pegcetacoplan is secreted in human milk or whether there is potential for absorption and harm to the infant. Animal data suggest that the risk of clinically relevant exposure to the infant following maternal intravitreal treatment is minimal. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, caution should be exercised when SYFOVRE is administered to a nursing woman.

Females and Males of Reproductive Potential

Contraception

Females: It is recommended that women of childbearing potential use effective contraception methods to prevent pregnancy during treatment with intravitreal pegcetacoplan. Advise female patients of reproductive potential to use effective contraception during treatment with SYFOVRE and for 40 days after the last dose. For women planning to become pregnant, the use of SYFOVRE may be considered following an assessment of the risks and benefits.

Pediatric Use

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

Geriatric Use

In clinical studies, approximately 97% (813/839) of patients randomized to treatment with SYFOVRE were ≥ 65 years of age and approximately 72% (607/839) were ≥ 75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies. No dosage regimen adjustment is recommended based on age.

PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing endophthalmitis, retinal detachments, retinal vasculitis with or without retinal vascular occlusion and neovascular AMD. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist. Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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

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TENACITY PAYS OFF


After the hubbub of 2023 with the approval of pegcetacoplan (Syfovre, Apellis), avacincaptad pegol (Izervay, Astellas), and 8 mg aflibercept (Eylea HD, Regeneron), we weren't too disappointed to have a quieter 2024 to regroup. Don't get us wrong, there have been plenty of innovations to keep us busy, but it's been more of a watchful year when it comes to the pharmaceutical pipeline.

Just as we were drafting this editorial with that sentiment in mind, two big news stories hit our inboxes. First, LumiThera received FDA authorization to market its Valeda Photobiomodulation (PBM) Light System for the treatment of intermediate AMD based on improvements in vision in treated eyes (+6.2 letters at 21 months [*P* = .0036] and +5.6 letters at 24 months [*P* = .0024] compared with sham controls.[1] Second, the FDA wanted more time to review data and changed Neurotech Pharmaceutical's PDUFA goal date to March 2025 for NT-501 (revakinagene taroretcel) for the treatment of macular telangiectasia (Mac-Tel) type 2.[2]

These updates were a nice reminder of the ups and downs that are so common in clinical research—two steps forward and one step back. Hopefully, by the time we figure out how to integrate PBM into our clinic workflows (treatment cycles comprise nine PBM sessions delivered over 3 to 5 weeks with each cycle performed two to three times annually),[3] we will have an FDA decision on the first potential Mac-Tel therapy.

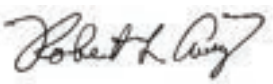
Speaking of ups and downs, an interesting research trend has come to light in this year's pipeline issue: an unwillingness to give up on promising therapies. Several drug candidates failed to reach their primary endpoints, yet the learnings from those failures have led to a continued push forward. So, don't dismiss a therapeutic approach just because a readout wasn't statistically significant. Remember, the phase 3 DERBY trial of pegcetacoplan did not meet its primary endpoint, and yet that drug is now showing a 42% reduction in growth for nonsubfoveal geographic atrophy lesions at 36 months.[4] EYP-1901 (EyePoint Pharmaceuticals), ANX007 (Annexon Biosciences), and elamipretide (Stealth Biotherapeutics) have all shown promising benefits without meeting some endpoints and are now in phase 3 clinical trials with updated trial designs, varied dosing schedules, narrowed indications, and/or adjusted primary endpoints.[5-7] We are learning better ways to identify clinical benefit and adjusting our trials accordingly.

A particularly good example of this is the tarcocimab tedromer (KSI-301, Kodiak Sciences) program, which has had one of the most fascinating pipeline journeys to date. Although discontinuing the program after GLEAM and GLIMMER failed to meet their primary endpoints for the treatment of diabetic macular edema,[8] the company continued to analyze the data and reassess its endpoints and indications.[9] The result? Kodiak initiated a new phase 3 trial (DAYBREAK, NCT06556368) investigating tarcocimab in patients with wet AMD—bringing the tally of phase 3 trials for this drug to eight: two are recruiting, two are complete, and four have been terminated (of note, the company released positive data from the GLOW trial currently listed as *terminated* on clinicaltrials.gov). The company announced plans to submit a biologics license application for three indications—wet AMD, diabetic retinopathy, and retinal vein occlusion—in 2026, pending trial results.[10]

Retina specialists are a tenacious group, particularly when we recognize the potential to help our patients. This is the type of hard work we love to highlight in our annual pipeline issue—and what drives our field forward. Within this issue, experts share updates on investigational therapies for wet AMD, geographic atrophy, and diabetic eye disease; the latest drug delivery innovations; and a look at the possible applications of nanotechnology in our field. We also have an article discussing the promise of AI in retina and a companion Letter to the Editor reminding everyone that AI faces just as many challenges as our therapeutic pipeline.

Next year is lining up to be another banner year with phase 2 and 3 readouts, potential BLA applications, and (likely) a few disappointments. But remember, failure isn't always a bad thing. A little tenacity goes a long way. ■

ALLEN C. HO, MD
CHIEF MEDICAL EDITOR



ROBERT L. AVERY, MD
ASSOCIATE MEDICAL EDITOR

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3. Do D. Photobiomodulation for dry AMD (phase 3 LIGHTSITE III study). Presented at AAO; October 20, 2024; Chicago.
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FEATURED ARTICLES

DEPARTMENTS

ONLINE EXCLUSIVE:

MEETING MINUTES
ASRS 2024: Looking Beyond Complement Inhibition
By Scott Krzywonos

Delivering Innovations for Subretinal Injections

New Silicone-Free MicroDose™ SF Injection Kit

Our MicroDose™ products set the standard for reliability and control during high precision subretinal injections. With the launch of our new MicroDose™ SF, we have added critical features such as a silicone-free syringe, removable plunger rod and dead-space reduction stopper. Combine either MicroDose™ device with one of our market leading specialized cannulas and create the ideal system for your surgical needs.

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NEW!

3315 MicroDose™ SF Injection Kit

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●	Syringe can be pneumatically filled	●
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●	Unique stopper design reduces dead-space to approximately 10 microliters	

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RT NEWS

NOVEMBER/DECEMBER 2024

VOL. 19, NO. 8 | RETINATODAY.COM

FIRST DEVICE APPROVED TO TREAT VISION LOSS IN DRY AMD

The FDA recently granted de novo authorization to LumiThera to market its Valeda Light Delivery System, the first FDA-authorized device to treat vision loss in patients with dry AMD. Valeda is designed to use multiwavelength photobiomodulation (PBM) to improve the visual acuity of patients with dry AMD.[1]

In the phase 3 LIGHTSITE III trial, Valeda met its primary endpoint of BCVA, showing a mean increase of > 5 ETDRS letters from baseline at 24 months in the PBM-treated patients ($P < .0001$).[2] The trial also demonstrated a statistically significant ($P = .003$) slowing of disease progression in treated eyes, with 5.7% of PBM-treated eyes versus 21.6% of sham-treated eyes progressing to new geographic atrophy.[2]

"We now have a noninvasive treatment option for dry AMD patients that may improve vision and address the disease earlier, before permanent vision loss," Clark Tedford, PhD, president and CEO of LumiThera, said in a company news release. "The FDA authorization of the Valeda treatment to improve vision in dry AMD now provides a significant option for our US patients."[1]

The Valeda Light System received a CE mark for the European Union in 2018.[3] The company announced a new Category III CPT code, "Photobiomodulation therapy of retina, single session," effective January 1, 2025.[4]

1. LumiThera obtains FDA authorization of Valeda treatment for dry AMD [press release]. Eyewire+. November 5, 2024. Accessed November 6, 2024. bit.ly/3UOSN8o
2. LumiThera announces sustained vision improvement for 24 months in dry age-related macular degeneration subjects from US LIGHTSITE III clinical trial data [press release]. LumiThera. March 15, 2023. Accessed November 13, 2024. bit.ly/4hTAAAr
3. LumiThera LT-300 device for treating dry advanced macular degeneration granted CE Mark [press release]. LumiThera. June 22, 2018. Accessed November 13, 2024. bit.ly/4fQLHs6
4. LumiThera announces first CPT code to report photobiomodulation therapy in retinal disease – first step toward reimbursement [press release]. LumiThera. August 7, 2024. Accessed November 13, 2024. bit.ly/3YSDdK4

CENCORA ACQUIRES RETINA CONSULTANTS OF AMERICA

Cencora has entered into a definitive agreement to acquire Retina Consultants of America (RCA) from Webster Equity Partners for approximately $4.6 billion.[1] According to the agreement, Cencora will hold approximately 85% ownership, while RCA's affiliated practices, physicians, and management will retain a minority interest.

"The acquisition of RCA will allow Cencora to broaden our relationships with community providers in a high growth segment and build on our leadership in specialty," said Bob Mauch, Cencora president and CEO, in a press release. "With a compelling value proposition for physicians, an impressive leadership team, and strong clinical research capabilities, RCA is well-positioned at the forefront of retinal care."[1]

He noted that Cencora aims to help RCA enhance the provider experience, conduct innovative new research, and promote more successful patient outcomes.[1]

Cencora, formerly AmerisourceBergen, is a global pharmaceutical solutions organization that partners with pharmaceutical innovators to facilitate and optimize market access to therapies.[2]

1. Cencora advances specialty leadership through acquisition of Retina Consultants of America [press release]. Cencora. November 6, 2024. Accessed November 6, 2024. bit.ly/309c5kT
2. AmerisourceBergen becomes Cencora, in alignment with the company's growing global footprint and central role in pharmaceutical access and care [press release]. Cencora. August 30, 2023. Accessed November 13, 2024. bit.ly/3070QA7

INVESTIGATIONAL DME THERAPY MAY OFFER SUSTAINED IMPROVEMENT IN BCVA AND CST

EyePoint Pharmaceuticals recently reported interim 16-week data from its ongoing phase 2 VERONA clinical trial assessing vorolanib (Duravyu), a selective tyrosine kinase inhibitor, for the treatment of diabetic macular edema.[1]

The interim study results demonstrate that 2.7 mg vorolanib provided an early, sustained, and meaningful improvement in BCVA and central subfield thickness (CST) compared with 2 mg aflibercept (Eylea, Regeneron). BCVA improved by 8.9 letters in the vorolanib group compared with 3.2 letters in the aflibercept group, while CST decreased by 68.1 µm for vorolanib patients and 30.5 µm for aflibercept controls. In addition, 82% of eyes in the vorolanib group were supplement-free at 16 weeks compared with 50% in the aflibercept group. Vorolanib maintained a favorable safety and tolerability profile, with no serious adverse events.[1]

EyePoint Pharmaceutals also announced that the first patient has been dosed in the phase 3 LUGANO clinical trial of vorolanib for the treatment of wet AMD,[2] and the second phase 3 trial, LUCIA (NCT06683742), in patients with wet AMD has been initiated.

1. EyePoint Pharma announces positive interim results for Duravyu in phase 2 VERONA trial for DME [press release]. Eyewire+. October 28, 2024. Accessed November 6, 2024. eyewire.news/news/eyepoint-pharma-announces-positive-interim-results-for-duravyu-in-phase-2-verona-trial-for-dme
2. EyePoint Pharmaceuticals doses first patient in phase 3 LUGANO trial for wet AMD therapy Duravyu [press release]. Eyewire+. October 24, 2024. Accessed November 13, 2024. eyewire.news/news/eyepoint-pharmaceuticals-doses-first-patient-in-phase-3-lugano-trial-for-wet-amd-therapy-duravyu

GENE THERAPY SHOWS PROMISE IN BILATERAL WET AMD

Regenxbio recently announced results from its phase 2 study evaluating the subretinal delivery of ABBV-RGX-314, a gene therapy candidate developed in partnership with AbbVie, in patients with bilateral wet AMD. This study is the first to explore gene therapy in the fellow eye of patients with bilateral wet AMD, according to the company.[1]

The 9-month results included nine patients who had previously received ABBV-RGX-314 in one eye and later underwent treatment in the other. The researchers reported a 97% reduction in annual anti-VEGF treatment burden. All patients required no or one supplemental injection, with 78% remaining injection-free at 9 months. The improvements in BCVA and central retinal thickness were sustained, with no serious adverse events reported.[1]

1. Regenxbio reports positive phase 2 data on ABBV-RGX-314 for bilateral wet AMD [press release]. Eyewire+. October 21, 2024. Accessed November 7, 2024. eyewire.news/news/regenxbio-reports-positive-phase-2-data-on-abbv-rgx-314-for-bilateral-wet-amd

RETINAL IMPLANT MAY HELP IMPROVE VISION IN GA PATIENTS

Science Corporation recently announced preliminary results from clinical trials of its PRIMA retinal implant. The technology demonstrated the ability to restore *form vision* in patients with geographic atrophy due to AMD, allowing them to perform high-acuity tasks such as reading text and recognizing faces.[1]

The PRIMA system includes a photovoltaic retinal implant surgically placed under the retina, a pair of glasses equipped with a camera and a projection system, and a pocket processor that enhances image clarity and magnification.[1]

The PRIMAvera clinical study involved 38 patients with geographic atrophy. Results showed a 23-letter (4.6-line) mean improvement in VA at 12 months post-implantation, with a favorable sustainability and safety profile.[1]

Science Corporation is working to secure European market approval for the PRIMA system.[1] ■

1. Science Corporation: PRIMA clinical trials show restoration of "form vision" [press release]. Eyewire+. October 23, 2024. Accessed November 7, 2024. eyewire.news/news/science-corporation-announces-breakthrough-in-retinal-implant-technology-prima-clinical-trials-show-restoration-of-form-vision

Eyewire+ Pharma Update

- **Nanoscope Therapeutics** announced plans to initiate a rolling submission of its biologics license application for its gene therapy candidate, MCO-010, for the treatment of retinitis pigmentosa.
- The FDA granted fast-track designation to **FLQ-101 (FELIQS)**, a drug in development for the treatment of retinopathy of prematurity. Phase 1b/2 trials of FLQ-101 are expected to begin in the first quarter of 2025 in Japan and the United States.
- **Astellas** withdrew its marketing authorization application for avacincaptad pegol (Izervay), an FDA-approved therapy for geographic atrophy (GA) from the European Medicines Agency. In addition, the Committee for Medicinal Products for Human Use of the European Medicines Agency upheld its negative opinion from June 2024 on Apellis' marketing authorization application for pegcetacoplan (Syfovre).
- **Oculis** announced progress in patient enrollment for both phase 3 DIAMOND trials of its OCS-01 eye drops for the treatment of diabetic macular edema: 70% of patients have been enrolled in the DIAMOND-1 trial and 40% in the DIAMOND-2 trial.
- **Aviceda Therapeutics** completed enrollment for its phase 2b SIGLEC study, which is comparing the safety and efficacy of AVD-104 with that of avacincaptad pegol for the treatment of GA secondary to AMD.

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In this episode:

- **Companies with Posterior Segment Product Candidates Provide Updates**
- **Ocuphire Acquires Gene Therapy Company Opus Genetics**
- **Astellas Withdraws European Application for Geographic Atrophy Drug Avacincaptad Pegol**

PARISA EMAMI-NAEINI, MD, MPH

WHERE IT ALL BEGAN

I grew up and attended medical school in Iran. My father, an ophthalmologist, first introduced me to the world of eyes and ophthalmology. Throughout medical school, I always knew I wanted to be a surgeon, though I was unsure of the specialty. During my ophthalmology rotation, I became fascinated with microsurgery, and retina surgery in particular. After medical school, I moved to the United States and spent 2 years doing bench research in immunology and corneal transplants with Reza Dana, MD, MSc, MPH. This experience deepened my interest in immunology and cytokines, shaping my future focus on uveitis.

I completed my residency at Kresge Eye Institute, followed by a vitreoretinal surgery fellowship at the University of California (UC) Davis and a uveitis fellowship at the Cole Eye Institute, Cleveland Clinic.

MY PATH TO RETINA

During residency, I worked with exceptional retina specialists and mentors such as Gary Abrams, MD, whose encyclopedic knowledge of retina history and clinical trials, combined with his patience for complex cases, deeply influenced me. The contagious passion of Rajiv Shah, MD, for uveitis and complex vitreoretinal cases, along with the personalized approach to patient care lauded by Asheesh Tewari, MD, further fueled my interest. Residency in Detroit also gave me a new perspective for caring for underserved and uninsured populations. These experiences solidified my passion for vitreoretinal surgery and uveitis.

SUPPORT ALONG THE WAY

I have had many mentors who have shaped my career, and I am always grateful for their generosity and support. Lawrence Morse, MD, has supported me throughout my career, Glenn Yiu, MD, helped me develop my research interests, and my other mentors at UC Davis include Susanna S. Park, MD, PhD, and Ala Moshiri, MD, PhD. At the Cole Eye Institute, Sunil Srivastava, MD; Sumit Sharma, MD; and Careen Lowder, MD, taught me how to approach the most complicated uveitis cases and tailor treatment based on patient needs. I still reach out to them with questions, and they are always supportive. Along the way, I was fortunate to meet Steven Yeh, MD, and Goldis Malek, PhD, who have been generous in offering mentorship and support, even though they have not worked with me directly.

Dr. Emami-Naeini's advice: Stay curious, stay humble, and learn from your mistakes.

AN EXPERIENCE TO REMEMBER

A few years ago, I started caring for a patient who had lost one eye to an explosive device overseas and was losing vision in the other due to sympathetic uveitis. Due to socioeconomic challenges, he struggled to maintain systemic immunosuppression. His biggest wish was to see his 6-month-old child, whom he had never been able to see. After months of treatment and surgery, he finally regained enough vision to see his child for the first time. It was an emotional moment that brought everyone in the clinic to tears. I saw him recently, and he told me that he is trying get his driver's license to help with school dropoff and pickup. ■

Parisa Emami-Naeini, MD, MPH, is an associate professor of ophthalmology and the director of the Uveitis Service at the Tschannen Eye Institute at the University of California Davis. In addition to her clinical work, she is a clinician-scientist with a strong interest in big data and AI research. She is a consultant for Bausch + Lomb, Genentech/Roche, Regenxbio, and Alimera Sciences and receives research support from Regeneron. She can be reached at **parisaemami@gmail.com.**

FOUR PEARLS FOR MANAGING INFERIOR RHEGMATOGENOUS RD

These surgical insights can help trainees and young surgeons tackle challenging cases.

BY LUIS ACABÁ-BERROCAL, MD

Inferior rhegmatogenous retinal detachments (RRDs) pose unique challenges, especially for fellows and early-career attendings. The complexities of managing these cases span from deciding the necessity and timing of surgery to determining the most appropriate surgical approach and follow-up care. Here, I present key considerations and strategies to aid in the management of this intricate condition.

PEARL NO. 1: OBTAINING THE DIAGNOSIS

A thorough history and examination are crucial for accurately diagnosing an inferior RRD. Scleral depression plays a pivotal role in identifying causative retinal breaks, holes, and other underlying pathology, such as lattice degeneration and proliferative vitreoretinopathy (PVR). If no breaks or holes are detected, consider the possibility of a serous RD. Positioning the patient supine or laterally for a few minutes may help reveal fluid shifts typical of serous RDs (Figure 1). B-scan ultrasound can also aid in the diagnosis by detecting masses that might be obscured by the RD or choroidal thickening, such as in cases of posterior scleritis-related serous RD.

PEARL NO. 2: DECIDING ON SURGERY

Not all inferior RRD cases require surgical intervention. Inferior RRDs with chronic features, such as a partial or complete demarcation line, can often be monitored with less than a 10% risk of progression (Figure 2).[1,2] Similarly, detachments distant from the macula may be managed with laser demarcation followed by close observation. Surgical intervention should be considered for symptomatic, large inferior RRDs, especially those associated with giant retinal tears, macula-off detachments, or signs of progression.

Decisions regarding surgery, including scleral buckling, vitrectomy, or a combination of both, should be based on patient-specific factors and intraocular conditions. As with all medical decisions, the patient's health, age, line of work, and lifestyle all need to be considered. For example, patients who cannot maintain positioning after surgery or who frequently travel may benefit more from scleral buckling. Consider other ocular factors, such as the presence of vitreous hemorrhage, status of the sclera, status of the lens (phakic vs pseudophakic), and identification of breaks.

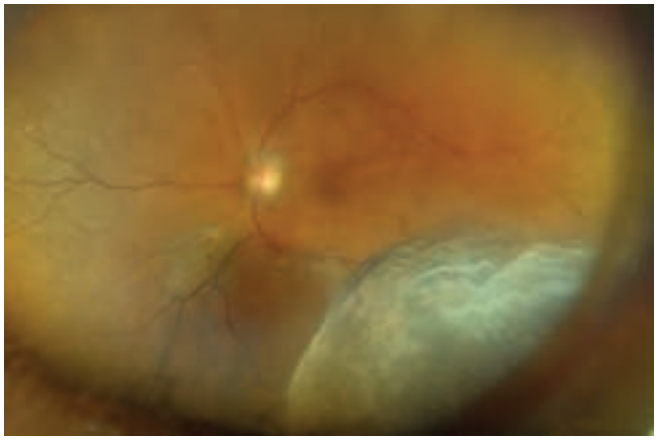

Figure 1. The fluid shifted during examination of this posterior scleritis-related inferior serous RD.

In general, inferior RRDs in phakic patients with non-giant retinal tears and minimal PVR can be managed with scleral buckling with or without drainage. Patients with pseudophakia, vitreous hemorrhage, or giant retinal tears are typically managed with vitrectomy. Combined scleral buckle/vitrectomy is particularly useful in cases of PVR but can also be employed for all RDs, depending on surgeon preference.

PEARL NO. 3: PINPOINTING SURGICAL TIMING

There is no consensus on the ideal timeframe for inferior RRD surgery, with progression generally occurring more slowly compared with superior RRDs due to gravitational effects.[3] This slower progression contributes to a higher rate of chronicity in inferior RRDs. Surgical timing should take

(Continued on page 14)

A SUTURELESS INTRASCLERAL FIXATION TECHNIQUE FOR THE CARLEVALE IOL


No flaps, extra sclerotomies, or scleral sutures are necessary with this approach.

BY EDUARDO RODITI, MD, AND BURKHARD DICK, MD, PHD, FEBOS-CR

A modified technique to implant a Carlevale IOL (FIL-SSF, Soleko) eliminates the need for scleral flaps by incorporating the T-shaped IOL haptics into the scleral wall and using the same sclerotomies to place the vitrectomy ports. This modification limits the risk of postoperative hypotony, reduces operative time, avoids iatrogenic damage to the sclera, and does not require scleral sutures. Here, we describe the modified intrascleral fixation technique (Video).

ABOUT THE CARLEVALE IOL

The Carlevale IOL is a secondary IOL specifically designed for intrascleral fixation characterized by a T-shaped haptic connector that serves as the primary source of stability.[1] It is a one-piece hydrophilic IOL with a wide range of powers from +5 D to +35 D and a 118.5 A constant. It is the only scleral-fixated lens that can be customized for astigmatic correction with a range of up to 10 D. The lens is placed from 0° to 180°, but its optic is designed to integrate the proper astigmatic axis correction for the cornea. It is also easily foldable to allow intraocular injection through a 2.2 mm corneal incision using a dedicated injector. The haptics have an anterior tilt of 10° with respect to the 6.5 mm optic plate, with a total IOL length of 13.2 mm. Its flexible, elastic design helps to maintain the IOL in the proper physiological position even in highly myopic or hyperopic eyes. This lens is approved for use in Europe, but not yet in the United States.

The original implantation technique involved opening 4 mm x 4 mm scleral flaps at 0° to 180° after a peritomy and diathermy and then creating a sclerotomy, from which the T-shape haptic was externalized[1]; however, this process is time-consuming, and at least four scleral sutures are needed to close the flaps. We are not aware of any description of using the same sclerotomies as ports for vitrectomy, but another two sclerotomies are commonly placed superiorly during vitrectomy, adding possible leakage wounds and hypotony complications. In other approaches, such as the Yamane technique, using the same sclerotomies as vitrectomy ports has proven to be an effective way to externalize the haptics, minimizing both scleral wounds and induced astigmatism.[2] We have incorporated this practice into the technique with great results.

Watch It Now
Video. Modified Carlevale Technique: No Flaps, No Extra Sclerotomies, No Scleral Sutures

STEP-BY-STEP APPROACH

1. Place the vitrectomy port for the infusion inferiorly and away from the peritomy sites.
2. Perform 1 to 2 clock hours of conjunctival peritomy from 0° to 180°.
3. Perform external diathermy to minimize bleeding and prepare the scleral bed for the groove and pockets.
4. Create a scleral groove of 2 mm to 3 mm at 0° to 180° using a 15° blade or a crescent blade.
5. Create scleral pockets above and below the scleral groove at the same two-thirds scleral thickness, where the haptic will rest intrasclerally (Figure 1).

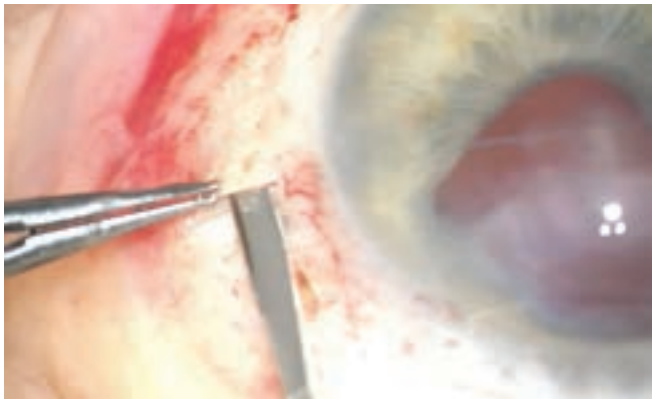

Figure 1. Create scleral pockets superiorly and inferiorly to the scleral groove.

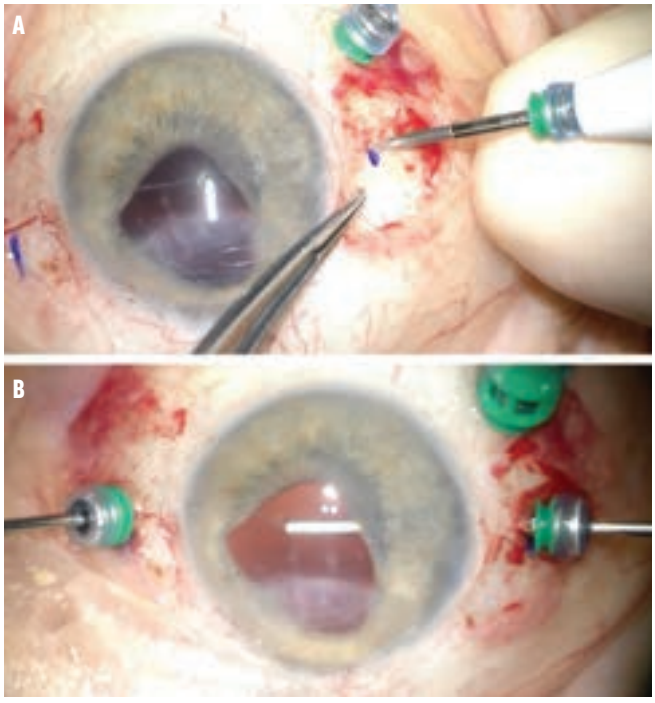

Figure 2. Place the vitrectomy ports at the same location as the future IOL plugs. Ensure the orientation is parallel to the iris (A) before proceeding with vitrectomy (B).

6. Place the vitrectomy trocar and port between 2 mm and 2.5 mm posterior to the limbus; the vitrectomy trocar should be inserted following the architecture of the wound, rotating it after passing the vertical flat component of the blade. Take care to have the correct orientation parallel to the iris and not to the optic nerve, as this will become the tunnel where the haptic will rest intrasclerally (Figure 2A).
7. Perform pars plana vitrectomy along with any special surgical considerations, such as epiretinal membrane peeling or panretinal photocoagulation (Figure 2B).
8. Create a 2.2 mm corneal wound with a corneal blade and fill the anterior chamber with OVD.
9. Place the lens in the injector and carefully inject it into the posterior chamber using forceps to hold the leading haptic, taking care to grasp the vertical component of the "T" parallel to it so that it can easily pass through the sclerotomy without damaging the haptic. Remember to completely remove the vitrectomy port or push it through the forceps before attempting to externalize the haptic.
10. Once the leading haptic is externalized, fully inject the IOL and grasp it with the forceps using the opposite sclerotomy.
11. After both haptics are externalized, carefully place the horizontal component of the "T" into the scleral pockets (Figure 3A).
12. Remove the OVD from the anterior chamber, and confirm the absence of leakage at both the scleral groove and the corneal wound (Figure 3B and C).
13. Close the conjunctiva with one absorbable 8-0 Vicryl suture on each side. Remove the infusion port.

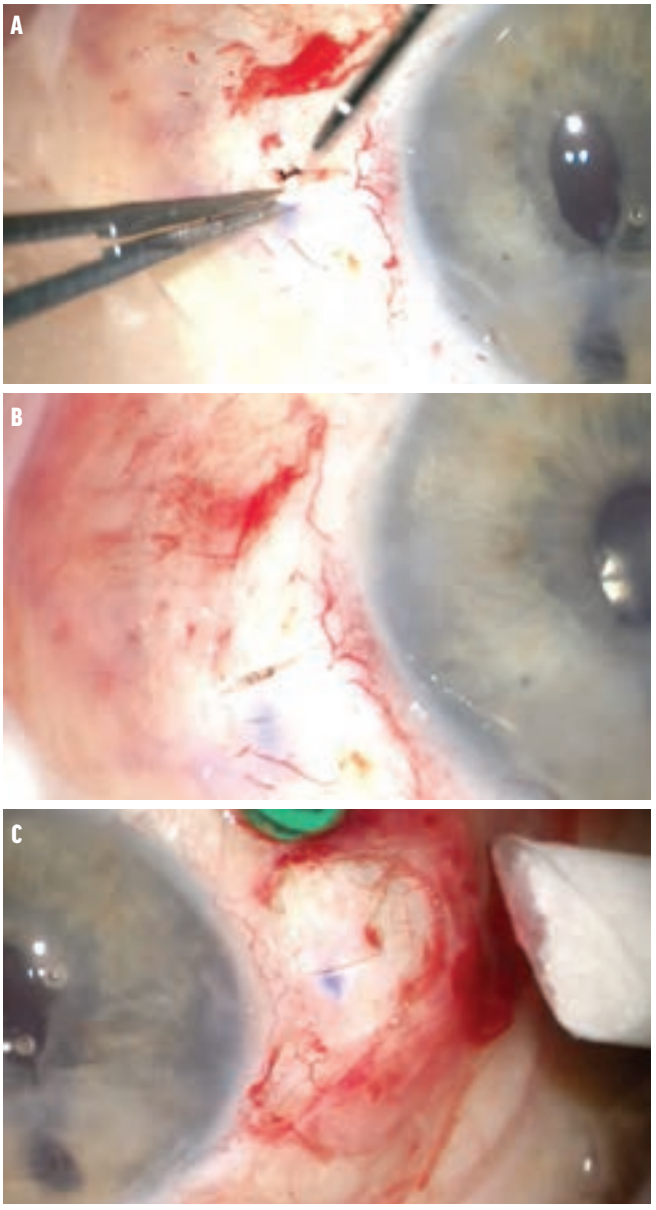

Figure 3. The T-shaped haptic should be internalized intrasclerally (A). In this example, both haptics are well-placed, with no leakage (B, C).

ADVANTAGES

Often, secondary IOLs require either large corneal incisions or many scleral and corneal accessory incisions; this technique requires only three 23- or 25-guage sclerotomies, as in a simple vitrectomy; the lens can also be implanted through a 2.2 mm main incision with other corneal incisions required. In addition, as only three sclerotomies are required, this technique may reduce hypotony, although this has not yet been confirmed in a controlled study.

By using the same incisions to place the vitrectomy ports, any posterior segment procedure can be performed, such as epiretinal membrane peeling or panretinal photocoagulation. Moreover, creating scleral flaps is time-consuming and requires multiple sutures to close. This technique requires only a small scleral pocket dissection for the haptic plug legs, which can be performed quickly and easily without the need for sutures.

Finally, this technique uses a custom lens design that can be regularly placed in the sclera at 0° to 180° to correct any corneal astigmatism through the toric optical axis built into the lens. Another option would be scleral fixation of a standard toric lens with eyelets, but the lens must be sutured along the meridian of the astigmatic axis, which is not always an ideal surgical location due to comorbidities (ie, glaucoma), filtering surgery, or surgical ergonomics.

DISADVANTAGES

The Carlevale IOL is still not FDA-approved, limiting its availability; moreover, few centers in Europe or elsewhere have the full range of dioptric powers in stock, so pre-ordering is required, reducing its usefulness in emergency or unexpected cases.

Another disadvantage is that peritomy is required for this technique. Although using a transconjunctival approach, such as the Yamene technique, shortens the surgical recovery time and is minimally invasive, this IOL was not designed to be covered by the conjunctiva alone. A modified transconjunctival surgical technique using the Carlevale IOL has been described with good results,[3,4] but long-term follow-up of these techniques hasn't been described, and the risks include erosion and exposure. Two-point fixation is another potential issue associated with this technique. However, the IOL is very stable, and IOL rotation and subsequent induced astigmatism are rare. ■

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BURKHARD DICK, MD, PHD, FEBOS-CR
- Chair of Department, Ruhr University Eye Hospital, Bochum, Germany
- Financial disclosure: None

EDUARDO RODITI, MD
- Physiology and Surgery Professor, Universidad Anahuac Mexico Norte, Mexico City, Mexico
- Vitreoretinal Consultant, Active Vision Center, Mexico City, Mexico
- eduardo.roditi@anahuac.mx
- Financial disclosure: None

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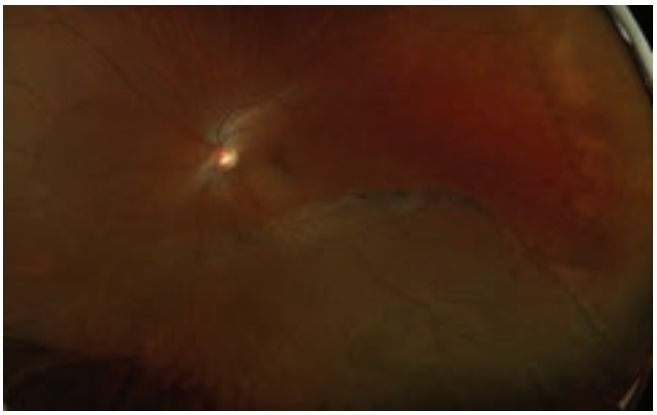

Figure 2. This inferior chronic RRD has a clear demarcation line.

into account patient health, symptom duration, macular involvement, progression, and associated giant retinal tears.

Typically, an inferior detachment threatening the fovea with recent symptoms (1 to 2 days) warrants prompt surgical intervention. Conversely, asymptomatic RRDs or those with symptom onset exceeding 1 week but not threatening the macula may not require immediate intervention. In cases of delayed surgery, provide the patient with an Amsler grid to monitor for progression, and schedule surgery sooner if significant progression is detected.

PEARL NO. 4: MANAGING SUBRETINAL FLUID

Persistent postoperative subretinal fluid can occur, with incidence rates varying significantly (up to 83%) at 1 month depending on the procedure.[4,5] This fluid can remain for an extended period of time, with reports of up to 30 months following scleral buckle surgery without drainage.[5] Patience is essential, but vigilance is required to identify progression, which could indicate new breaks, breakthrough of previously treated breaks, or inadequate treatment. Serial OCTs are crucial for monitoring. If fluid worsens, carefully examine for missed or new breaks and consider reoperation. Peripheral OCTs directed at areas of concern can be used to evaluate if subretinal fluid tracts to a potential break. ■

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LUIS ACABÁ-BERROCAL, MD
- Vitreoretinal Surgery Fellow, Wills Eye Hospital Retina Service, Mid-Atlantic Retina, Philadelphia
- acabaluis@gmail.com
- Financial disclosure: None

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In a Phase III clinical study of IHEEZO,

NO supplemental treatment needed to maintain anesthesia*†[1]

NO serious adverse events with an established safety profile[2]

NO patients reported experiencing pain[2]

*In the clinical trial, no patient undergoing routine cataract surgery receiving IHEEZO required supplemental treatment to maintain anesthesia; this was not the case for patients receiving tetracaine. Supplemental treatment was defined as general anesthesia, intraoperative systemic analgesia, or local anesthesia. Though supplemental administration was not required by any patient in the clinical trial, IHEEZO may be reapplied as needed to maintain anesthesia.[1,2]

†Sufficient anesthesia with IHEEZO lasted an average of 21.5 minutes in the clinical trial, while mean total surgical time was 13.9 minutes.[2]

APPROVED USE

IHEEZO is indicated for ocular surface anesthesia.

IMPORTANT SAFETY INFORMATION

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

IHEEZO should not be injected or intraocularly administered.

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

Do not touch the dropper tip to any surface as this may contaminate the gel.

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

The most common adverse reactions in studies following IHEEZO administration (incidence greater than or equal to 5%) were mydriasis, conjunctival hyperemia, and eye irritation.

You are encouraged to report suspected adverse reactions to the FDA. Visit **www.fda.gov/medwatch**, or call **1-800-FDA-1088**.

Please see Brief Summary of Full Prescribing Information for IHEEZO on adjacent page.

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References: 1. Iheezo. Prescribing information. Harrow IP, LLC; 2022. **2.** Data on File. Harrow IP, LLC; 2023.

IHEEZO™

(chloroprocaine HCl ophthalmic gel) 3%

BRIEF SUMMARY OF PRESCRIBING INFORMATION

1 INDICATIONS AND USAGE

IHEEZO™ (chloroprocaine hydrochloride ophthalmic gel) 3% is a preservative-free ester anesthetic indicated for ocular surface anesthesia.

4 CONTRAINDICATIONS

IHEEZO is contraindicated in patients with a history of hypersensitivity to any component of this preparation.

5 WARNINGS AND PRECAUTIONS

5.1 Not for Injection or Intraocular Administration

IHEEZO should not be injected or intraocularly administered.

5.2 Corneal Injury Due to Insensitivity

Patients should not touch the eye for at least 10 to 20 minutes after using anesthetic as accidental injuries can occur due to insensitivity of the eye.

5.3 Corneal Opacification

Prolonged use of a topical ocular anesthetic may produce permanent corneal opacification and ulceration with accompanying visual loss.

5.4 Risk of Contamination

Do not touch the dropper tip to any surface as this may contaminate the gel.

5.5 For Administration by Healthcare Provider

IHEEZO is indicated for administration under the direct supervision of a healthcare provider. IHEEZO is not intended for patient self-administration.

6 ADVERSE REACTIONS

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 data described below reflect 201 patients undergoing various surgical ocular procedures in two placebo-controlled trials (Study 1 and Study 2). Patients in Study 1 were randomized to receive a single instillation of 3 drops of IHEEZO or placebo. Patients in Study 2 were randomized to receive a single or multiple instillations of 1, 3, or 3+3 drops of IHEEZO or placebo.

The most common adverse reactions in these studies (incidence greater than or equal to 5%) following IHEEZO administration were mydriasis, conjunctival hyperemia, and eye irritation.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Risk Summary

There are no adequate and well-controlled studies of IHEEZO use in pregnant women to inform a drug-associated risk. There are no animal reproduction studies for chloroprocaine.

8.2 Lactation

Risk Summary

There are no data on the presence of chloroprocaine in human milk, the effects on the breastfed infant, or the effects on milk production. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IHEEZO and any potential adverse effects on the breastfed infant from IHEEZO.

8.4 Pediatric Use

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

8.5 Geriatric Use

No overall differences in safety or effectiveness of IHEEZO have been observed between elderly and younger patients.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Chloroprocaine, like other local anesthetics, blocks the generation and the conduction of nerve impulses, presumably by increasing the threshold for electrical excitation in the nerve, slowing the propagation of the nerve impulse, and reducing the rate of rise of the action potential. In general, the progression of anesthesia is related to the diameter, myelination, and conduction velocity of affected nerve fibers. Clinically, the order of loss of nerve function is as follows: (1) pain, (2) temperature, (3) touch, (4) proprioception, and (5) skeletal muscle tone.

12.3 Pharmacokinetics

The systemic exposure to chloroprocaine following topical ocular administration of IHEEZO has not been studied.

Elimination

Metabolism

Chloroprocaine is metabolized by plasma pseudocholinesterases and nonspecific esterases in ocular tissues. Chloroprocaine is rapidly metabolized in plasma by hydrolysis of the ester linkage by pseudocholinesterase. The hydrolysis of chloroprocaine results in the production of ß-diethylaminoethanol and 2-chloro-4-aminobenzoic acid, which inhibits the action of the sulfonamides.

Excretion

Chloroprocaine plasma half-life in vitro is approximately 25 seconds in adults and approximately 43 seconds in neonates. The kidney is the main excretory organ for most local anesthetics and their metabolites. Urinary excretion is affected by urinary perfusion and factors affecting urinary pH.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis

Long-term studies in animals to evaluate carcinogenic potential of chloroprocaine have not been conducted.

Mutagenesis

2-chloroprocaine and the main metabolite, ACBA, were negative in the in vitro bacterial reverse mutation test (Ames assay) and the in vitro chromosome aberrations assay.

Impairment of Fertility

Studies in animals to evaluate the impairment of fertility have not been conducted with chloroprocaine.

14 CLINICAL STUDIES

14.1 Study 1 and Study 2

Study 1 (NCT04779606) and Study 2 (NCT04753710) were randomized, double-blinded, placebo-controlled studies conducted to evaluate the efficacy, safety, and local tolerability of IHEEZO in 145 healthy volunteers.

In Study 1, 85 healthy males and females were randomized in a 4:1 ratio to receive a single ocular instillation of IHEEZO (n=68) or placebo (n=17). The double-blinded treatment included an IHEEZO or a placebo dose of 3 drops instilled at 1-minute (±15 seconds) intervals in the right eye of each volunteer. The median age was 39 years (range 19 to 55 years); 59% female and 41% male.

In Study 2, 60 healthy males and females were randomized (40:20) to receive single or multiple ocular instillations of an IHEEZO dose of 3 drops in the right eye. The median age was 25 years (range 18 to 59 years); 54% female and 46% male.

The efficacy in Study 1 and Study 2 was determined by proportion of patients achieving full conjunctival anesthesia evaluated by conjunctival pinching 5 minutes after administration.

Efficacy results of Study 1

The proportion of subjects with successful anesthesia was 90% in the IHEEZO group and 12% in the placebo group ($P<0.01$). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 14.3 minutes.

Efficacy results of Study 2

The proportion of subjects with successful anesthesia was 95% in the IHEEZO group and 20% in the placebo group ($P<0.01$). The median time for the IHEEZO group achieving anesthesia was 0.67 minutes. The median duration of anesthesia was 19.3 minutes.

14.2 Study 3

Study 3 (NCT04685538) was a randomized, prospective, multicenter, active-controlled, observer-masked study conducted to evaluate the efficacy and safety of IHEEZO (n=166) versus tetracaine ophthalmic solution 0.5% (n=172) in patients undergoing cataract surgery.

The primary endpoint was defined as the proportion of patients in each treatment group gaining successful anesthesia without any supplementation. On average, patients needed 1 to 1.5 minutes to obtain sufficient anesthesia to successfully perform the surgical procedure, which lasted on average 22 minutes.

No patient treated with IHEEZO required supplemental treatment to complete the intended surgical procedure.

17 PATIENT COUNSELING INFORMATION

Eye Care Precaution

Do not touch the dropper tip to any surface as this may contaminate the gel. Advise patients that their eyes will be insensitive for up to 20 minutes due to the effect of the anesthetic, and that care should be taken to avoid accidental injuries.

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CONSIDERATIONS FOR COMBINED PHACOEMULSIFICATION VITRECTOMY

All-in-one or staged approach? Here's what we have learned in our practice.

BY JAMES DOSSETT, MD; CHRISTINE CLAVELL, MD; AMI PATEL, MD; AND GHASSAN GHORAYEB, MD, MBA

There are circumstances in surgical retina that give rise to the utility of performing concurrent cataract surgery at the time of vitrectomy. According to the 2023 PAT survey, only 3.2% of US-based retina specialists consider cataract extraction at the time of vitrectomy in the management of trace nuclear sclerosis in a patient requiring vitrectomy for macula-involving tractional retinal detachment (RD); compare that with 37.4% of international respondents.[1]

Simultaneous anterior and posterior segment intervention requires the careful consideration of numerous patient- and disease-specific factors; recent research has found similar results between combined and sequential surgery. For example, one study of 120 patients with proliferative diabetic retinopathy showed similar long-term visual acuity results, with equal rates of postoperative inflammation, ocular hypertension, corneal edema, neovascular glaucoma, and tractional RD between patients who underwent vitrectomy and those who had phacovitrectomy.[2] In addition, electing to perform the procedures sequentially may render cataract surgery more challenging in a vitrectomized eye, where zonular dehiscence or stretching from tamponade agents and increased anterior chamber depth are more likely.[3] Here, we offer pre-, intra-, and postoperative considerations.

PREOPERATIVE FACTORS

During an eye examination, the surgeon should document any coexisting ocular conditions that could affect the timing of surgery, intraoperative decision making, and final visual outcome (eg, guttae, scleral thinning, pupillary dilation degree, anterior chamber depth, zonular weakness, cataract severity, red reflex, and posterior vitreous detachment). Corneal pathology may lead to corneal decompensation during long surgeries, rendering fine macular work more challenging. Patients with multiple medical comorbidities or mental disability or who require general anesthesia may benefit from combined procedures to reduce the risk of morbidity.

When selecting a lens, optical biometry may be influenced by vitreoretinal pathology, such as vitreous hemorrhage or posterior staphyloma, or a history of scleral buckling. Ultrasound may help obtain an accurate axial length.

In eyes that may require silicone oil tamponade, caution should be exercised with silicone IOLs, given the possibility of silicone oil droplet deposition with subsequent reduction in visual quality.[4] If future zonular or capsular stability is a concern, electing to implant a three-piece lens that can be fixated to the sclera will eliminate the need for lens exchange later, should it dislocate. However, the risk of tilt and decentration does exist with scleral fixation of these lenses (Figure 1).[5]

Vitreoretinal pathology is not necessarily a contraindication for premium multifocal IOLs, with limited data assessing visual outcomes for these lenses in patients with coexisting retinal diseases.[6] However, these lenses are generally avoided in eyes with severe macular pathology, such as geographic atrophy or large macular holes. Vitreoretinal surgeons should discuss the visual prognosis with patients after cataract surgery when retinal disease is present.

INTRAOPERATIVE FACTORS

We prefer to perform phacoemulsification and IOL implantation prior to vitrectomy. When an anterior

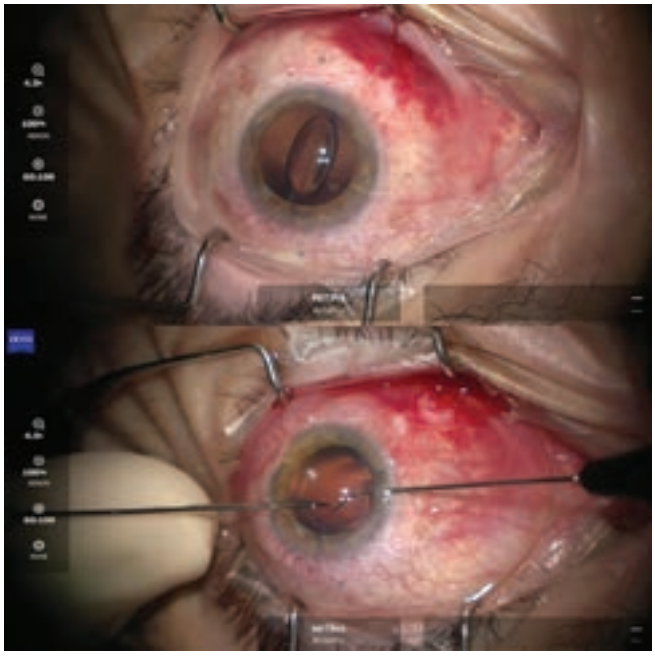

Figure 1. Implanting IOLs amenable to scleral fixation can be beneficial if there are concerns about long-term capsular stability. Lens tilt after scleral fixation has been reported, as in this case. The tilt was corrected with laser, eliminating the need for an IOL exchange.

segment surgeon is present, the sequence of surgical steps should be discussed thoroughly between the two surgeons. Typically, we initiate combined cases with a sub-Tenon block (Figure 2). The resulting mild proptosis can be beneficial in cases with enophthalmos but counterproductive in cases with a shallow anterior chamber and high IOP, such as in eyes with a complete silicone oil fill. It is especially important in these cases to ensure you have dissected fully into the sub-Tenon space to minimize conjunctival chemosis prior to cataract extraction. Flexibility in wound placement is important in cases where there is underlying retinal pathology requiring scleral depression to minimize anterior chamber shallowing; the primary surgeon should be comfortable operating both temporally and at the head of the bed.

In cases where silicone oil removal is planned in addition to cataract surgery, we typically perform cataract surgery prior to oil removal to maintain anterior chamber depth and allow for more stable fluidics (Figure 3). However, in cases of zonular compromise with anterior migration of silicone oil, it may be preferable to remove the oil first. In cases of a hypermature cataract, it may be helpful to partially remove the oil first to reduce posterior pressure and minimize the risk of an *Argentinian flag* sign. If the infusion line is in the eye while phacoemulsification is being performed with a Centurion machine (Alcon), surgeons should clamp the infusion to prevent aberrant fluidics between the machines.

In cases of macular hole or RD repair where gas tamponade is anticipated, a smaller capsulorhexis (4.5 mm – 5 mm) will reduce the likelihood of IOL prolapse

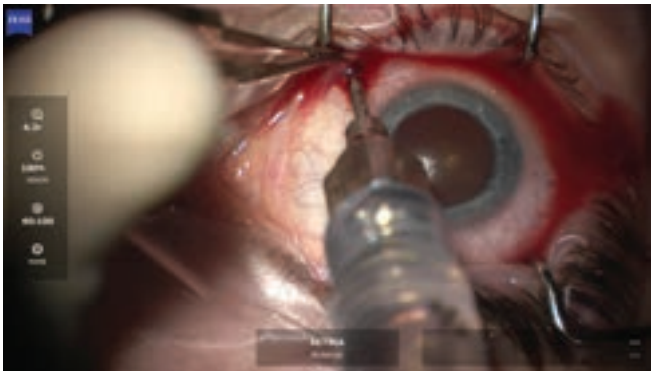

Figure 2. In cases not performed under general anesthesia, a conjunctival cutdown is performed in the inferonasal quadrant, and a sub-Tenon block is administered.

into the anterior chamber (Figure 4). Care should be taken to not perform an overly aggressive hydrodissection that may unintentionally prolapse the cataract into the anterior chamber; keeping it in the capsular bag will minimize contact with the corneal endothelium, reducing the likelihood of corneal edema.

Phacoemulsification should be performed using the minimum amount of energy possible. Collaborating with an experienced anterior segment surgeon is advised to maximize corneal clarity and reduce operating time. Care should be taken during cataract extraction to avoid contact with the iris to minimize constriction.

After IOL implantation, we typically place a 10-0 nylon or vicryl suture into the main wound to reduce the likelihood of chamber shallowing during vitrectomy. Avoid wound overhydration, as this may negatively affect visualization; aggressive hydration may also generate small bubbles in the anterior chamber, which can degrade the view. During vitrectomy, posterior capsulotomy can be performed centrally using the cutter, if needed. In situations with capsular compromise requiring sulcus placement or scleral fixation of the IOL, intracameral carbachol may reduce the risk of IOL prolapse or displacement. Reassessing the lens centration (and the axis of alignment in toric cases) after posterior segment surgery is advised, as positioning can shift during vitrectomy.

POSTOPERATIVE FACTORS

Postoperative hypotony is more likely in combined cases given the presence of at least three trocar wounds, a main corneal wound, and paracenteses; thus, we suture all ports at the end of surgery. Prolonged inflammation after phacovitrectomy may also be seen in longer, more complex cases. Postoperative steroid doses may need to be higher with longer tapers. In our practice, when gas is used in phacovitrectomy, we typically forgo the use of postoperative cycloplegic agents and avoid dilation until 1 month after surgery. Ultra-widefield imaging is useful in these circumstances in lieu of dilated examinations.

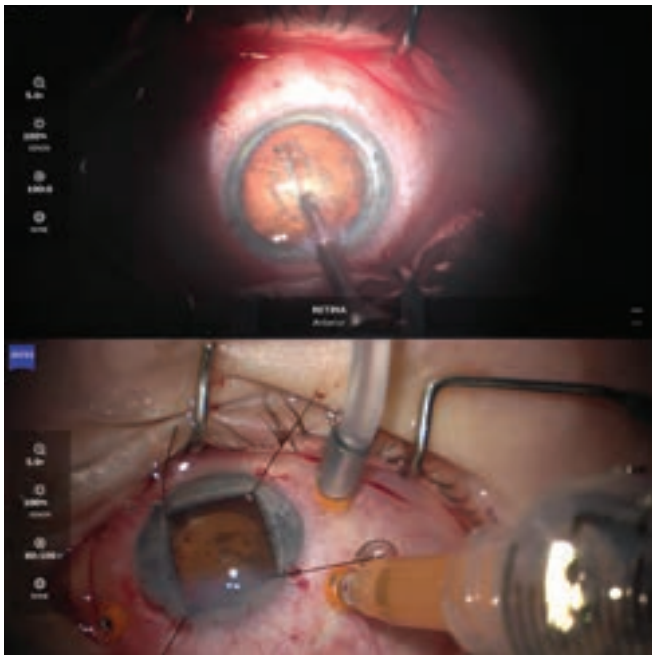

Figure 3. Cataract extraction and IOL implantation prior to silicone oil removal in a patient with a history of macula-involving RD who underwent vitrectomy and complex RD repair 3 months prior.

A recent study comparing vitrectomy with phacovitrectomy in patients with proliferative diabetic retinopathy demonstrated that patients treated with vitrectomy had a lower risk of neovascular glaucoma, iris rubeosis, and iris synechiae to the anterior lens capsule compared with patients undergoing combined surgery.[7] Another study used ultrasound biomicroscopy to show that supraciliary effusions are more common after phacovitrectomy (80% of patients) compared with vitrectomy (46%).[8] Patients with supraciliary effusions more commonly had abnormal IOP, intraocular fibrin, and formation of posterior synechia in the first 2 months postoperatively; however, visual outcomes were comparable.[8]

COMBINATION SUCCESS

Phacovitrectomy benefits patients by reducing the number of office visits without compromising visual outcomes.[9,10] This is especially important in circumstances where there is limited access to care and follow-ups. Careful planning will help ensure the best possible anatomic and visual outcomes for patients undergoing a combination procedure. ■

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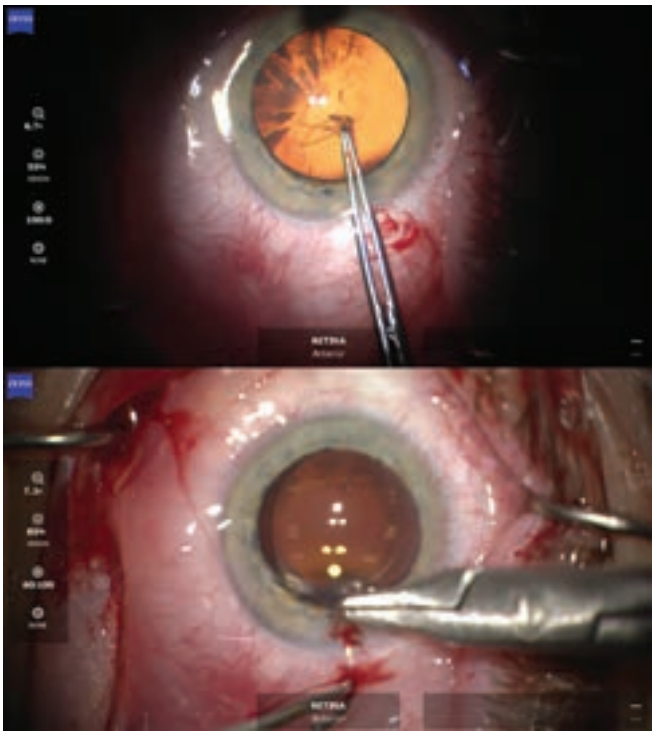

Figure 4. A smaller capsulorhexis during phacovitrectomy in a patient with a history of tractional RD and epiretinal membrane. A partial fluid-air exchange was performed, and a 10-0 vicryl suture was used to close the wound to reduce the risk of anterior chamber shallowing during vitrectomy.

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CHRISTINE CLAVELL, MD
- Vitreoretinal Surgeon, Eye Associates of New Mexico, Albuquerque, New Mexico
- Financial disclosure: None

JAMES DOSSETT, MD
- Vitreoretinal Surgery Fellow, West Virginia University Eye Institute, Morgantown, West Virginia
- jamespdossett@gmail.com
- Financial disclosure: None

GHASSAN GHORAYEB, MD, MBA
- Vitreoretinal Surgery Fellowship Director, West Virginia University Eye Institute, Morgantown, West Virginia
- Financial disclosure: None

AMI PATEL, MD
- Ophthalmology Resident, West Virginia University Eye Institute, Morgantown, West Virginia
- Financial disclosure: None

AN UPDATE ON SUSTAINED DRUG DELIVERY IN RETINA

Unique ways to address treatment burden for patients with retinal conditions.

BY DEEPAK SAMBHARA, MD, AND MARIN STOWE, BS


Anti-VEGF and steroid agents have revolutionized how we treat many retinal vascular diseases such as wet AMD, diabetic retinopathy (DR), diabetic macular edema (DME), and uveitis.[1,2] Real-world data show that patients who receive more frequent or continuous fixed dosing of these agents achieve more favorable anatomical and visual outcomes. In contrast, those who receive less frequent dosing than those in clinical trials have worse outcomes.[3] However, the high treatment burden associated with managing these diseases has underscored the need for novel treatments and sustained-release drug delivery (SRDD) platforms. Here, we examine some of the latest therapeutics in the pipeline and the evolution of SRDD platforms in the vitreoretinal space.

POLYMER-BASED SRDD

Polymer platforms can broadly be classified into bioerodible implants (BIs) and nonbioerodible implants (NBIs). Several NBIs have been FDA approved to treat retinal diseases, many of which are polyvinyl alcohol (PVA) implants made from hydrolyzed polymers of vinyl acetate. PVAs help to regulate drug diffusion and can be combined with ethylene vinyl alcohol to control the surface area of diffusion. Although PVAs are bioerodible structures, the implants are often nonbioerodible due to the reservoirs used to modulate and control drug release.

Nonbioerodible Implants

Retisert (Bausch + Lomb), an intravitreal NBI of fluocinolone acetonide, was FDA approved in 2005 for the treatment of chronic noninfectious uveitis.[4] This surgically placed implant releases fluocinolone acetonide at an initial rate of 0.6 µg/day, decreasing to a steady state of 0.3 µg/day to 0.4 µg/day over 30 months.

In 2014, Iluvien (Alimera Sciences) was the first intravitreally injected NBI to receive FDA approval for the treatment of DME. This implant releases 0.19 g fluocinolone acetonide at an average rate of 0.2 µg/day for up to 36 months.

Yutiq (Alimera Sciences) is a nearly identical NBI of fluocinolone acetonide approved by the FDA in 2018 to treat chronic noninfectious uveitis.[5] The implant is injected into the vitreous cavity and releases 0.18 g fluocinolone acetonide at 0.25 µg/day for up to 36 months.

Bioerodible Implants

Bioerodible platforms provide the additional benefit of resorption over time without leaving significant remnants of the delivery system.[6] BI platforms include polylactide acids (PLAs), polylactic-co-glycolic acids (PLGAs), and hydrogels. PLA metabolites are nontoxic, are hydrolyzed into constituent α-hydroxy acid, and can be eliminated naturally. PLA degradation depends on several factors, including molar mass, conformation, and copolymer composition.

PLGAs are bioerodible through the hydrolytic cleavage of

their polyester backbones into lactic and glycolic acids that are soluble in the vitreous cavity. Metabolism and degradation rates of PLGAs can be manipulated to control drug release based on the lactic acid-to-glycolic acid ratio. Due to pH imbalances, these nontoxic metabolites can create a locally acidic environment, which has the potential to cause damage to other structures in the eye.

Ozurdex (Abbvie) is a PLGA-based intravitreal implant of 0.7 mg dexamethasone FDA approved for the treatment of macular edema secondary to retinal vein occlusion, DME, and noninfectious uveitis with a duration of up to 6 months.[7,8] Despite the implant's ability to hydrolyze and be resorbed, persistent, nondissolving, tubular foreign bodies in the vitreous have been reported.[9,10]

Hydrogels are created with natural or synthetic biopolymers, connected by physical or chemical bonds, and crosslinked to maintain a 3D macrostructure.[11] Hydrogel platforms are often used in drug delivery due to their ability to contain significant water content, mimicking biological soft tissues. Given the ability to respond to temperature and pH shifts, drug release can be tailored to specific environmental changes. The active ingredient is dissolved or suspended within the hydrogel network during crosslinking, and drug release occurs through diffusion or dissolution of the hydrogel matrix—the drug release rate hinges on the degree of physical or covalent crosslinking of the hydrogel polymers.

The Elutyx platform (Ocular Therapeutix) consists of a preservative-free, polyethylene glycol-based triglycine hydrogel fiber that biodegrades via ester hydrolysis in the presence of water. Elutyx is customizable to release an active ingredient anywhere from days to months. Currently, it is used in Dextenza (Ocular Therapeutix), an FDA approved bioerodible intracanalicular insert that releases dexamethasone through passive diffusion to treat postoperative inflammation and allergic conjunctivitis.[12]

The Elutyx platform is also being investigated for wet AMD and DR with the OTX-TKI (Axpaxli, Ocular Therapeutix) clinical program. OTX-TKI is an SRDD BI containing the tyrosine kinase inhibitor (TKI) axitinib, which is injected into the vitreous cavity. OTX-TKI (450 µg) is being evaluated in two phase 3 registration trials (NCT06495918 and NCT06223958) for wet AMD and a phase 1 clinical trial (NCT05695417) for the treatment of DR.

Durasert E (EyePoint Pharmaceuticals) is an SRDD BI developed for the treatment of wet AMD, DR, and DME. EYP-1901 (Duravyu, EyePoint Pharmaceuticals) is an intravitreal injection using the Durasert E platform to deliver the TKI vorolanib. The implant is under investigation in two phase 3 trials, LUCIA (NCT06683742) and LUGANO (NCT06668064) for the treatment of wet AMD.[13] EYP-1901 is also in phase 2 studies for nonproliferative DR (NCT05381948) and DME (NCT06099184).

DRUG-ELUTING RESERVOIRS

In 2021, the FDA approved the port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) for the treatment of wet AMD based on the pivotal phase 3 clinical trial (NCT03677934).[14] Susvimo is a refillable reservoir that holds up to 200 µL of medication. Passive diffusion of ranibizumab is controlled via a titanium release control element that acts as a medium between the vitreous and the device. A self-sealing septum is located on the extraskeletal surface of the device, which allows for repeated refills with a custom refill-exchange needle. A silicone encasement sits superficial to the sclera, acting as an extraskeletal flange to anchor the device into the deep conjunctiva without the need for suture fixation.

In October 2022, Genentech/Roche voluntarily recalled the device due to concerns about septum displacement.[15] The product was relaunched in July 2024 with changes to the septum and overmold interfaces while doubling the bond strength. Lubrication was added to the refill-exchange needle to reduce injection forces during refill.[16]

The PDS is still under investigation for the treatment of DR and DME in two phase 3 clinical trials (NCT04503551 and NCT04108156).

SUPRACHOROIDAL APPROACH

The suprachoroidal space (SCS) has become a therapeutic target for retinovascular disease due to the ability to achieve higher drug concentrations, increased bioavailability, and longer duration of action with a more favorable side effect profile.[17]

Xipere (Bausch + Lomb) is an SCS injection of 4 mg triamcinolone acetonide that was FDA approved in 2021 for the treatment of macular edema secondary to noninfectious uveitis.[18] The SCS Microinjector (Clearside Biomedical) used in Xipere is a piston syringe and needle approximately 1 mm

AT A GLANCE

- The high treatment burden associated with managing retinal diseases has underscored the need for novel treatments and sustained-release drug delivery platforms.
- The suprachoroidal space has become a therapeutic target for retinovascular disease due to the ability to achieve higher drug concentrations, increased bioavailability, and longer duration of action.
- Innovation in drug delivery has led to durable, efficacious, and long-acting treatments that have the potential to decrease treatment burden and improve patient outcomes.

in length (900 µm and 1,100 µm needles).

The phase 2b ODYSSEY clinical trial (NCT05891548) evaluated CLS-AX (Clearside Biomedical), a proprietary suspension of 1.0 mg axitinib delivered by SCS injection, for the treatment of wet AMD.[19]

GENE THERAPY PLATFORMS

In gene therapy, a viral vector designed explicitly with a therapeutic gene transfects host cells, leading to endogenous expression of the therapeutic gene product. In retinovascular disease, these gene products are anti-VEGF proteins, which offer the possibility of SRDD and minimized treatment burden.

Ixoberogene soroparvovec (ixo-vec, Adverum Biotechnologies) is an intravitreal gene therapy using an AAV2.7m8 viral capsid to express aflibercept. Ixo-vec was assessed in a phase 1 trial (NCT03748784) and long-term observational study (NCT04645212) for wet AMD and continues in the phase 2 LUNA trial (NCT05536973) evaluating an intravitreal injection of two dose concentrations in conjunction with prophylactic steroids. The phase 2 trial (NCT04418427) for DME was stopped due to severe adverse events reported in patients receiving the higher dose, leading to the termination of the DME clinical program.[20]

4D Molecular Therapeutics used a process of directed evolution to help develop their R100 capsid, the backbone of their investigational product for the treatment of wet AMD, DR, and DME. 4D-150 is a single-dose intravitreal gene therapy that encodes an inhibitory RNAi targeting VEGF-C and a codon-optimized sequence of aflibercept. The gene therapy is under investigation in the phase 1/2 PRISM trial (NCT05197270) for wet AMD and the phase 2 SPECTRA trial (NCT05930561) for DME.

ABBV-RGX-314 (Regenxbio/Abbvie) is a gene therapy delivered in the subretinal space or SCS that codes for a transgene on an AAV8 vector that expresses a ranibizumab-like monoclonal antibody fragment. Two phase 2b/3 studies (NCT04704921 and NCT05407636) are investigating subretinal ABBV-RGX-314 in wet AMD, and a phase 2 study (NCT04567550) is assessing the gene therapy for moderately severe or severe nonproliferative DR or mild proliferative DR. ABBV-RGX-314 is also being investigated in a phase 2 study (NCT04514653) as an SCS injection—delivered using Clearside Biomedical's SCS Microinjector—for patients with wet AMD.

NEXT STEPS

The evolution of SRDD in the vitreoretinal space has dramatically transformed the landscape over the past three decades. Innovation in drug delivery has led to durable, efficacious, and long-acting treatments that have the potential to decrease treatment burden and improve patient outcomes. As we head into 2025, we expect to see further clinical development of investigational products with the hope of expanding our clinical armamentarium for patient care. ■

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24 Wet AMD Therapies in the Pipeline
By Saumya M. Shah, MD, and Daniel Su, MD

28 The Therapeutic Landscape For Diabetic Eye Disease
By Yingna Snowy Liu, MD; Shane Griffin, MD, MCR; and Chirag D. Jhaveri, MD

DEEPAK SAMBHARA, MD
- Partner, Medical Director of Research, Medical Retina and Diseases of the Vitreous, Eye Clinic of Wisconsin, Wausau, Wisconsin
- sambhad@eyeclinicwi.com
- Financial disclosure: Advisor/Consultant (Genentech/Roche, iDocSocial, Ocular Therapeutix, Regeneron); Research Funding (Ocular Therapeutix, Regeneron); Speaker/Speaker's Bureau (Apellis, Astellas, Evolve Medical, Heidelberg Engineering, iDocSocial, Regeneron); Stock (Eclipse Life Sciences)

MARIN STOWE, BS
- Medical Student, Medical College of Wisconsin-Central Wisconsin, Wausau, Wisconsin
- Financial disclosure: None

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WET AMD THERAPIES IN THE PIPELINE

A review of clinical trials investigating novel approaches to wet AMD in 2024.

BY SAUMYA M. SHAH, MD, AND DANIEL SU, MD


There are a multitude of effective agents available for the treatment of wet AMD, including anti-VEGF medications, biosimilars, higher-dose variations of standard drugs, and combination dual-target therapies (Figure). New contenders aim to offer a primary versus adjuvant treatment route through other targets/mechanisms or extended treatment duration. Here, we summarize some of the ongoing innovation in the wet AMD landscape (Table).

TYROSINE KINASE INHIBITORS

Tyrosine kinase inhibitors (TKIs) prevent tyrosine kinase phosphorylation and the resulting downstream signaling cascade involving VEGF receptors.

EYP-1901 (Duravyu, EyePoint Pharmaceuticals) is an intravitreal insert of voralinib delivered using the Durasert E platform. The phase 2 DAVIO2 trial (NCT05381948) compared 2 mg and 3 mg EYP-1901 after loading aflibercept (Eylea, Regeneron) injections with aflibercept every 8 weeks; the trial met its primary endpoint of stable BCVA at 14 months, with 44% of patients not requiring rescue therapy.[1] The phase 3 LUCIA (NCT06683742) and LUGANO (NCT06668064) trials include treatment-naïve and previously treated patients with wet AMD.[2]

OTX-TKI (Axpaxli, Ocular Therapeutix) is a bioresorbable hydrogel delivered via an intravitreal implant. SOL-1 (NCT06223958) is a phase 3 clinical trial with treatment-naïve wet AMD patients receiving either the axitinib implant or aflibercept after two monthly injections of aflibercept during the screening period. The primary endpoint is the percentage of patients with < 15 ETDRS letters of BCVA loss at week 36. Patient enrollment began in early 2024.

D-4517.2 (Ashvattha Therapeutics) is a monthly subcutaneous or oral therapy that was found to be safe and well-tolerated in the phase 1 study.[3] An ongoing two-stage phase 2 clinical trial (NCT05387837) is looking at subcutaneous D-4517.2 at dose-escalating concentrations in 30 patients with wet AMD. Stage 1 results demonstrated safety, and visual and anatomical outcomes indicated a biological response. Stage 2, the chronic dosing study, has been initiated with the aim of enrolling at least 20 patients with wet AMD or diabetic macular edema who will receive the therapy biweekly or monthly for up to 40 weeks.

PAN 90806 (PanOptica) is a topical eye drop found to be safe and effective in a phase 1/2 trial (NCT03479372). A total of 51 treatment-naïve wet AMD patients randomly received varying doses of once-daily topical PAN 90806, and 79% of patients had a reduction in injection burden with stable BCVA throughout the study period.[4] Currently, the drug formulation is being modified after PanOptica entered into a license agreement with Zhaoke Ophthalmology.[5]

CLS-AX (Clearside Biomedical) is a suprachoroidal injection of an axitinib suspension delivered via the

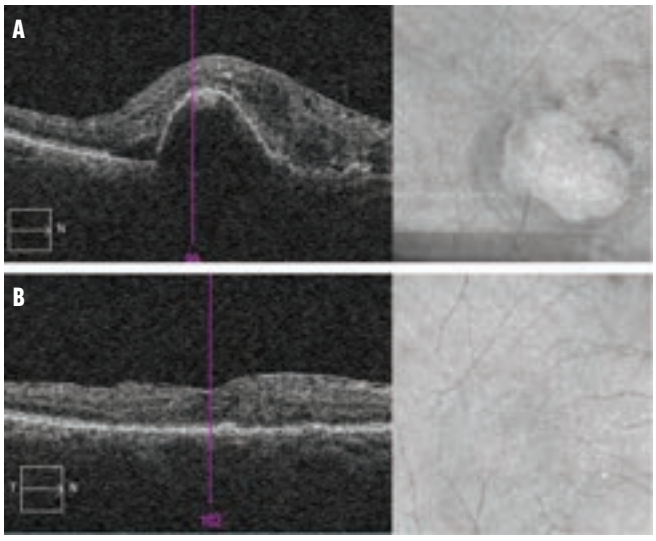

Figure. OCT and the corresponding near-infrared image of a patient with wet AMD undergoing treatment with anti-VEGF injection every 4 weeks with persistent subretinal fluid and a pigment epithelial detachment (A). After one injection of a recently approved therapeutic, OCT and the corresponding near-infrared image demonstrate resolution of subretinal fluid and pigment epithelial detachment (B).

company's SCS Microinjector. The phase 2b ODYSSEY trial (NCT05891548) is assessing the safety and efficacy of suprachoroidal 1.0 mg CLS-AX with a flexible dosing regimen in previously treated wet AMD patients versus controls receiving aflibercept every 8 weeks. The trial met its primary and secondary endpoints, with stable BVCA and central subfield thickness and an 84% reduction in injection frequency compared with pre-study treatment regimens.[6]

AR-14034 (Aerie Pharmaceuticals) is a sustained-release implant of axitinib currently being studied in the NOVA-1 phase 1/2 study (NCT05769153) for safety and durability.

GENE THERAPY

There are many investigational gene delivery methods that can continuously produce proteins, such as anti-VEGF.

ABBV-RGX-314 (Regenxbio/Abbvie) delivers ranibizumab-like proteins via a viral vector. It is currently being investigated as a subretinal injection in two phase 3 studies, ATMOSPHERE (NCT04704921) and ASCENT (NCT05407636), compared with monthly ranibizumab (Lucentis, Genentech/Roche) and bimonthly aflibercept, respectively. In the phase 2 pharmacodynamic study, up to 73% of patient were free of rescue injections at 6 months, and all cohorts demonstrated stable to improved BCVA and retinal thickness.[7]

ABBV-RGX-314 is also being evaluated with a suprachoroidal delivery approach in the phase 2 AAVIATE study (NCT04514653). The interim 6-month trial results showed stable anatomical and visual endpoints and an 80% reduction in annualized injection rate.[8]

Ixoberogene soroparvovec (ixo-vec, Adverum Biotechnologies) is in the phase 2 LUNA trial (NCT05536973) evaluating a single intravitreal injection of one of two dose concentrations in conjunction with prophylactic steroids in patients with wet AMD. The positive 52-week data show that 54% and 69% of patients treated with the $6^{E}10$ and $2^{E}11$ doses, respectively, remained injection-free, with an 88% and 92% reduction in treatment burden. No patients treated with the $6^{E}10$ dose and topical steroids had inflammation at week 52 or at any subsequent visit.[9] The company announced plans to initiate the phase 3 ARTEMIS noninferiority study in early 2025.[9]

4D-150 (4D Molecular Therapeutics) is a synthetic viral capsid that expresses aflibercept and a VEGF-C inhibitory RNAi that is delivered via an intravitreal injection. It is being evaluated in the phase 1/2 PRISM trial (NCT05197270), in which patients randomly receive high- or low-dose gene therapy with concurrent prophylactic topical corticosteroid compared with controls receiving bimonthly aflibercept. Interim 24-week analysis showed an 85% to 89% decrease in injection burden across both doses, with 77% of patients remaining injection-free in the high-dose group versus 60% in the low-dose group. Visual acuity remained stable across both groups, and no significant adverse events were reported.[10] The phase 3 study, 4FRONT-1, is scheduled to begin in 2025.[10]

MULTITARGET THERAPY

Since the approval of faricimab (Vabysmo, Genentech/Roche), a bispecific antibody targeting angiopoietin-2 and VEGF-A, other multitargeted therapies have shown promise.

OPT-302 (sozinibercept, Opthea) is a Fc-fusion protein designed to inhibit VEGF-C and VEGF-D. There are currently two phase 3 studies, ShORe (NCT04757610) and COAST (NCT04757636). Controls receive ranibizumab plus sham every 4 weeks in ShORe and 2 mg aflibercept

AT A GLANCE

- Investigational wet AMD treatments aim to offer a primary versus adjuvant treatment route through targets/mechanisms other than anti-VEGF, cost-conscious biosimilars, or extended treatment duration.
- Ongoing innovation for the treatment of wet AMD includes tyrosine kinase inhibitors, gene therapy, multitarget therapy, alternative targets, and biosimilars.
- With time, the treatment of wet AMD may have frontline contenders beyond anti-VEGF injections or may involve a multimechanism approach with therapeutics with various delivery methods.

TABLE. WET AMD TREATMENT PIPELINE

Study Drug (Company)	Target	Delivery Method	Trial NCT	Trial Status	Completion
Phase 3					
ONS-5010 (bevacizumab-vikg, Lytenava, Outlook Therapeutics)	Anti-VEGF	Intravitreal	NCT06190093	Active, not recruiting	October 2024
ABBV-RGX-314 (Regenxbio/Abbvie)	Gene therapy	Subretinal	NCT05407636 NCT04704921	Recruiting	February 2025 May 2025
OPT-302 (sozinibercept, Opthea)	Anti-VEGF-C and VEGF-D	Intravitreal	NCT04757610 NCT04757636	Active, not recruiting	July 2025
RC28-E (RemeGen)	Anti-VEGF/anti-fibroblast growth factor 2	Intravitreal	NCT05727397	Recruiting	November 2025
Tarcocimab tedromer/tabirafusp tedromer (KSI-301/KSI-501, Kodiak Sciences)	Antibody biopolymer conjugate (ABC)/ anti-interleukin-6 and VEGF trap ABC	Intravitreal	NCT06556368	Recruiting	January 2026
OTX-TKI (Axpaxli, Ocular Therapeutix)	Tyrosine kinase inhibitor	Implant	NCT06223958	Recruiting	April 2026
EYP-1901 (EyePoint Pharmaceuticals)	Tyrosine kinase inhibitor	Implant	NCT06668064 NCT06683742	Recruiting Not yet recruiting	August 2026 October 2026
IBI302 (efdamrofusp alfa, Innovent Biologics)	Recombinant VEGFR-Fc-human CR1 fusion protein	Intravitreal	NCT05972473	Recruiting	February 2027
Phase 2					
RBM-007 (Ribomic)	Anti-fibroblast growth factor 2 aptamer	Intravitreal	NCT04200248 NCT04640272 NCT04895293	Complete	
AG-73305 (Allgenesis Biotherapeutics)	Anti-VEGF/integrins	Intravitreal	NCT05301751	Active, not recruiting	February 2024
CLS-AX (Clearside Biomedical)	Tyrosine kinase inhibitor	Suprachoroidal	NCT05891548	Active, not recruiting	July 2024
D-4517.2 (Ashvattha Therapeutics)	Tyrosine kinase inhibitor	Subcutaneous/oral	NCT05387837	Active, not recruiting	November 2024
ABBV-RGX-314 (Regenxbio/Abbvie)	Gene therapy	Suprachoroidal	NCT04514653	Recruiting	October 2025
KHK4951 (Kyowa Kirin Group)	Anti-VEGF	Topical	NCT06116890	Recruiting	November 2025
Ixo-vec (Adverum Biotechnologies)	Gene therapy	Intravitreal	NCT05536973	Active, not recruiting	August 2028
Phase 1/2					
PAN 90806 (PanOptica)	Tyrosine kinase inhibitor	Topical	NCT03479372	Complete	
MK-3000 (restoret, EyeBio/Merck)	Wnt signaling pathway agonist	Intravitreal	NCT05919693	Complete	
AXT107 (AsclepiX Therapeutics)	Anti-VEGF-A and VEGF-C/Tie2 activation	Suprachoroidal	NCT05859776	Active, not recruiting	March 2025
4D-150 (4D Molecular Therapeutics)	Gene therapy	Intravitreal	NCT05197270	Recruiting	November 2025
AR-14034 (Aerie Pharmaceuticals/Alcon)	Tyrosine kinase inhibitor	Implant	NCT05769153	Recruiting	March 2027

plus sham for three loading doses every 4 weeks and then every 8 weeks thereafter in COAST. The primary endpoint is superiority in BCVA gains at 12 months. One-year results are expected in 2025 for both studies.

RC28-E (RemeGen) is a chimeric decoy receptor trap fusion protein with dual blockage of VEGF and fibroblast growth factor 2. The drug was well-tolerated with an overall favorable safety profile and evidence of improvements in BCVA and anatomical parameters in its phase 1b trial.[11] It is currently enrolling patients in a phase 3 trial (NCT05727397).

IBI302 (efdamrofusp alfa, Innovent Biologics) is a recombinant VEGFR-Fc-human CR1 fusion protein that underwent a phase 2 trial that met its primary endpoint of noninferior BCVA gains in patients in both dose groups versus the aflibercept group from baseline to week 40.[12] The phase 3 STAR trial (NCT05972473) began enrollment in mid-2023.

AXT107 (AsclepiX Therapeutics) is an integrin-regulating peptide that inhibits VEGF-A and VEGF-C and activates Tie2 and is delivered as a single suprachoroidal injection. The phase 1/2 DISCOVER trial (NCT05859776) evaluating the safety and tolerability of three dose strengths of AXT107 for wet AMD completed enrollment in May 2024.

AG-73305 (Allgenesis Biotherapeutics), a bispecific molecule that simultaneously binds to VEGF and integrins, is currently undergoing a phase 2a study (NCT05301751).[13] Preliminary data on six patients showed an excellent safety

profile and improvements in BCVA as early as 1 week post-injection that were maintained over 3 months.[13]

Tarcocimab tedromer and tabirafusp tedromer (KSI-301 and KSI-501, Kodiak Sciences) are under investigation in the phase 3 DAYBREAK trial (NCT06556368). Tarcocimab is an intravitreal antibody biopolymer conjugate (ABC), while tabirafusp is a bispecific anti-interleukin-6 and VEGF trap ABC. The trial includes two treatment arms (tarcocimab and tabirafusp) and an aflibercept comparator arm.[14]

ALTERNATIVE TARGETS

MK-3000 (restoret, EyeBio/Merck) is an intravitreal trispecific antibody that acts as an agonist of the Wnt signaling pathway. The 12-week data from the phase 1b/2 AMARONE clinical trial (NCT05919693) demonstrated that monthly doses of MK-3000, in combination with aflibercept, were well-tolerated with a mean change in VA of +6.8 letters and an absolute reduction in central subfield thickness of -268 µm.[15]

RBM-007 (Ribomic), an anti-fibroblast growth factor 2 aptamer that inhibits angiogenesis and scar formation, has been investigated in three phase 2 clinical trials (NCT04200248, NCT04640272, and NCT04895293), all of which are complete. Data published in *Eye* suggest that the therapeutic is effective in treatment-naïve wet AMD patients or those with a short history of anti-VEGF treatment.[16] However, the drug showed no additional benefit over aflibercept for patients with a long history of anti-VEGF therapy.[16]

Researchers are also investigating adjuvant oral doxycycline/MMP-9 inhibition in a phase 2 trial (NCT04504123).

Other therapeutic approaches currently in phase 1 for the treatment of wet AMD include:

- CG-P5 peptide eye drops (Caregen, NCT06132035)
- Lenvatinib periocular gel injections (AIV-007, AiViva BioPharma; NCT05698329)
- Episcleral brachytherapy (NCT02988895)
- RNA interference-based gene silencing technology (OLX10212, OliX Pharmaceuticals; NCT05643118)
- Gene therapy targeting all subtypes of VEGF and angiopoietin-2 (EXG102-031, Exegenesis Bio; NCT05903794)
- Gene therapy that expresses fusion VEGF receptor proteins targeting multiple subtypes of VEGF and placental growth factor (KH631, Chengdu Origen/Vanotech; NCT05657301)
- Fusion protein targeting VEGF and angiopoietin-2 (AM712, AffaMed; NCT05345769)

ANTI-VEGF AND BIOSIMILARS

KHK4951 (tivozanib, Kyowa Kirin Group) is a topical anti-VEGF therapy in a phase 2 trial (NCT06116890) evaluating three dosages of KHK4951 compared with aflibercept. The primary outcome is the reduction of 15 or more letters in BCVA at week 44.

A variety of anti-VEGF biosimilars are under investigation in phase 3 trials to gain FDA approval. Four different biosimilars for aflibercept and two for ranibizumab have been FDA-approved. To date, there are no FDA-approved biosimilars for bevacizumab specifically for ophthalmic use. However, ONS-5010 (bevacizumab-vikg, Lytenava, Outlook Therapeutics) is currently being evaluated in an ongoing phase 3 noninferiority study, NORSE EIGHT, for the treatment of wet AMD (NCT06190093).[17] The trial is expecting completion by the end of 2024.

LOOKING AHEAD

The therapies in the pipeline for wet AMD are abundant and exciting. With time, the treatment of wet AMD may have frontline contenders beyond anti-VEGF injections or may involve a multimechanism approach with various delivery methods. ■

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SAUMYA M. SHAH, MD
- Vitreoretinal Surgery Fellow, USC Roski Eye Institute, Los Angeles
- saumyashahmd@hotmail.com
- Financial disclosure: None

DANIEL SU, MD
- Partner, Retina-Vitreous Associates Medical Group, Los Angeles
- Adjunct Clinical Assistant Professor, Keck School of Medicine, University of Southern California, Los Angeles
- dsu@laretina.com
- Financial disclosure: Consultant/Speaker (Ocuphire, Regeneron)

THE THERAPEUTIC LANDSCAPE FOR DIABETIC EYE DISEASE

Many novel approaches are chugging through the pipeline, with promising data from phase 2 and 3 trials.

BY YINGNA SNOWY LIU, MD; SHANE GRIFFIN, MD, MCR; AND CHIRAG D. JHAVERI, MD



The treatment of diabetic retinopathy (DR) currently includes panretinal photocoagulation to prevent severe vision loss due to proliferative DR (PDR) and intravitreal anti-VEGF agents. Although these treatments have reduced the rate of vision loss from DR and its sequelae,[1,2] many patients have treatment-resistant disease or struggle with treatment burden. Thus, many advances are under investigation, not only in terms of treatment delivery but also for targeting pathways other than anti-VEGF. In this article, we highlight some of the latest therapeutic developments (Table).

INTRAVITREAL DELIVERY

Tarcocimab tedromer (KSI-301, Kodiak Sciences) is an anti-VEGF antibody biopolymer conjugate that blocks all VEGF-A isoforms. The phase 3 GLOW trial (NCT05066230) compared tarcocimab with sham in moderately severe to severe nonproliferative DR (NPDR). After receiving four injections of the study drug, a significantly higher proportion of patients had a 2-step or more DRSS improvement from baseline (41.1%) compared with sham (1.4%) at week 48.[3] The similarly designed phase 3 GLOW2 clinical trial (NCT06270836) is recruiting.

RC28-E (RemeGen), a fusion protein targeting FGF2 and VEGF, is in a phase 3 trial (NCT05885503) for the treatment of diabetic macular edema (DME). The trial is comparing 2 mg RC28-E with 2 mg aflibercept (Eylea, Regeneron) with the primary outcome being change in BCVA at week 52.

MK-3000 (restoret, EyeBio/Merck) is a tetravalent, trispecific antibody that acts as an agonist of the Wnt signaling pathway.[4] The phase 2b/3 BRUNELLO trial (NCT06571045) is investigating the safety and efficacy of two dosages of MK-3000 compared with ranibizumab (Lucentis, Genentech/Roche) in patients with DME.[4] Primary endpoints are safety and mean change in BCVA from baseline to week 52.

UBX1325 (foselutoclax, Unity Biotechnology) is a senolytic small-molecule inhibitor of antiapoptotic protein BCL-xL. In the phase 2 BEHOLD study (NCT04857996), one injection of UBX1325 led to an improvement of 6.2 letters from baseline, 5.6 more than sham, at 48 weeks.[5] Of UBX1325-treated patients, 53% did not require rescue injections before 48 weeks.[5] The phase 2b ASPIRE study (NCT06011798) is comparing the safety and efficacy of UBX1325 with 2 mg aflibercept for patients with NPDR and DME.[6]

AG-73305 (Allgenesis Biotherapeutics), a bispecific Fc-fusion protein designed to block VEGF and integrin pathways, showed positive preliminary results from the phase 2a trial (NCT05301751) for DME. The data for

22 patients treated with a single intravitreal injection showed a mean BCVA improvement of +6.4 ETDRS letters and central subfield thickness (CST) reduction of 100 µm at 4 weeks, which lasted between 12 and 24 weeks.[7]

RG6179 (vamikibart, Roche) is a monoclonal antibody that binds interleukin-6 cytokines. The phase 2 trial (NCT05151731) is evaluating the safety and efficacy of two dosages of RG6179 compared with ranibizumab for DME. A second phase 2 trial (NCT05151744), now complete, is evaluating the therapy in combination with ranibizumab.

OPT-302 (Opthea), an intravitreal anti-VEGF therapy that blocks VEGF-C and VEGF-D, is designed as a combination therapy with current anti-VEGF agents. In the completed phase 2 trial (NCT03397264), 52.8% of patients with DME treated with OPT-302 in combination with aflibercept achieved a visual gain of ≥ 5 ETDRS letters at 12 weeks compared with baseline.[8] The company has not announced plans to pursue further trials for DME.

BI 764524 (Boehringer Ingelheim) is a humanized monoclonal anti-semaphorin 3A antibody.[9] The tolerability of BI 764524 in patients with diabetic macular ischemia was evaluated in a phase 1/2 trial (NCT04424290), which met its primary safety endpoints. The study also showed early efficacy of foveal avascular zone area stabilization at week 16.[10]

SUPRACHOROIDAL INJECTION

OXU-001 (Oxular) consists of dexamethasone-containing microspheres that are delivered suprachoroidally for the treatment of DME. The phase 2 OXEYE study (NCT05697809) is comparing the safety, tolerability, efficacy, and durability of two dose levels of OXU-001 with the intravitreal dexamethasone implant (Ozurdex, Abbvie). Another phase 2 study (NCT05512962) evaluated the same delivery approach with triamcinolone acetonide suspension in patients with DME; the trial is complete with data pending.

IMPLANTS IN THE WORKS

The port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche) remains in the pipeline for DR/DME as the company awaits an FDA decision.[11] The supplemental biologics license application is based on the 1-year results of the phase 3 Pagoda (NCT04108156) and Pavilion (NCT04503551) trials, both of which met their primary endpoints. The 2-year data show that 95% and 98% of patients treated with the PDS in Pagoda and Pavilion, respectively, did not need supplemental injections at 2 years.[11]

IBE-814 IVT (Ripple Therapeutics) is an intravitreal dexamethasone implant that showed efficacy and safety in the phase 2 RIPPLE-1 trial (NCT04576689). At 6 months, patients treated with the high dose had a mean BCVA improvement of 8.7 ETDRS letters; at 9 months, treatment with the high dose led to an 82% reduction in treatment burden. Future studies will focus on the high dose.[12]

EYP-1901 (Duravyu, EyePoint Pharmaceuticals) delivers vorolanib, a selective tyrosine kinase inhibitor (TKI), in a bioerodible insert.[13] It is a pan-VEGF receptor inhibitor. The phase 2 VERONA clinical trial (NCT06099184) is comparing low and high doses of EYP-1901 with aflibercept for the treatment of DME. Interim 16-week data show improvements in BCVA and CST compared with baseline, and 82% of eyes in the 2.7 mg arm were supplement-free compared with 50% in the aflibercept control arm at 16 weeks.[14]

The phase 2 PAVIA trial (NCT05381948) for moderately severe to severe NPDR did not meet its primary endpoint.[15]

OTX-TKI (Axpaxli, Ocular Therapeutix) is an intravitreal implant containing the TKI axitinib. Interim phase 1 data (NCT05695417) showed that 23.1% of treated patients had a 2-step DRSS improvement at week 48; no patients in the treatment arm developed PDR or center-involving DME at week 48 compared with 37.5% in the sham arm.[16]

TOPICAL/SUBCUTANEOUS APPROACHES

OCS-01 (Oculis) is a topical dexamethasone suspension for the treatment of DME. There was a VA improvement of 2.6 ETDRS letters with OCS-01 drops three times daily for 12 weeks in the phase 2 study (NCT05066997), which was not statistically significant.[17] Preliminary results from the first stage of the phase 3 DIAMOND-1 trial (NCT05066997) showed statistically significant improvement in mean BCVA at 12 weeks.[18] There was also a significant decrease in CST at 6 and 12 weeks. The second stage of the trial is ongoing, and the phase 3 DIAMOND-2 trial (NCT06172257) is recruiting.

KHK4951 (tivozanib, Kyowa Kirin) is a VEGF-1, -2, and -3 TKI eye drop in a phase 2 trial (NCT06116916) for the treatment of DME. The topical medication is delivered in either high, medium, or low doses in conjunction with intravitreal aflibercept. The primary outcome is BCVA at 36 weeks.

D-4517.2 (Ashvattha Therapeutics) is a subcutaneous therapy consisting of a nanoparticle that inhibits VEGF receptors 1 and 2 tyrosine kinases. The phase 2 study (NCT05387837) is evaluating the safety, tolerability, pharmacokinetics, and efficacy of various dosages of D-4517.2 in patients with wet AMD or DME.

AT A GLANCE

- Many hopeful advances are under investigation for the treatment of diabetic eye disease in terms of therapy, delivery, and targeting pathways other than anti-VEGF.
- At least five therapies are in phase 3, one of which is an oral formulation.
- Seven therapies have completed phase 2, three of which are oral therapies, and one is suprachoroidal.

EYLEA® HD
(aflibercept) Injection 8 mg

Permanent J-code
J0177

Approved for Wet AMD

Long-Lasting Control, Fewer Injections[1]

As demonstrated by vision outcomes in PULSAR at Week 48 —fewer injections vs EYLEA® (aflibercept) Injection 2 mg

EYLEA HD is the first and only anti-VEGF treatment approved in Wet AMD for immediate dosing at Q8W and up to Q16W intervals following 3 initial monthly doses[1]

PULSAR primary endpoint: Mean change in BCVA (ETDRS letters) from baseline at Week 48 was 6.2 letters gained for EYLEA HD Q16W, 6.7 letters for EYLEA HD Q12W, and 7.6 letters for EYLEA 2 mg Q8W.* LS mean differences were noninferior to EYLEA 2 mg using a margin of 4 letters: -1.1 letters (95% CI, -3.0 to 0.7) for EYLEA HD Q16W and -1.0 letters (95% CI, -2.9 to 0.9) for EYLEA HD Q12W. Patients received 3 initial monthly doses.[1]

- Fewer mean number of injections: 5.2 for EYLEA HD Q16W and 6.1 for EYLEA HD Q12W vs 6.9 for EYLEA 2 mg Q8W[††]

*FAS at baseline: EYLEA HD Q16W (n=338), EYLEA HD Q12W (n=335), EYLEA 2 mg Q8W (n=336). FAS; observed values (censoring data post ICE) at Week 48: EYLEA HD Q16W (n=289), EYLEA HD Q12W (n=299), EYLEA 2 mg Q8W (n=285).[1,2]

†Patients who completed Week 48: EYLEA HD Q16W (n=312), EYLEA HD Q12W (n=316), EYLEA 2 mg Q8W (n=309).[1]

See the outcomes at EYLEAHDhcp.us

IMPORTANT SAFETY INFORMATION FOR EYLEA HD AND EYLEA

CONTRAINDICATIONS

- EYLEA HD and EYLEA are contraindicated in patients with ocular or periocular infections, active intraocular inflammation, or known hypersensitivity to aflibercept or to any of the excipients in EYLEA HD or EYLEA.

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis and retinal detachments and, more rarely, retinal vasculitis with or without occlusion. Proper aseptic injection technique must always be used when administering EYLEA HD or EYLEA. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis, retinal detachment, or retinal vasculitis without delay and should be managed appropriately.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA HD and EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA HD and EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).
  - EYLEA HD: The incidence of reported thromboembolic events in the wet AMD study (PULSAR) from baseline through week 48 was 0.4% (3 out of 673) in the combined group of patients treated with EYLEA HD compared with 1.5% (5 out of 336) in patients treated with EYLEA 2 mg. The incidence in the DME study (PHOTON) from baseline to week 48 was 3.1% (15 out of 491) in the combined group of patients treated with EYLEA HD compared with 3.6% (6 out of 167) in patients treated with EYLEA 2 mg.
  - EYLEA: The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

- EYLEA HD:
  - The most common adverse reactions (≥3%) reported in patients receiving EYLEA HD were cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage.
- EYLEA:
  - Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
  - The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.
- Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA HD or EYLEA and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

INDICATIONS

EYLEA® HD (aflibercept) Injection 8 mg is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

EYLEA® (aflibercept) Injection 2 mg is indicated for the treatment of patients with Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

Please see Brief Summary of Prescribing Information for EYLEA HD and EYLEA on the following page.

anti-VEGF, anti-vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; FAS, full analysis set; ICE, intercurrent event; LS, least squares; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks.

References: 1. EYLEA HD full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. December 2023. **2.** Brown DM; PULSAR Study Investigators. Aflibercept 8 mg in patients with nAMD: 48-week results from the phase 3 PULSAR trial. Presented at: Angiogenesis, Exudation, and Degeneration 2023; February 11, 2023; virtual.

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EYLEA® HD (aflibercept) Injection 8 mg, for intravitreal use AND EYLEA® (aflibercept) Injection 2 mg, for intravitreal use

BRIEF SUMMARY OF PRESCRIBING INFORMATION

4. CONTRAINDICATIONS

4.1 Ocular or Periocular Infections EYLEA HD and EYLEA are contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation EYLEA HD and EYLEA are contraindicated in patients with active intraocular inflammation.

4.3 Hypersensitivity EYLEA HD and EYLEA are contraindicated in patients with known hypersensitivity to aflibercept or any of the excipients in EYLEA HD or EYLEA. Hypersensitivity reactions may manifest as rash, pruritus, urticaria, severe anaphylactic/anaphylactoid reactions, or severe intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis, Retinal Detachments, and Retinal Vasculitis with or without Occlusion Intravitreal injections including those with aflibercept have been associated with endophthalmitis and retinal detachments *[see Adverse Reactions (6.1)]* and, more rarely, retinal vasculitis with or without occlusion *[see Adverse Reactions (6.2)]*. Proper aseptic injection technique must always be used when administering EYLEA HD or EYLEA. Patients and/or caregivers should be instructed to report any signs and/or symptoms suggestive of endophthalmitis, retinal detachment or retinal vasculitis without delay and should be managed appropriately [*see Dosage and Administration (2.6 EYLEA HD, 2.4 EYLEA) in the full Prescribing Information and Patient Counseling Information (17)*].

5.2 Increase in Intraocular Pressure Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA HD and EYLEA [*see Adverse Reactions (6.1)*]. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately [*see Dosage and Administration (2.6 EYLEA HD, 2.4 EYLEA) in the full Prescribing Information*].

5.3 EYLEA HD, 5.4 EYLEA Thromboembolic Events There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA HD and EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).

- **EYLEA HD:** The incidence of reported thromboembolic events in the wet AMD study (PULSAR) from baseline through week 48 was 0.4% (3 out of 673) in the combined group of patients treated with EYLEA HD compared with 1.5% (5 out of 336) in patients treated with EYLEA 2 mg. The incidence of reported thromboembolic events in the DME study (PHOTON) from baseline to week 48 was 3.1% (15 out of 491) in the combined group of patients treated with EYLEA HD compared with 3.6% (6 out of 167) in patients treated with EYLEA 2 mg.
- **EYLEA:** The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

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

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis, retinal detachments and retinal vasculitis with or without occlusion [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3 for EYLEA HD, 5.4 for EYLEA)*]

6.1 Clinical Trials Experience Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.

- **EYLEA HD:** A total of 1164 patients were treated with EYLEA HD and 503 patients were treated with EYLEA 2 mg in two clinical studies. The most common adverse reactions reported in ≥3% of patients treated with EYLEA HD were cataract, conjunctival hemorrhage, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, vision blurred, vitreous floaters, vitreous detachment, corneal epithelium defect, and retinal hemorrhage.
- **EYLEA:** A total of 2980 adult patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (Wet AMD)

EYLEA HD: The data described below reflect exposure to EYLEA HD or EYLEA 2 mg in 1009 patients with Wet AMD, in 1 double-masked, controlled clinical study (PULSAR) for 48 weeks [*see Clinical Studies (14.1) in the full Prescribing Information*].

EYLEA: The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW 1 and VIEW 2) for 24 months (with active control in year 1) [*see Clinical Studies (14.1) in the full Prescribing Information*].

Safety data observed in the EYLEA group in a 52-week, double-masked, phase 2 study were consistent with these results.

Table 1: Most Common Adverse Reactions (≥1%) in Wet AMD Studies

	PULSAR ARs (≥1%) in at least one group			VIEW 1 and VIEW 2 Baseline to Week 52		VIEW 1 and VIEW 2 Baseline to Week 96	
Adverse Reactions	**EYLEA HD q12 (n=335)**	**EYLEA HD q16 (n=338)**	**EYLEA 2q8 (n=336)**	**EYLEA (n=1824)**	**Active Control (ranibizumab) (n=595)**	**EYLEA (n=1824)**	**Control (ranibizumab) (n=595)**
Conjunctival hemorrhage[a]	3%	2%	1%	25%	28%	27%	30%
Eye pain	-	-	-	9%	9%	10%	10%
Ocular discomfort/eye pain/eye irritation[a]	3%	3%	2%	-	-	-	-
Cataract[a]	4%	4%	4%	7%	7%	13%	10%
Vitreous detachment[a]	2%	3%	2%	6%	6%	8%	8%
Vitreous floaters[a]	1%	4%	3%	6%	7%	8%	10%
Intraocular pressure increased[a]	4%	4%	2%	5%	7%	7%	11%
Ocular hyperemia[a]	-	-	-	4%	8%	5%	10%
Corneal epithelium defect[a]	2%	2%	3%	4%	5%	5%	6%
Retinal pigment epithelial detachment[a]	1%	1%	2%	3%	3%	5%	5%
Injection site pain	-	-	-	3%	3%	3%	4%
Foreign body sensation in eyes[a]	1%	1%	2%	3%	4%	4%	4%
Lacrimation increased	-	-	-	3%	1%	4%	2%
Vision blurred[a]	4%	6%	7%	2%	2%	4%	3%
Intraocular inflammation[a]	1%	1%	1%	2%	3%	3%	4%
Retinal pigment epithelial tear	-	-	-	2%	1%	2%	2%
Retinal pigment epithelial tear/epitheliopathy[a]	2%	1%	2%	-	-	-	-
Injection site hemorrhage	-	-	-	1%	2%	2%	2%
Eyelid edema	-	-	-	1%	2%	2%	3%
Corneal edema	-	-	-	1%	1%	1%	1%
Retinal detachment[a]	1%	<1%	0%	<1%	<1%	1%	1%
Retinal hemorrhage	3%	3%	4%	-	-	-	-
Vitreous hemorrhage	<1%	1%	1%	-	-	-	-

Reported terms differ between the PULSAR and VIEW 1 and VIEW 2 studies, as indicated by dashes in the table.

[a]Represents grouping of related terms in PULSAR

Adverse drug reactions (ADRs) reported in <1% of participants treated with EYLEA HD were ocular hyperemia (includes adverse events of conjunctival hyperemia, conjunctival irritation, ocular hyperemia), lacrimation increased, eyelid edema, hypersensitivity (includes adverse events of rash, urticaria, pruritus), retinal tear, and injection site hemorrhage.

Less common serious adverse reactions reported in <1% of the patients treated with EYLEA in VIEW 1 and VIEW 2 were hypersensitivity, retinal tear, and endophthalmitis.

6.2 Postmarketing Experience The following adverse reactions have been identified during postapproval use of aflibercept. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Eye disorders: retinal vasculitis and occlusive retinal vasculitis related to intravitreal injection with aflibercept (reported at a rate of 0.6 and 0.2 per 1 million injections, respectively, based on postmarketing experience from November 2011 until November 2023).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary Adequate and well-controlled studies with EYLEA HD and EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposure (based on AUC for free aflibercept) was approximately 0.9-fold of the population pharmacokinetic estimated exposure in humans after an intravitreal dose of 8 mg for EYLEA HD and approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose of 2 mg for EYLEA [*see Data*].

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA HD or EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1) in the full Prescribing Information*], treatment with EYLEA HD or EYLEA may pose a risk to human embryofetal development. EYLEA HD and EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

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

Data *Animal Data* In two embryofetal development studies, aflibercept produced adverse embryofetal effects when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days during organogenesis at subcutaneous doses ≥0.1 mg per kg.

Adverse embryofetal effects included increased incidences of postimplantation loss and fetal malformations, including anasarca, umbilical hernia, diaphragmatic hernia, gastroschisis, cleft palate, ectrodactyly, intestinal atresia, spina bifida, encephalomeningocele, heart and major vessel defects, and skeletal malformations (fused vertebrae, sternebrae, and ribs; supernumerary vertebral arches and ribs; and incomplete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Aflibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was not identified. At the lowest dose shown to produce adverse embryofetal effects in rabbits (0.1 mg per kg), systemic exposure (AUC) of free aflibercept was approximately 0.9-fold of the population pharmacokinetic estimated systemic exposure (AUC) in humans after an intravitreal dose of 8 mg for EYLEA HD and approximately 6 times higher than systemic exposure (AUC) observed in adult patients after a single intravitreal dose of 2 mg for EYLEA.

8.2 Lactation Risk Summary There is no information regarding the presence of aflibercept in human milk, the effects of the drug on the breastfed infant, or the effects of the drug on milk production/excretion. Because many drugs are excreted in human milk, and because the potential for absorption and harm to infant growth and development exists, EYLEA HD and EYLEA are not recommended during breastfeeding. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for EYLEA HD or EYLEA and any potential adverse effects on the breastfed child from EYLEA HD or EYLEA.

8.3 Females and Males of Reproductive Potential Contraception Females of reproductive potential are advised to use effective contraception prior to the initial dose, during treatment, and for at least 4 and 3 months after the last intravitreal injection of EYLEA HD or EYLEA, respectively.

Infertility There are no data regarding the effects of EYLEA HD or EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose 91 times higher (based on AUC of free aflibercept) than the corresponding systemic level estimated based on population pharmacokinetic analysis in humans following an intravitreal dose of 8 mg for EYLEA HD and at a dose approximately 1500 times higher than the systemic level observed in adult patients with an intravitreal dose of 2 mg for EYLEA. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment [*see Nonclinical Toxicology (13.1) in the full Prescribing Information*].

8.4 Pediatric Use The safety and effectiveness of EYLEA HD in pediatric patients have not been established.

The safety and effectiveness of EYLEA have been demonstrated in two clinical studies of pre-term infants with Retinopathy of Prematurity. These two studies randomized pre-term infants between initial treatment with EYLEA or laser. Efficacy of each treatment is supported by the demonstration of a clinical course which was better than would have been expected without treatment [*see Dosage and Administration (2.9), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.6) in the full Prescribing Information for EYLEA*].

8.5 Geriatric Use In PULSAR, approximately 90% (604/673) of the patients in the HDq12 and HDq16 groups were 65 years of age or older and approximately 51% (343/673) were 75 years of age or older.

In PHOTON, approximately 44% (214/491) of the patients in the HDq12 and HDq16 groups were 65 years of age or older and approximately 10% (50/491) were 75 years of age or older.

In the clinical studies for EYLEA 2 mg, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

10 OVERDOSAGE Overdosing with increased injection volume may increase intraocular pressure. Therefore, in case of overdosage, intraocular pressure should be monitored and if deemed necessary by the treating physician, adequate treatment should be initiated.

17 PATIENT COUNSELING INFORMATION In the days following EYLEA HD or EYLEA administration, patients are at risk of developing endophthalmitis, retinal detachment or retinal vasculitis with or without occlusion. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients and/or caregivers to seek immediate care from an ophthalmologist [*see Warning and Precautions (5.1)*]. Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA HD or EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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TABLE. NOVEL THERAPIES FOR THE TREATMENT OF DIABETIC EYE DISEASE

Study Drug (Company)	Condition	Target	Delivery	Trial NCT	Trial Status	Completion
Phase 3						
Port delivery system with ranibizumab (Susvimo, Genentech/Roche)	DR/DME	Anti-VEGF	Implant	NCT04108156 NCT04503551	Active, not recruiting	September 2022 October 2022
Fenofibrate (DRCR Retina Network)	DR	Peroxisome proliferator activated receptor alpha	Oral	NCT01320345 NCT04661358	Recruiting	December 2024 April 2029
KSI-301 (tarcocimab tedromer, Kodiak Sciences)	NPDR	Anti-VEGF antibody biopolymer conjugate	Intravitreal	NCT06270836	Recruiting	December 2025
OCS-01 (Oculis)	DME	Dexamethasone	Topical	NCT06172257 NCT05066997	Recruiting	December 2025 June 2026
RC28-E (RemeGen)	DME	Fusion protein targeting FGF2/VEGF	Intravitreal	NCT05885503	Recruiting	June 2026
MK-3000 (Restoret, EyeBio/Merck)	DME	Wnt signaling agonist	Intravitreal	NCT06571045	Recruiting	December 2027
Phase 2						
CU06 (Curacle)	DME	VEGF/angiopoietin-2 inhibitor	Oral	NCT05573100	Complete	
APX3330 (Opus [formerly Ocuphire])	NPDR	Ref-1 protein	Oral	NCT04692688	Complete	
Runcaciguat (Bayer)	NPDR	Guanylate cyclase activator	Oral	NCT04722991	Complete	
AG-73305 (Allgenesis Biotherapeutics)	DME	Bifunctional Fc-fusion protein	Intravitreal	NCT05301751	Complete	
IBE-814 IVT (Ripple Therapeutics)	DME	Dexamethasone	Implant	NCT04576689	Complete	
OPT-302 (Opthea)	DME	VEGF-C and VEGF-D inhibitor	Intravitreal	NCT03397264	Complete	
OXU-001 (Oxular)	DME	Dexamethasone	Suprachoroidal	NCT05512962 NCT05697809	Complete Active, not recruiting	November 2024
EYP-1901 (Duravyu, EyePoint Pharmaceuticals)	NPDR DME	TKI	Intravitreal	NCT05381948 NCT06099184	Complete Fully enrolled	January 2025
RG6179 (vamikibart, Roche)	DME	Interleukin-6 cytokine inhibitor	Intravitreal	NCT05151744 NCT05151731	Complete Active, not recruiting	November 2024
RZ402 (Rezolute)	DME	Plasma kallikrein inhibitor	Oral	NCT05712720	Active, not recruiting	May 2024
ABBV-RGX-314 (Regenxbio/Abbvie)	NPDR/mild PDR	Gene therapy	Suprachoroidal	NCT04567550	Recruiting	May 2024
OPL-0401 (Valo Health)	NPDR/PDR	Rho kinase signaling inhibitor	Oral	NCT05393284	Active, not recruiting	August 2024
D-4517.2 (Ashvattha Therapeutics)	DME	VEGF-1 and VEGF-2 TKI	Subcutaneous	NCT05387837	Active, not recruiting	November 2024
UBX1325 (foselutoclax, Unity Biotechnology)	DME	BCL-xL inhibitor	Intravitreal	NCT06011798	Active, not recruiting	March 2025
Tonabersat	DME	Connexin43 hemichannel inhibitor	Oral	NCT05727891	Recruiting	May 2025
KHK4951 (Tivozanib, Kyowa Kirin)	DME	VEGF-1, VEGF-2, and VEGF-3 TKI	Topical	NCT06116916	Recruiting	December 2025
4D-150 (4D Molecular Therapeutics)	DME	Gene therapy	Intravitreal	NCT05930561	Recruiting	February 2028
Phase 1, 1/2						
BI 764524 (Boehringer Ingelheim)	DMI	Semaphorin 3A inhibitor	Intravitreal	NCT04424290	Complete	
OTX-TKI (Axpaxli, Ocular Therapeutix)	NPDR	TKI	Implant	NCT05695417	Active, not recruiting	January 2024

Abbreviations: DME, diabetic macular edema; DMI, diabetic macular ischemia; DR, diabetic retinopathy; NPDR, nonproliferative DR; PDR, proliferative DR; TKI, tyrosine kinase inhibitor

ORAL OPTIONS

Fenofibrate activates peroxisome proliferator activated receptor alpha, altering systemic lipid synthesis. The phase 3 FAME 1 EYE trial (NCT01320345) is evaluating 145 mg of fenofibrate versus placebo in adults with type 1 diabetes. Patients are followed for 36 months to assess DR progression. Patient recruitment is occurring in Australia, New Zealand, Hong Kong, and the United Kingdom. In the United States, Diabetic Retinopathy Clinical Research (DRCR) Retina Network Protocol AF (NCT04661358) is evaluating the effect of 160 mg fenofibrate compared with placebo in eyes with mild to moderately severe NPDR and no center-involving DME at baseline with a follow-up of 6 years.

APX3330 (Opus [formerly Ocuphire]) is an oral drug

that targets the Ref-1 protein. Although the phase 2 trial (NCT04692688) failed to meet its primary endpoint, the company is planning a phase 2/3 trial in patients with NPDR.[19] The company recently acquired Opus Genetics and has discontinued internal development of APX3330.[20]

Tonabersat is an oral Connexin43 hemichannel inhibitor, which is a gap-junction modulator used in migraine treatment. It is being investigated in a phase 2 clinical trial (NCT05727891), DRCR Retina Network Protocol AN, comparing the efficacy of tonabersat versus placebo to reduce CST in eyes with center-involving DME and good visual acuity after 6 months.

Runcaciguat (Bayer) is a soluble guanylate cyclase activator under investigation as an oral therapy for the treatment of NPDR. The phase 2 NEON-NPDR trial (NCT04722991), now complete, evaluated the safety and efficacy of runcaciguat versus placebo in 104 patients, with a primary endpoint of a ≥ 2-step DRSS improvement at 24 weeks.

RZ402 (Rezolute) is an orally administered selective plasma kallikrein inhibitor designed to treat DME. The phase 2 trial (NCT05712720) met its primary endpoint of safety and a clinically significant reduction in CST from baseline.[21]

OPL-0401 (Valo Health) is an oral Rho kinase signaling inhibitor in phase 2 (NCT05393284) for NPDR and mild PDR. The trial is evaluating twice-daily dosing of OPL-0401 versus placebo in 114 patients for 24 weeks.[22] The primary endpoint is the proportion of patients with a ≥ 2-step DRSS improvement from baseline at 24 weeks.

CU06 (Curacle) is an oral anti-VEGF and angiopoietin-2 inhibitor. The phase 2a study (NCT05573100) evaluated once-daily 100 mg, 200 mg, or 300 mg CU06 versus placebo in patients with DME; the primary outcomes are change in CST at 12 weeks and determination of the optimal dose.[23]

GENE THERAPIES IN THE PIPELINE

ABBV-RGX-314 (Regenxbio/Abbvie) is a single-dose subretinal or suprachoroidal injection of an AAV gene vector that expresses an anti-VEGF-A antigen-binding fragment leading to sustained VEGF suppression. The phase 2 dose-escalation ALTITUDE study (NCT04567550) is assessing the efficacy, safety, and tolerability of suprachoroidal delivery of ABBV-RGX-314 in patients with NPDR or mild PDR. Preliminary 1-year data show that dosage levels 1 and 2 were well tolerated. At 1 year, dose level 2 in NPDR patients prevented disease progression and reduced the risk of developing vision-threatening events by 89%.[24]

4D-150 (4D Molecular Therapeutics) is a single-dose intravitreal retinotropic AAV vector that delivers two transgenes. These encode aflibercept and an miRNA sequence that inhibits VEGF-C.[25] 4D-150 is being investigated in the phase 2 SPECTRA study (NCT05930561) for the treatment of DME. This study is assessing the need for aflibercept rescue injections over 52 weeks, as well as BCVA and CST. ■

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YINGNA SNOWY LIU, MD
- Vitreoretinal Surgeon, Bay Area Associates, San Francisco
- sliu@bayarearetina.com
- Financial disclosure: None

SHANE GRIFFIN, MD, MCR
- Ophthalmology Resident, California Pacific Medical Center, San Francisco
- shnmchlgrffn@gmail.com
- Financial disclosure: None

CHIRAG D. JHAVERI, MD
- Vitreoretinal Surgeon, Retina Consultants of Austin, Austin, Texas
- Investigator, Retina Research Center, Austin, Texas
- Clinical Assistant Professor, Dell Medical School, The University of Texas at Austin, Austin, Texas
- cjhaveri@e-retina.net
- Financial disclosure: Consultant (Astellas, Genentech/Roche); Research Support (Boehringer Ingelheim, DRCR Retina Network, Genentech/Roche, Novartis, Perfuse Therapeutics, Regeneron, Regenxbio, Sanofi)

GEOGRAPHIC ATROPHY THERAPIES TO WATCH

An update on complement inhibitors, gene and cell therapies, and novel approaches.

BY REBECCA HEPP, MA, EDITOR-IN-CHIEF
REVIEWED BY ROBERT L. AVERY, MD, AND ALLEN C. HO, MD

Patients with geographic atrophy (GA) are now presenting to US retina clinic to discuss their treatment options with one of two FDA approved therapies, pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izervay, Astellas). While these complement inhibitors provide a much-needed option to slow lesion growth, they do not stop GA in its tracks, pushing researchers to find other novel approaches. Here are the many drugs in the pipeline that aim to slow GA lesion growth and, hopefully, preserve vision (Table).

PHASE 3 TRIALS

ALK-001 (gildeuretinol, Alkeus Pharmaceuticals) is an oral therapy designed to reduce the dimerization of vitamin A. Topline data from the phase 3 SAGA trial (NCT03845582) show a 13.4% reduction in GA lesion growth rate from baseline to 24 months (P = .075), which was not statistically significant. However, from 6 to 24 months, treatment reduced the lesion growth rate by 15.3% (P = .047) in a prespecified analysis.[1]

ANX007 (Annexon Biosciences) is an intravitreal C1q inhibitor. Although the phase 2 ARCHER trial (NCT04656561) did not meet its primary endpoint of statistically significant reduction in GA lesion growth at 12 months, 6% of patients treated with ANX007 lost 15 letters versus 21% of patients treated with sham (P = .0021).[2] The primary endpoint for the phase 3 ARCHER II trial (NCT06510816) is the proportion of patients experiencing a BCVA ≥ 15-letter loss from baseline through 18 months.

Elamipretide (Stealth Biotherapeutics) is a subcutaneous medication designed to normalize mitochondrial structure and function and improve cell viability in the setting of AMD. The phase 2 ReCLAIM-2 trial (NCT03891875) did not meet the primary endpoints of GA lesion progression and mean change in low-luminance visual acuity; however, patients treated with subcutaneous elamipretide had a 43% reduction in ellipsoid zone total attenuation at 48 weeks (P = .003) compared with those treated with placebo.[3] The primary endpoint of the phase 3 ReNEW trial (NCT06373731) is the rate of change in the macular area of photoreceptor loss at 48 weeks compared with baseline.[4] A second phase 3 trial, ReGAIN, is in the works.[4]

Tinlarebant (LBS-008, Belite Bio) is an oral agent in a clinical trial for the treatment of GA. This antagonist of retinol-binding protein is used to reduce the accumulation of vitamin A-based toxins (ie, bisretinoids). The phase 3 PHOENIX trial (NCT05949593) is investigating once-daily oral 5 mg tinlarebant versus placebo in approximately 430 patients with GA. The primary endpoint is the rate of change in GA lesion size, and the secondary endpoints include change in BCVA and changes in the inner/outer segment junction of photoreceptors.[5]

PHASE 2 INVESTIGATIONS

AVD-104 (Aviceda Therapeutics) is an intravitreal glycan-coated nanoparticle with a dual mechanism of action that is designed to repolarize activated microglia/macrophages to their healing state and inhibit complement cascade amplification. Results from part 1 of the phase 2 SIGLIC trial (NCT05839041) demonstrated a 48% reduction in lesion growth rate compared with the fellow eye at 3 months. Results of part 2 of the trial are expected in late 2025.[6]

CT1812 (Cognition Therapeutics) is an oral selective sigma-2 antagonist binding retinal pigment epithelium cells designed to regulate the damage-response processes impaired in GA. The phase 2 study (NCT05893537) is assessing the efficacy, safety, and tolerability of a single oral dose of CT1812 compared with placebo in approximately 246 patients. The primary endpoint is the change in GA lesion area from baseline at 104 weeks.[7]

Danicopan (ALXN2040, Alexion Pharmaceuticals/Astrazeneca), a complement factor D inhibitor, is under investigation as an oral therapy. The phase 2 trial (NCT05019521) is evaluating four treatment arms: 100 mg or 200 mg twice daily, 400 mg once daily, and matching placebo. The trial includes a 6-week screening period, a 104-week treatment period, and a 30-day follow-up period.

JNJ-1887 (Janssen) is an intravitreal gene therapy that expresses soluble CD59 and is designed to treat GA and wet AMD. The pooled phase 1 safety data showed that the therapy was well tolerated with no dose-limiting toxicities or serious or systemic adverse events.[8] The phase 2 trial (NCT05811351) is evaluating a high and low dose in combination with prophylactic steroids compared with sham.

ONL1204 (ONL Therapeutics) is an intravitreal therapy aimed at reducing Fas-mediated retinal cell apoptosis and inflammatory cytokines. The open label/dose escalation portion of the phase 1b trial (NCT04744662) found that a single injection of ONL1204 led to a 42% reduction in GA lesion growth at 24 weeks compared with the untreated fellow eye. The natural history/treatment component of the trial showed that treatment with 200 µg ONL1204 (two injections 12 weeks apart) led to an approximate 50% lower rate of lesion growth compared with sham-treated eyes at 24 weeks. The phase 2 trial (NCT06659445) is evaluating two dose levels of ONL1204 and two treatment frequencies in approximately 324 patients with GA.[9]

RG6501 (OpRegen, Lineage Cell Therapeutics and Genentech/Roche) is an allogeneic retinal pigment epithelial cell therapy that is delivered subretinally. In the phase 1/2a trial (NCT02286089), treatment led to a mean BCVA gain of 5.5 letters and improvements in the retinal pigment epithelium drusen complex in cohort 4 at 24 months.[10] The phase 2 trial (NCT05626114) is evaluating the success and safety of subretinal delivery and preliminary activity of the cell therapy in 60 patients with GA.

PROMISING PHASE 1 DRUG CANDIDATES

ASP7317 (Astellas) is a subretinal cell therapy derived from human embryonic stem cells. The phase 1b trial (NCT03178149) is evaluating three doses of ASP7317 with immunosuppressive therapy. The primary outcomes focus on safety and tolerability at 52 weeks, and secondary endpoints include change in GA lesion area and vision.

BI 771716 (Boehringer Ingelheim/CDR-Life) is an intravitreal antibody fragment designed to penetrate all retinal layers and target areas of GA. The phase 1 trial (NCT06006585) of single and multiple doses met its primary safety endpoint in 20 patients followed for up to 112 days. The company plans to launch a phase 2 trial in early 2025.[11]

OCU410 (AAV5-hRORA, Ocugen) is a gene therapy that delivers the *RORA* gene, which affects lipid metabolism, demonstrates an antiinflammatory role, and inhibits the complement system. Preliminary results from part 1 of the phase 1/2 trial (NCT06018558) showed a 21.4% slower lesion growth in treated eyes versus untreated eyes at 6 months, with no reported drug-related serious adverse events.[12]

SURGICAL APPROACHES TO RESTORING VISION IN GA

The PRIMA retinal implant (Science Corporation) is a visual prosthesis that incorporates a photovoltaic implant, glasses with a camera and a projection system, and a pocket processor. The preliminary results of the PRIMAvera trial (NCT04676854) of 38 patients with central visual field loss due to GA demonstrate a 23-letter (4.6 lines) mean improvement in vision at 12 months post-implantation compared with baseline. The most successful patient experienced a gain of 59 letters (11.8 lines).[13]

An intraocular lens implant, the Smaller-Incision New-Generation Implantable Miniature Telescope (SING IMT, Samsara Vision), remains under investigation in the United States with the CONCERTO study (NCT05438732) for patients with late-stage AMD. This trial is evaluating the safety and efficacy of the SING IMT implanted in approximately 125 patients. The device received a CE mark for the European Union in 2020.[14]

AT A GLANCE

- Four therapies are now in phase 3 investigations, two of which are oral agents targeting vitamin A and its role in the geographic atrophy disease process.
- Many therapies have novel delivery methods, including oral, subcutaneous, and subretinal.
- Retinal and intraocular implants are under investigation to restore vision in patients with late-state AMD.

TABLE. INVESTIGATIONAL THERAPIES FOR GEOGRAPHIC ATROPHY

Study Drug (Company)	Mechanism	Delivery	Trial NCT	Trial Status	Completion	Last Update
Phase 3						
ALK-001 (gildeuretinol, Alkeus Pharmaceuticals)	Visual cycle modulator	Oral	NCT03845582	Complete	July 2023	November 2024
Elamipretide (Stealth Biotherapeutics)	Mitochondrial enhancer	Subcutaneous	NCT06373731	Recruiting	August 2026	November 2024
ANX007 (Annexon Biosciences)	Immunomodulator	Intravitreal	NCT06510816	Recruiting	October 2026	November 2024
Tinlarebant (LBS-008, Belite Bio)	Visual cycle modulator	Oral	NCT05949593	Recruiting	August 2027	March 2024
Phase 2						
Danicopan (ALXN2040, Alexion Pharmaceuticals/AstraZeneca)	Immunomodulator	Oral	NCT05019521	Active, not recruiting	July 2024	November 2024
AVD-104 (Aviceda Therapeutics)	Immunomodulator	Intravitreal	NCT05839041	Active, not recruiting	June 2025	November 2024
JNJ-1887 (Janssen)	Gene therapy	Intravitreal	NCT05811351	Active, not recruiting	July 2025	October 2024
CT1812 (Cognition Therapeutics)	Immunomodulator	Oral	NCT05893537	Recruiting	July 2027	October 2024
ONL1204 (ONL Therapeutics)	Immunomodulator	Intravitreal	NCT06659445	Not yet recruiting	November 2027	October 2024
RG6501 (OpRegen, Lineage Cell Therapeutics/Genentech/Roche)	Cell therapy	Subretinal	NCT05626114	Recruiting	April 2029	October 2024
Phase 1, 1/2						
BI 771716 (Boehringer Ingelheim/CDR-Life)	Antibody fragment	Intravitreal	NCT06006585	Complete	May 2024	June 2024
OCU410 (AAV5-hRORA, Ocugen)	Gene therapy	Subretinal	NCT06018558	Recruiting	September 2025	October 2024
ASP7317 (Astellas)	Cell therapy	Subretinal	NCT03178149	Recruiting	June 2026	November 2024

THE ROAD AHEAD

This year has been marked by significant advances within the GA pipeline. We now have four therapies in phase 3, all of which offer alternative treatment approaches beyond complement C3 and C5—two of which are oral agents. Several gene and cell therapies are showing promise as potentially one-and-done treatments. We look forward to watching the clinical trial data develop in the hopes that we will one day have better, more durable therapies to offer patients with GA. ■

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OUT OF THE PIPELINE AND INTO PRACTICE

LumiThera received FDA authorization to market its Valeda Light Delivery System, the first therapy to use photobiomodulation (PBM) to improve visual acuity in patients with intermediate AMD. The approval is based on LIGHTSITE III trial (NCT04065490) data, which demonstrated durable BCVA improvements of more than 5 letters that were maintained over 24 months.[1] This noninvasive treatment approach delivers PBM to the eye at wavelengths of 590 nm, 660 nm, and 850 nm. Each treatment cycle includes nine PBM treatment sessions delivered over 3 to 5 weeks, with each treatment lasting less than 5 minutes per eye (without the need for dilation). The LIGHTSITE III data were the result of six PBM treatment cycles (every 4 months) over 2 years.[2]

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BROADENING THE SCOPE OF COMPLEMENT INHIBITOR TREATMENT

Identifying and treating patients earlier in their geographic atrophy journey comes with new challenges and considerations.

Durga S. Borkar, MD, MMCi

Expanding the treatment of geographic atrophy (GA) to a broader patient population presents several challenges, particularly in balancing the benefits of early intervention with the practicalities of treatment burden and patient adherence. There are several strategies that retina specialists can use when evaluating their patient population for candidates who would most benefit from complement inhibitor treatments.

Early Intervention Versus Patient Adherence: The Dilemma in GA Treatment

Recent data from the pegcetacoplan (SYFOVRE, Apellis) GALE extension trial and the two-year data from the GATHER 2 study of avacincaptad pegol (IZERVAY, Astellas) suggest that treatment efficacy improves with prolonged treatment duration.[1,2] Therefore, initiating treatment for patients with earlier-stage GA and continuing treatment could significantly benefit them over the long term, as these medications are designed to prevent disease progression rather than reverse it. However, retinal specialists are hesitant to prescribe complement inhibitors due to the treatment burden associated with a long-term commitment to injections. Despite improved outcomes over time, convincing patients to adhere to a long-term frequent injection schedule is challenging, particularly for those with minimal functional impairment. In contrast, patients who have already lost significant vision in one eye due to GA may be more receptive to frequent treatments, as they understand the consequences of lesion progression better than bilateral early-stage patients.

Leveraging Imaging Data to Optimize Treatment Decisions

A key challenge in treating GA is identifying which patients might benefit the most from the available therapies. Factors like multifocal lesions, proximity to the center point, and perilesional autofluorescence—indicating cells adjacent to the lesion are actively dying but could potentially be saved—are worth considering. In addition, tracking the growth trajectory of the lesions over time is informative. Many patients already have historical autofluorescence or near-infrared OCT images from prior visits, making historical imaging data crucial for patient assessment. By comparing current images to those taken 6 months or a year earlier, clinicians can illustrate the progression of the disease to patients, emphasizing the enlargement of lesions and the potential benefits of slowing this process with treatment.

Patient Support and Education in Managing GA

Beyond medical considerations, patient selection also involves practical factors, such as the patient's ability to understand the treatment regimen and consistently attend appointments for injections, which are critical for successful outcomes. Educating patients early in their GA journey about the importance of continuous treatment is crucial. Many patients already manage chronic systemic conditions; therefore, emphasizing the progressive nature of GA and its potential functional impacts—such as difficulties with reading—can help convey the necessity of treatment. It is also important to discuss low vision services, which can provide support even for those with minimal impairment. Referrals to specialists who can assist in optimizing remaining vision and coping strategies makes the conversation about the disease more constructive and focused on a path forward for this debilitating retinal disease. ■

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DURGA S. BORKAR, MD, MMCI
- Associate Professor of Ophthalmology, Director of Clinical Data Science, Duke Eye Center, Durham, North Carolina
- durga.borkar@duke.edu
- Financial disclosures: Consultant (AbbVie/Allergan, Alimera Sciences, Apellis, Astellas, Eyepoint, Genentech/Roche, Glaukos, ONL Therapeutics, Regeneron)

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THE CONVERGENCE OF NANOTECHNOLOGY AND RETINAL DISEASE

A look at the next generation of diagnostics and therapeutics.

BY NALIN J. MEHTA, MD, MS, AND SACHIN N. MEHTA, BA, BS


Nanobiotechnology can prove useful in retinal diagnostics, pharmacologic and surgical interventions, and drug delivery (Table). Regenerative medicine also stands to benefit from nanoscience. The retina—for which therapeutics and surgery are in the range of micrograms and microns, respectively, combined with its relative immune privilege and accessibility—is ideally suited for nanobiotechnological innovations. Here, we review the state of nanotechnology in the field of retina.

DIAGNOSTICS

Today's retinal imaging, although a far cry from the tools used decades ago, remains imperfect in several ways. For example, the specificity of neovascular structures on OCT can be limited by optical artifacts from adjacent vascular structures. Furthermore, OCT angiography is unable to directly demonstrate leakage. Nanotechnology may be a useful innovation to combat these limitations.

Researchers are exploring the utility of gold nanoparticles (AuNPs) as contrast agents for OCT because they are small enough (almost 3 µm in diameter) to pass through retinal and choroidal vessels, with wavelength absorption efficiencies higher than conventional angiographic dyes.[1] For example, researchers used AuNPs to enhance boundary contrast and increase OCT signaling when examining rabbit skin.[1] Iron-titanium dioxide NPs have also been investigated as a viable contrast agent in swept-source OCT.[2]

Atomic force microscopy can create 3D surface profiles of retinal cells, organelle membranes, and nanostructures such as rhodopsin molecules.[3] Using this technology, researchers discovered that rhodopsin assembles in rows of dimers and paracrystals; they also realized that the rhodopsin dimer is the building block of higher-order structures.[3]

Another tool under investigation, photoacoustic microscopy, uses high-resolution identification of endogenous chromophores (such as hemoglobin and melanin) which, when integrated with OCT, can enhance chorioretinal localization of oxygen saturation measurements.[4,5]

Transistor-like circuitry incorporating functionalized carbon nanotubules and gold nanoarrays (with dimensions less than 10 nm) can detect single molecules of DNA and other biologic molecules by changing surface conductivity.[6] Similarly, nanopore DNA sequencing takes advantage of changes in conductivity when DNA nucleotides are sequentially passed through 2 nm nanopores.[7] By increasing diagnostic sensitivity at the molecular level,

Check out a listing of retinal nanodiagnostics in the pipeline at *retinatoday.com:*

these next-generation sequencing technologies may one day replace time-consuming, off-site analyses with rapid point-of-service testing.

THERAPEUTICS: DRUGS, DELIVERY SYSTEMS, AND TARGETING

Nanoscale therapeutics allow for successful penetration of the blood-brain barrier via endocytosis without the inflammation noted with viral vectors. Self-assembled nanoparticles are coated to form poly(lactic-co-glycolic acid) nanoparticles with slow-release properties.[8] One study found that the biodegradable biopolymer poly(E-caprolactone) embedded with resveratrol demonstrates antioxidant and antiinflammatory properties. The surface was coated with metformin (known to inhibit choroidal neovascularization) and cell-penetrating peptides that increased retinal permeability 15-fold after intravitreal injection.[9]

Topical nanoparticles deliver high potency because of their high surface area-to-volume ratio.[10] In one AMD model, a nanoparticle formulation of aminocaproic acid-Diosgenin delivered antiangiogenic activity with low cellular toxicity.[11] Similarly, research has shown that topical celecoxib-loaded poly(ortho ester) nanoparticles possess antiinflammatory and antiproliferative properties.[12] Another study found that nanoparticles of apatinib—an anti-VEGFR2 tyrosine kinase inhibitor—can penetrate the cornea and target retinal cells.[13]

Dendrimers are highly branched molecules as small as 1.5 nm in diameter that can allow for delivery of multiple drugs, as well as effective sustained delivery. Systemic dendrimer-based molecules have demonstrated selective, passive retinal pigment epithelium (RPE) uptake of a steroid in damaged cells, which can suppress both inflammation and choroidal neovascularization.[14]

SURGICAL ADJUNCTS

Researchers have investigated the utility of coating surgical instruments with silver nanoparticles, which confer antiinfective and antioxidative properties.[15] Other investigators have designed nanotube tweezers by fusing together two carbon nanotubes with a spacing of 10 nm.[16] Others have proposed direct nerve fiber axon repairs using a knife edge with a 20 nm radius of curvature, with attachment of a transplanted axon segment performed by electrofusion.[17]

Hyaluronic acid-coated AuNPs have been found to cluster on vitreous opacities in vivo. Sauvage et al found that low-energy nanosecond laser pulses can create vitreous nanobubbles by heating the AuNPs and ablating vitreous opacities with lower energy levels, reducing the risk of complications compared with Nd:YAG vitreolysis.[18]

NANOPROSTHESES

The smallest nanoscale transistors are 1 nm long, and diodes are as small as one molecule in size—technology that could increase the resolution of current subretinal implants. For example, researchers are investigating poly(3-hexylthiophene) nanoparticles injected into the subretinal space, mimicking the spatial distribution of photoreceptors, to form a light-sensitive interface.[19] Others are exploring carbon nanotubule prosthetics integrated with neural tissue to guide synaptic development during neuronal repair,[20] which could help patients with trauma or retinal degeneration.

REGENERATIVE NANOBIOTECHNOLOGY

Future therapies will not only protect retinal tissues, but also repair and regenerate structure and function. AuNPs, for instance, are relatively inert and possess intrinsic antiinflammatory and antiangiogenic properties.[21] Nanoceria is another powerful example of a reactive oxygen species scavenger that can help to promote and regulate healthy angiogenesis while demonstrating anti-VEGF properties.[22] Dexamethasone-conjugated dendrimers demonstrate selective affinity for damaged retinal Müller glial cells, promoting regenerative stem cell-like properties in mammals while minimizing the potential for systemic toxicity.[23]

Carbon nanotubules are not only useful in diagnostics, but also can function as radical scavengers,[24] potentially reducing oxidative stress thought to play a vital role in progression to wet AMD. Similarly, fullerenes are inherently antioxidative and antiinflammatory and are showing promise as a therapeutic approach to arthritis.[25]

Intravitreal oxygen nanobubbles have been used to deliver oxygen to the inner retina for rescue from ischemic damage.[26] Furthermore, platinum nanozymes have been used to counteract light-induced photoreceptor degeneration and inflammation in a rodent AMD model.[27]

Magnetic nanoparticles are being used for targeted stem cell delivery within the eye. Yanai et al describe a technique of magnetizing rat mesenchymal stem cells and, after intravenous injection, inducing migration and localization to the inner and outer retina with a magnet placed in the orbit.[28]

Researchers are also exploring natural nanofiber scaffolds from gelatin, chitosan, collagen, and hyaluronic acid. These

AT A GLANCE

- Nanotechnology, such as gold nanoparticles, atomic force microscopy, and photoacoustic microscopy, may help to address the limitations of current imaging modalities.
- Nanoscale therapeutics allow for successful penetration of the blood-brain barrier via endocytosis without the inflammation common with viral vectors.
- Inorganic nanoparticles hold much promise for improving the success of various gene therapies.

TABLE. POTENTIAL RETINAL NANOTHERAPEUTICS AND THERANOSTICS

Retinal Application	Nanoparticle	Model	Conclusion
Precision cell ablation (ie, tumors)	Gold nanoparticles[14]	Various cellular targets	Aggregate gold nanoparticles enhance detection and treatment over single nanoparticles
Gene therapy	Gold nanoparticles[15]	Various plasmid, minivector DNA and siRNA vectors	Gold nanoparticles enhance nucleic acid delivery
AMD	Antiangiogenic peptides[19]	Murine	Angiogenesis decreases for at least 14 weeks after a single dose
AMD	Cell-penetrating peptides[20]	Rat	Single dose improves retinal permeability, increases antioxidant retention, and suppresses neovascularization for 56 days
Ocular tumors	Functionalized Q-dots[16]	Human osteosarcoma cells	For single-cell microscopy, exhibit strong fluorescence and hypersensitivity and are non-toxic and biologically inactive
Ocular tumors	Magnetic nanoparticle (MNP) hyperthermia[17,18]	Zebrafish embryos,[17] humans[18]	Functionalized MNPs preferentially localize to the choroid and RPE,[17] thermotherapy using MNPs was proven safe and effective[18]
AMD	Topical nanoemulsions[22,23,25]	Primate,[22] human embryonic kidney cells, rat Müller cells,[23] rats[25]	Topical drug could penetrate the cornea and blood-retina barrier,[22] improve long-acting intraocular bioavailability of hydrophobic celecoxib,[23] and enhance retinal accumulation of anti-VEGF apatinib[25]
AMD	Dendrimers[31]	Human donor eyes, rats	Pathology-dependent biodistribution, suppression of choroidal neovascularization, and cytokine suppression
AMD	Self-assembling polymeric micelles[28]	Various in vitro and in vivo	Improved bioavailability, bioactivity, intracellular penetration, controlled delivery, and retention time
AMD	Nanoceria[22]	Human ARPE-19 and umbilical endothelium cell lines	Antiinflammatory, antiangiogenic, and antiapoptotic properties

have been shown to promote RPE growth and release of regenerative factors, with superior cellular adhesion to that of synthetic scaffolds.[29] Electrospinning, a technique whereby nanofibers are created by extrusion of a polymer solution, has recently been used to create a nanofiber scaffold upon which RPE cells can be cultured with the possibility of subsequent subretinal transplantation.[30]

FUTURE DIRECTIONS

Nanotechnology holds much promise for improving the success of various gene therapies. For example, carefully designed inorganic nanoparticles (eg, polymers, silicone, and organometallic composites) may overcome the challenges of crossing the blood-retina barrier, rapid degradation, and gene/cellular toxicity.[31] Researchers have also harvested IPSC-derived RPE cells from fibroblasts or mononuclear blood cells by incubation with various protein-coding genes, such as *LEFTY2*.[32] Müller glial cells, furthermore, have been shown to transdifferentiate to rod photoreceptors using the sonic hedgehog gene, *SHH*.[33] Targeted delivery of mRNA to the RPE, Müller glia, and neural retina has been accomplished using lipid nanoparticles.[34,35] Laser-enhanced delivery of genetic material to precise areas of retinal degeneration using optoporation is a novel technique that could be used to deliver gene-laden lipid nanoparticles or other non-viral nanoparticles.[36,37]

Exosomes, bilayered nanovesicles that can be as small as 30 nm in size, are showing promise as disease biomarkers, intercellular communication vehicles, and drug delivery vehicles.[38] Exosomes have been shown to transport microRNA between RPE cells and retinal glial cells, which could prove useful in modulating senescence and apoptosis of the retina in conditions such as AMD and diabetic retinopathy.[39]

Scientists have successfully used external magnetic fields to guide magnetic nanoscale micropropellers to traverse the vitreous cavity with the potential to deliver therapeutics to the retina (Figure); such nanorobots could conceivably be engineered to diameters approaching 2 nm.[40,41]

Others have investigated a polyacrylamide nanoparticle integrated with neurotrophin nerve growth factor with an affinity for retinal rods and cones to prevent retinal cell apoptosis.[42] Similarly, oligochitosan-coated nanoceria demonstrates antiangiogenic, antiinflammatory, and antiapoptotic characteristics in cellular AMD models.[43]

Researchers have found that lipid nanoparticles combined with targeting peptides and messenger RNA can bypass retinal barriers that have otherwise limited access to photoreceptors, a critical target in designing gene therapies for inherited retinal diseases.[44]

Simna et al recently engineered photoreceptors using

a nanoparticle-mediated delivery of a full-length human rhodopsin gene to murine rod photoreceptors, which could be useful in future treatment of retinitis pigmentosa.[45] Kwon et al synthesized melanin-like nanoparticles that could be used as an artificial melanin substitute in murine RPE cells.[46]

ONLY THE BEGINNING

We have only begun to scratch the surface of what is possible with therapeutic and regenerative applications of nanotechnology in the field of retina. We look forward to seeing where this field of investigation takes us. ■

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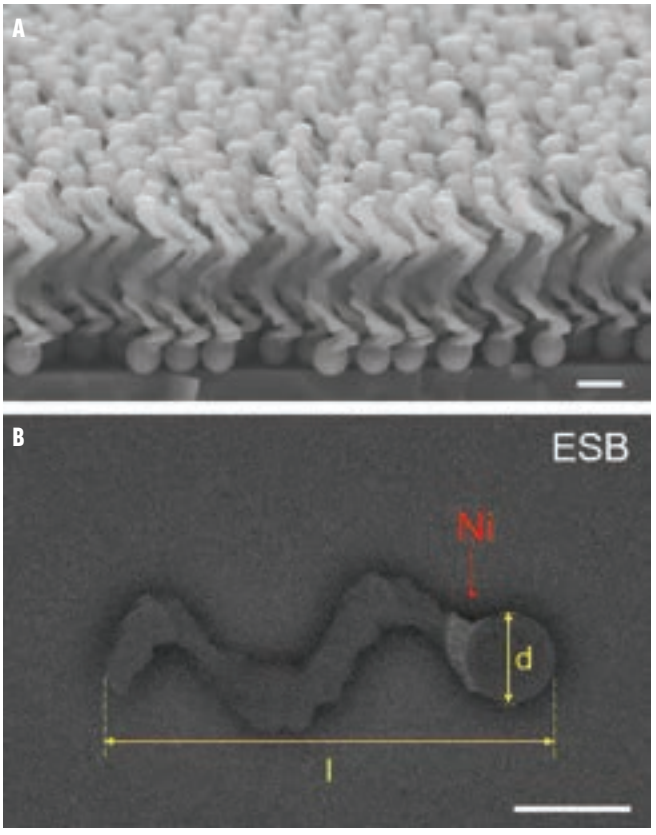

Figure. These scanning electron microscope (A) and energy-selective backscatter scanning electron microscope (B) images depict micropropellers that can cross the vitreous cavity. Scale bar = 500 nm. Reprinted with permission from Wu et al.[40]

NALIN J. MEHTA, MD, MS
- President, CEO, Retina Specialist, Colorado Retina Center, Denver
- fovea1@comcast.net
- Financial disclosure: Advisory Board (Eyetech, Genentech/Roche, Notal Vision, Novartis, Pfizer); Speaker's Bureau (Novartis, Sightpath); Valiant Consultant (Gerson Lehrman Group, Guidepoint Global, M3 Global Research, Reckner Healthcare, Sightpath)

SACHIN N. MEHTA, BA, BS
- Albert Einstein College of Medicine, New York
- Financial disclosure: None

PROGRESS IN AI FOR RETINAL IMAGE ANALYSIS

This technology is showing promise for disease risk stratification, diagnostic imaging, patient scheduling, and educational applications.

BY SAYENA JABBEHDARI, MD, MPH, MBA, AND J. FERNANDO AREVALO, MD, PHD


Health care is rapidly evolving due to technological advances and the accessibility of big data. In retina, the growing interest in AI is driven by the field's reliance on routine imaging data that require daily review and interpretation for managing retinal pathologies.[1-3] AI holds significant promise for revolutionizing ophthalmology by advancing diagnostic, predictive, and management processes. AI has evolved into sophisticated tools applicable across three primary research domains: prediction, causal inference, and description.[2] Supervised AI excels in predictive tasks, such as classifying retinal pathologies using labeled data and training sets of images to identify the characteristics of normal versus abnormal conditions.[1]

Clinically, AI has been employed in disease risk stratification, diagnostic imaging, patient scheduling, and educational applications, with surveys indicating that ophthalmologists anticipate significant improvements in patient care and screening efficiency through AI integration.[2]

AI IN FUNDUS IMAGING

AI has emerged as a promising tool for enhancing screening capabilities in both acute and chronic clinical settings. The Retinopathy Online Challenge, established in 2010 by the University of Iowa, exemplifies efforts to advance AI in this domain by evaluating algorithms for microaneurysm detection on a standardized dataset of fundus images.[4] Notable AI systems, such as those developed by Antal et al and Budak et al, have demonstrated significant accuracy in identifying microaneurysm lesions (Figure 1).[5,6]

Recent innovations have also targeted retinal vessel detection despite the variation in vascular morphology and crowded background. In addition, a deep convolutional neural network (CNN) model for retinal vessel extraction, which achieved high accuracy and area under the receiver operating characteristic curve (AUC) values, has been introduced.[2] Despite these advances, challenges remain in detecting neovascular changes associated with diabetic retinopathy (DR). AI systems, such as those developed by Rajalakshmi et al, have shown high sensitivity and specificity for DR detection using fundus images, while models by Pawar et al have outperformed ophthalmologists in identifying sight-threatening DR.[7,8]

FDA-approved AI systems—VoxelCloud Retina, IDx-DR (Digital Diagnostics) and EyeArt (EyeNuk)—are currently used for the screening of more-than-mild cases of DR, with others like CLAiR, BioAge, and Theia (Toku Eyes) undergoing approval processes for the detection

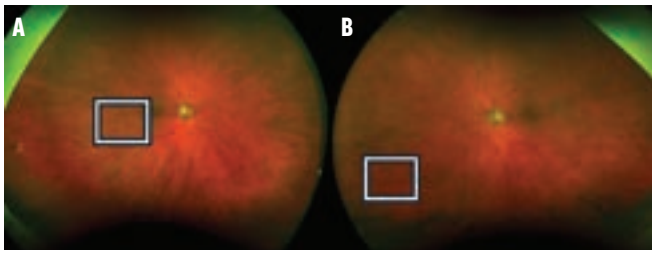

Figure 1. Widefield pseudocolor fundus photographs of the right (A) and left (B) eye show areas of microaneurysms, dot-and-blot hemorrhages, intraretinal microvascular abnormalities, and regions suspicious for neovascularization. The white rectangles show the labelling used by AI to detect DR.

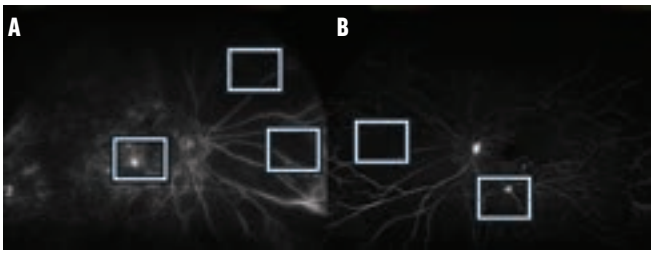

Figure 2. FA of the right (A) and left (B) eye reveals hyperfluorescent areas corresponding to leakage from neovascularization and hypofluorescent areas corresponding to severe ischemia indicating proliferative DR in each eye. The white rectangles show the labelling used by AI to detect DR.

of systemic cardiovascular risk factors based on fundus imaging.[9,10] AI's application extends to detecting multiple retinal pathologies, including AMD and retinal vascular occlusion (RVO). For instance, algorithms developed by Stevenson et al and Bhuiyan et al have achieved high accuracy in diagnosing various retinal conditions.[2]

Moreover, novel approaches, such as those integrating style transfer networks with registration networks, have enhanced image alignment and accuracy. However, real-world validation of retinal imaging data remains imperative.[3] A study by Lee et al revealed performance discrepancies between AI models in controlled studies compared with real-world clinical settings, highlighting the necessity for comprehensive validation before broader clinical implementation.[11]

AI IN OCT IMAGES

OCT is instrumental in detecting intra- and subretinal fluid accumulation and abnormalities in retinal layer thickness, which are critical biomarkers in the diagnosis and management of numerous retinal pathologies, such as diabetic macular edema, AMD, RVO, and central serous retinopathy (CSR).[12-14] Early applications of deep learning (DL) in OCT involved boundary detection of retinal layers, a critical step for evaluating disease states. For example, Fabritius et al achieved 96.7% accuracy in retinal pigment epithelium segmentation using DL on 1,022 macular OCT images, marking a significant advancement in retinal imaging.[12]

Subsequent models have made improvements, with Hussain et al's algorithm demonstrating superior performance in detecting retinal layer boundaries, such as the internal limiting membrane and retinal pigment epithelium.[15] Their model outperformed earlier tools like OCTRIMA-3D and AURA, with improved root-mean-square error for key retinal layers.[15,16] In addition to boundary detection, DL models have been applied to pathology identification in OCT.

Chakravathy et al developed a DL algorithm that detected intraretinal and subretinal fluid with an AUC of 0.97 and 91% accuracy, comparable with expert retina specialists.[17] Zang et al created a model capable of screening for DR and staging disease severity using both OCT and OCT angiography, achieving an AUC of 0.96.[18] Occlusion testing has also been employed to identify novel regions of interest in OCT images. For example, Lee et al used occlusion testing to identify fluid accumulation in AMD images, generating heat maps that highlighted areas potentially missed by human graders. These advances demonstrate the utility of DL in enhancing diagnostic accuracy and staging in retinal diseases, making it a valuable tool for clinical decision making.[19]

Taking this one step further, researchers have developed an AI algorithm (Deepeye) that uses OCT images to identify AMD disease activity and provide treatment recommendations to help clinicians optimize vision outcomes with anti-VEGF therapy.[20]

AI IN FLUORESCEIN ANGIOGRAPHY

Traditional clinical assessment of nonperfusion areas on fluorescein angiography (FA) is based on indirect markers of ischemia, such as the ischemic index, which typically manifest in advanced stages of disease. This limitation underscores the need for automated detection systems capable of identifying subtle ischemic changes at earlier stages, thereby providing timely and reliable guidance for clinical decision making.[21,22]

AT A GLANCE

- AI has been employed in disease risk stratification, diagnostic imaging, patient scheduling, and educational applications.
- Early applications of deep learning in OCT involved boundary detection of retinal layers, and recent advances have led to the use of deep learning for pathology identification in OCT.
- Despite its advantages, AI in clinical practice faces several challenges, including data integrity, medicolegal accountability, and potential shifts in the patient-physician relationship.

AI HAS EMERGED AS A PROMISING TOOL FOR ENHANCING SCREENING CAPABILITIES IN BOTH ACUTE AND CHRONIC CLINICAL SETTINGS.

Recent advances in DL have shown promise in improving the detection of nonperfusion and other pathological features in FA images (Figure 2). Gao et al compared the performance of three CNNs—VGG16, ResNet50, and DenseNet—for identifying nonperfusion in DR.[23] Using a dataset of 11,214 FA images from 705 patients, the VGG16 model demonstrated superior performance, with an accuracy of 94.17% and an AUC of 0.972, outperforming human graders. Similarly, Jin et al employed ResNet50 on 3,014 FA images from 221 patients with diabetic macular edema, achieving an AUC of 0.8855 for nonperfusion areas, further highlighting the potential of DL models for automated retinal analysis.[24]

In other retinal conditions, such as neovascular AMD and CSR, DL models have also been successfully applied to detect choroidal neovascularization and leakage. For instance, Chen et al used an attention-gated CNN to identify leakage points in CSR with an accuracy of 93.4%, surpassing the 89.7% accuracy achieved by ophthalmologists. These studies illustrate the growing utility of DL-based models in enhancing the diagnostic capabilities of FA in clinical practice.[25]

PROCEED WITH CAUTION

The integration of AI into ophthalmology presents significant potential to enhance diagnostic precision, optimize patient outcomes, and increase health care efficiency. However, the clinical application of AI faces several challenges, including data integrity, medicolegal accountability, and potential shifts in the patient-physician relationship. The *garbage in, garbage out* phenomenon highlights the critical need for high-quality input data to ensure the reliability and accuracy of AI-driven predictions. Furthermore, ethical and legal concerns, particularly related to data privacy and the delegation of decision making, require robust regulatory frameworks. Despite these challenges, ongoing prospective trials and advances in multimodal AI systems underscore the promise of AI in complementing ophthalmologists, improving retinal diagnostics, and enhancing clinical workflows. The successful integration of AI into ophthalmology could lead to more efficient, cost-effective, and accurate retinal care in the future. ■

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SAYENA JABBEHDARI, MD, MPH, MBA
- Ophthalmology Resident, Jones Eye Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas
- jabbehdarisayena@gmail.com
- Financial disclosure: None

J. FERNANDO AREVALO, MD, PHD
- Edmund & Virginia Ball Professor of Ophthalmology, Wilmer Eye Institute, Johns Hopkins School of Medicine, Baltimore, Maryland
- arevalojf@jhmi.edu
- Financial disclosure: None

Raising the Bar

BVI Medical is improving vision care through purpose-driven innovation.

BY SHERVIN KORANGY (PRESIDENT & CEO, BVI), MIKHAIL BOUKHNY, PHD (SENIOR VICE PRESIDENT OF RESEARCH AND DEVELOPMENT, BVI); AND AIMEE SHIMAMOTO (VICE PRESIDENT, CO-HEAD GLOBAL MARKETING, BVI)

Retinal diseases are expected to grow to 458 million in 2027.[1] Most of these individuals are affected by age-related macular degeneration (AMD), diabetic retinopathy (DR), and diabetic macular edema (DME). To help address the rising demand, BVI Medical (Waltham, MA) recognizes that ophthalmologists will need tools to develop a scalable model of patient care so they may deliver the best, most predictable outcomes and surgical experience.

GLOBAL GROWTH

Through strategic partnerships, acquisitions, and investments in both people and R&D, BVI has been on a mission to grow its global footprint and curate a comprehensive portfolio of premium ophthalmic solutions across instrumentation, IOLs, equipment, and more—all with a reputation of precision, innovation, and quality. The company's growth strategy has been centered on investing in a robust pipeline of internal R&D to drive differentiated innovation into the market. The company has coupled this with a thoughtful and creative external investment and acquisition model to turbo charge the growth of the business and establish it as one of the larger diversified player in the surgical ophthalmic industry.

In the past 5 years, BVI has undergone what CEO and President Shervin Korangy described as a "soup-to-nuts transformation of the business." Toward its goal of evolving into a global market leader of ophthalmic products, the company has doubled its R&D investment into treatments across surgical ophthalmology. Mr. Korangy summarized BVI's strategy: "Our focus has been on becoming a broad-based player, capable of offering a comprehensive array of solutions across cataract, retina and glaucoma. We want to have market-leading products in each category."

BROAD MARKET ACCESS AND THE RIGHT TEAM

BVI has an expansive presence and distribution footprint across North America, the United Kingdom, Europe, the Middle East, and Asia—90 countries in total. To ensure it can meet the growing demand for ophthalmic care across the globe, the company has added innovation hubs and manufacturing facilities across America, Europe, and Asia. Mikhail Boukhny, Senior Vice President of R&D for BVI, explained that each country presents unique needs, both in its clinical populations and its regulatory requirements. "Our strategy to tackle these challenges hinges on having a team of knowledgeable, professional, and hard-working individuals in R&D and regulatory affairs and across various functions. The expertise and dedication of the team enable us to create innovative products and navigate complex regulatory landscapes effectively," he said.

A DEDICATION TO INNOVATION AND RETINA CARE

BVI has made powerful commitments to enhance its global presence in retina vision care and continues to partner with world-class retinal specialists to identify the next great wave of innovation. BVI's current pipeline includes nine surgical ophthalmic devices and equipment platforms that it expects to launch over the next 3 years worldwide. This diversified pipeline portfolio will offer end-to-end integrated platforms that empower surgeons and their staff to significantly improve patient outcomes, efficiency, proficiency of care, and the profitability of surgical service lines.

BVI's portfolio spans a variety of high-performance surgical tools that includes Vitreq®, a leader in retina instrumentation worldwide. BVI has also invested R&D, engineering, and its manufacturing plant based in the Netherlands to develop a suite of retina products that include a wide range of micro forceps and scissors, laser probes, chandelier, backflush instruments, vitreoretinal consumables, bipolar erasers, and IVT kits. Globally, many retina practitioners rely on BVI's custom IVT kits to help optimize their ability to deliver reproducible quality outcomes for intravitreal injections. Omar Shakir, MD, MBA, CEO of Coastal Eye and Coastal Eye Surgery Center in Greenwich, Connecticut, says BVI retina products' "reliability and exceptional quality let me focus on my patients, knowing I have great instruments in hand with one less worry. Honestly speaking, I have never used better membrane peeling forceps with that butter-smooth action. Also, BVI CustomEyes® procedure packs provide consistency, efficiency, and the established high quality that I need for every case, making them an indispensable partner in my surgical center."

Further, BVI's Endo Optiks® Laser Microendoscopy provides crucial visualization when treating areas of the eye that are otherwise inaccessible, thus optimizing surgical outcomes.

PATIENT CARE IS NOT JUST SURGICAL

BVI is developing new clinical services and solutions to improve eye care providers' decision-making and patient care. "Globally, we are seeing that business and educational needs are just as important to practitioners as devices are," explained Mr. Boukhny. He also described the importance the BVI team places on developing a partnership with ophthalmic physicians: "Our commitment to excellence drives us to seek continuous feedback from those on the front lines of patient care. By developing close relationships with surgeons, BVI's team members are learning from their experience in the clinic."

To enhance the OR experience for clinicians and their staff, BVI developed an online application to streamline surgical pack customization, called CustomEyes®. Through the app, the BVI team works with surgeons and OR staff to create a digital model of surgical packs that meet their unique needs. ■

1. 2022 Retinal Surgical Device Market Scope Report (Market-Scope.com).

Letter to the Editor: Hurdles to AI Adoption in Retina

Deep-learning algorithms have yet to meaningfully affect clinical practice–here's why.

BY HASENIN AL-KHERSAN, MD; ELIOT DOW, MD, PHD; AND CHARLES C. WYKOFF, MD, PHD



For years, we have been hearing about the AI revolution that will transform the field of retina. Multiple AI algorithms for retinal diseases have received FDA clearance,[1,2] including LumineticsCore (formerly IDx-DR, Digital Diagnostics), EyeART (EyeNuk), and AEYE-DS (AEYE), all of which are designed more for primary eye care settings than the retina clinic.[3] Outside of the United States, several AI algorithms for biomarker identification have been cleared for clinical use. These newest developments exist alongside traditional computer vision methods for tasks such as OCT retinal layer segmentation, retinal thickness mapping, and retinal nerve fiber layer quantification.[4]

Although these innovations represent important steps in the application of AI to the field of retina, such technology has failed to make a significant effect on the day-to-day activities of most retina clinics. What prevents this technology–already shaping the cutting-edge consumer products that surround us–from revolutionizing the practice of retina? Here, we focus on five key hurdles to the development and implementation of AI in retina.

Hurdle No. 1: Data Limitations

The deep-learning algorithms that power today's AI technologies rely on large, diverse datasets with high-quality, often labelled images.[5] However, accessing ophthalmic data with these characteristics can be difficult. While there are several publicly available fundus photograph and OCT datasets for diseases such as diabetes and AMD, the data domain does not entirely overlap with that generated in a typical US retina clinic, which has hindered model accuracy in real-world settings.[6-8]

Data collected during routine patient care might better represent the model's end use and could be advantageous for model training. However, real-world data can present challenges in data quality and heterogeneity. Imaging protocols that are expeditious but adequate for a busy retina clinic may lack the quality or completeness necessary for AI model training or inference. Images acquired under uniform parameters–including high-resolution scans and small step sizes–may improve model performance but can be difficult to implement in the real world due to increased acquisition times and disruptions in clinical workflow.

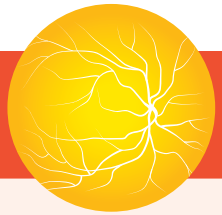
Hurdle No. 2: Clinical Integration

Even with high-quality data and effective algorithms, integration into clinical workflows is a major hurdle to AI implementation. AI tools must seamlessly fit into the existing processes of patient care without disrupting efficiency. Retina clinics already rely on many applications for the acquisition and display of clinical and imaging data. Therefore, AI systems that require separate interfaces and additional clicks will inevitably struggle to gain traction. Retina specialists should be involved early and often in device development to ensure that a high-performing device fits naturally into existing practice ecosystems.

Developers may be stymied in achieving this due to barriers of interoperability. Unlike other medical fields (eg, radiology), ophthalmology lacks a universal imaging standard. Additionally, electronic health record proprietors rarely have ready routes for integration of third-party AI modules. Adoption of Digital Imaging and Communications in Medicine (DICOM) and Fast Healthcare Interoperability Resources (FHIR) may improve device interoperability, and the ophthalmic community must continue to advocate through professional organizations for mandating these standards.

Hurdle No. 3: Practice Economics

Integrating AI programs into the clinical workflow requires time and resources; they may require specific clinical workflows, image types, and third-party applications. Practices must see a path to a return on their investment if they are expected to shoulder the burden of these costs. In a fee-for-service model, favorable reimbursement is the most immediate mechanism to support AI device implementation. In 2021, CPT code 92229 was introduced to reimburse the automated analysis of retinal images in the identification of diabetic retinopathy, typically using the devices mentioned above in a primary care setting.[9] Billing codes have been approved for AI-enabled home OCT monitoring as well.[10] However, there is no billing code that is used with frequency by retina specialists. Moreover, while billing codes are necessary, they may not be sufficient; insurers must also be willing to cover these costs.



Hurdle No. 4: Regulation

FDA regulation of AI technologies in health care is important to ensure algorithms are safe and accurate; those that are fully automated must meet a higher standard than those that are merely assistive to the doctor. However, the current regulatory framework for AI in medicine is still evolving.[7] Additionally, as with drug development, regulation of AI can be costly and time intensive, particularly for first-in-class de novo approvals.

The field of radiology, a frontrunner in AI with hundreds of FDA-approved AI-based algorithms, serves as a good case study.[11] Many of the radiology AI programs underwent approval through a 510(k) pathway, which involves a less burdensome review process if devices are substantially similar to previously approved devices.[11] This suggests that approvals in ophthalmology will proliferate as initial de novo approvals are obtained.

Another unique consideration is that AI models can be dynamic; they can learn and evolve as they process more data. This adaptability raises regulatory questions about how to ensure patient safety and efficacy over the lifecycle of the AI system.[12]

Hurdle No. 5: Data Protection

AI systems in retina clinics will have access to sensitive patient information, including images, medical histories, and diagnostic results. This introduces risks related to data breaches and cyberattacks. Ensuring that patient data is encrypted and protected is paramount, particularly as AI systems become more integrated into clinical practice and electronic health records.[13] Data may also be used by AI developers for applications unbeknownst to the data sharer, for instance, developing valuable intellectual property. Where strong legal protections seem insufficient, approaches such as federated learning may be necessary, whereby AI models may be applied to or trained on data without the data leaving its local network.[6]

Forging Ahead

While these challenges to the implementation of AI in retina are considerable, they can be overcome. In many ways, the most difficult problems—those of computing and technology—have already been solved. Ophthalmology, and retina specifically, has always been at the technological forefront in medicine, eager to adopt and adapt. We as a field should and will continue this leadership through collaboration with technology partners to overcome the implementation obstacles highlighted here. We are certain that our field will meet the moment and bring the benefits of AI to our patients. ■

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HASENIN AL-KHERSAN, MD
- Vitreoretinal Surgeon, Retina Consultants of Texas, Houston
- haseninrh@gmail.com
- Financial disclosure: Consultant (Alimera, Annexon, Apellis, Genentech/Roche, Ocular Therapeutix, Regeneron)

ELIOT DOW, MD, PHD
- Retina Specialist, Retina Consultants Medical Group, Sacramento, California
- dowel@retinalmd.com
- Financial disclosure: Consultant (Annexon, Ocular Therapeutix)

CHARLES C. WYKOFF, MD, PHD
- Director of Research, Retina Consultants of Texas
- Chairman of Research, Retina Consultants of America
- Deputy Chair of Ophthalmology, Blanton Eye Institute
- Professor of Clinical Ophthalmology, Houston Methodist Hospital
- Editorial Advisory Board Member, *Retina Today*
- charleswykoff@gmail.com
- Financial disclosure: Consultant (4DMT, Abbvie, Adverum, Alcon, Annexon, Apellis, Astellas, Boehringer Ingelheim, Clearside, Curacle, EyePoint, Genentech/Roche, Gyroscope, IACTA, Janssen, Kiora, Kodiak, Nanoscope, NGM, Novartis, Ocular Therapeutix, OcuTerra, ONL, Opthea, Oxular, Perceive Bio, Perfuse, Ray, Recens Medical, Regeneron, Re-genxbio, Stealth Biotherapeutics, Thea, Valo); Research Support (4DMT, Adverum, AffaMed, Alexion, Alimera, Alkahest, Annexon, Apellis, Astellas, Bayer, Boehringer Ingelheim, Clearside, Curacle, EyePoint, Genentech/Roche, Ionis, Kodiak, Nanoscope, Neurotech, NGM, Novartis, Ocular Therapeutix, Ocuphire, OcuTerra, Opthea, Oxular, Perceive Bio, Regeneron, Regenxbio)

TOP DISCUSSIONS AT ARDS 2024

This year's panels focused on treating geographic atrophy, the latest surgical techniques, and rare conditions.

BY HESHAM GABR, MD

The panel discussions are a hallmark of the annual Aspen Retinal Detachment Society (ARDS) meeting. During the 52nd ARDS meeting, held March 2 – 6, 2024, in Snowmass Village, Colorado, we hosted three fantastic panels that focused on imaging and treating complex disease, the latest approaches to vitreoretinal surgery, and managing rare conditions. I hope you enjoy this recap and join us March 1 – 5, 2025, for the 53rd ARDS meeting for more exceptional education and skiing.

– Timothy G. Murray, MD, MBA

PANEL 1: TREATING GEOGRAPHIC ATROPHY

The first panel was moderated by Timothy G. Murray, MD, MBA, and included Maura Di Nicola, MD; Giovanni Staurenghi, MD; K. Bailey Freund, MD; and Daniel F. Martin, MD (Figure 1). The conversation began with the treatment of choroidal neovascularization (CNV) in the setting of geographic atrophy (GA). Some argued that treating the CNV with anti-VEGF therapy is unnecessary, while others believed it can be beneficial, particularly if there are signs of progression or hemorrhage at the margins of the GA lesions. The decision to treat depends on individual factors, including lesion location, visual acuity, and new symptoms such as metamorphopsia. The panelists agreed that there is no one-size-fits-all approach; instead, the decision is made on a case-by-case basis.

The panel then discussed the case of an 89-year-old patient with a VA of 5/200 OD due to GA and 20/200 OS due to GA with an underlying type 1 macular neovascularization (MNV). There was a debate about treating the MNV; it is thought that MNV could be protective in GA, given that MNV might be under the only viable photoreceptors and retinal pigment epithelium (RPE). Drs. Di Nicola, Martin, and Freund argued that, because it was silent, observation may be best. Drs. Murray and Staurenghi were concerned that it could worsen and eventually lead to vision loss due to fluid leakage and recommended anti-VEGF injection.

The discussion then turned to treating GA itself. Drs. Di Nicola and Martin explained that complement inhibitors should be offered to certain patients with GA without MNV at baseline who meet the criteria of the OAKS, DERBY, and GATHER trials. Dr. Di Nicola highlighted the importance of carefully explaining to patients that these medications will not improve vision but might slow GA progression. Dr. Martin acknowledged the potential for preserving photoreceptors with the available GA treatments, although he believes the treatment burden, cost, and risks outweigh the benefits for most patients. He emphasized the importance of informed decision making and the need for further research to better understand the long-term effects of GA therapy.

Image courtesy of Kevin Caldwell Photography

Figure 1. During the first panel (from left to right), Drs. Martin, Di Nicola, Murray, Freund, and Staurenghi discussed imaging and treating complex retinal disease.

PANEL 2: VITREORETINAL SURGERY

The second panel, moderated by Donald J. D'Amico, MD, and including Justis P. Ehlers, MD; Barbara Parolini, MD; and Basil K. Williams Jr, MD, focused on cutting-edge surgery (Figure 2). They started with the current treatments for macular holes and agreed that the initial surgery of choice for uncomplicated cases should be vitrectomy with internal limiting membrane (ILM) peeling because it increases the closure rate to more than 90%.[1] Dr. D'Amico then discussed the work done by Zofia A. Nawrocka, MD, PhD, on large holes, which showed that an inverted flap technique was better than standard ILM peeling.[2] The panelists then touched on complications of the inverted flap technique, such as flap dislocation, failure of hole closure, and formation of a cauliflower configuration. The panel discussed the case of a patient with myopic foveoschisis and a VA of 20/30. Dr. Parolini recommended a macular buckle given the possibility of progression with worsening vision. However, Drs. Ehlers, D'Amico, and Murray recommended close observation given the lack of symptoms and good vision.

The panel also discussed vitrectomy for symptomatic vitreous opacities (SVOs). Some surgeons do not recommend vitrectomy due to the lack of objective assessment and potential risks associated with surgery. Others weigh the risks against the potential benefits for patients experiencing significant functional impairment. Factors favoring surgery include significant visual dysfunction, longer duration of symptoms, the presence of a posterior vitreous detachment, and pseudophakia. However, the lack of a standardized, objective method to measure SVO severity and the effect on vision make decision making a challenge.

PANEL 3: RARE RETINAL DISEASES

Moderated by Dr. D'Amico, the final panel included Dean Eliott, MD, and Drs. Di Nicola, Martin, and Staurenghi. The group discussed unique retinal conditions and offered management advice. They started with acute retinal necrosis. The standard of care involves a combination of intravitreal foscarnet and oral acyclovir to prevent spread to the other eye. Systemic therapy should continue for at least 12 weeks, but lifelong antiviral therapy might be necessary, especially if the patient had an unfavorable outcome with the first eye.

The panel then discussed a case of retinoblastoma in a 4-year-old boy. The patient presented with unilateral anterior chamber nodular material on the iris and vitritis. The B-scan showed noncalcified lesions, and a biopsy confirmed the diagnosis. The key message was to keep retinoblastoma in the differential diagnosis when evaluating children with uveitis.

Next, the panel discussed a patient who presented with profound bilateral vision loss with a normal eye examination. The panelists highlighted the importance of considering cancer-associated retinopathy (CAR) and melanoma-associated retinopathy (MAR) when the severity of vision loss does not match the clinical examination. To diagnose CAR and MAR, visual field testing, imaging, and serological testing for CAR antibodies are essential, along with oncology evaluation and a PET scan. While systemic steroids have been used, there is growing interest in local therapies. Recent case reports suggest that an intravitreal dexamethasone implant (Ozurdex, Abbvie) can be an effective treatment approach.[3]

Dr. D'Amico then showed a picture of an enucleated eye of a patient with bilateral diffuse uveal melanocytic proliferation (BDUMP). The patient initially presented with severe angle-closure glaucoma and iris bulging that did not respond to medical or surgical treatment. BDUMP is often

Image courtesy of Kevin Caldwell Photography

Figure 2. The second panel focused on surgical considerations and included (from left to right) Drs. Williams, Parolini, Ehlers, and D'Amico.

associated with highly malignant tumors, and, despite the benign nature of the ocular tumor, patients with BDUMP have a poor prognosis due to the underlying systemic cancer.

The group also discussed distinguishing congenital hypertrophy of the RPE (CHRPE), which may indicate Gardner syndrome and require a gastrointestinal evaluation, from other pigmented lesions, such as bear tracks, which do not necessitate further testing. CHRPE lesions appear torpedo-shaped on examination, are excavated on OCT, have high near-infrared reflectance, and lack autofluorescence.

Dr. D'Amico also shared a case of choroidal metastases, in which the patient presented with occasional flashing lights and scotomas. The panelists discussed the role of OCT in the diagnosis, noting that the imaging tool often reveals a choroidal mass with a lumpy appearance, which might be associated with subretinal fluid. Breast cancer is the most common primary tumor that metastasizes to the choroid in women, while lung cancer is more common in men.

The final case was a 54-year-old man with recent vision loss who presented with retinal hemorrhages, exudates, and disc edema. The patient was diagnosed with malignant hypertension and referred to the emergency department. The primary treatment goal is to gradually lower blood pressure to prevent complications. Some experts also recommend intravitreal anti-VEGF therapy to reduce the risk of scarring and neovascularization.

These panels highlight the diversity of opinions, even within a field of experts, and the insights derived from an extended discussion of imaging, diagnosis, and treatment of complex conditions. ■

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HESHAM GABR, MD
■ Retina Specialist, Tennessee Retina, Nashville
■ heshamgabr1986@gmail.com
■ Financial disclosure: None

THE 2024 MEE VITRECTOMY COURSE: A TRAINING CAMP FOR FELLOWS

First-year vitreoretinal fellows enjoyed 2 days of education and hands-on surgical training.

BY MELISSA YUAN, MD; ELIZABETH ROSSIN, MD, PHD; NIMESH A. PATEL, MD; AND JOHN B. MILLER, MD

Surgical retina fellows face a steep learning curve in the first summer of their fellowship program. The annual Mass Eye and Ear Vitrectomy Course is designed to help fellows get up to speed on core surgical principles and techniques. The course, founded by John Loewenstein, MD, and Demetrios Vavvas, MD, PhD, gained increased recognition with the addition of Dean Eliott, MD, as an honorary founder and the third course director in 2012 and John B. Miller, MD, 4 years later. The 14th annual meeting, held July 12 – 13, 2024, in Boston, was led by current course directors Dr. Miller; Elizabeth Rossin, MD, PhD; and Nimesh A. Patel, MD. Each year, the course trains upwards of 60 retina fellows from across the country. It is perhaps best known for its incredible faculty, who are notable for their high character and surgical skills, combined with a nearly one-to-one faculty-to-fellow ratio.

KNOWLEDGE IS POWER

Day one consisted of talks on foundational surgical concepts. The first session focused on primary retinal detachment repair with talks on pneumatic retinopexy by Yewlin Chee, MD; scleral buckling by Lucy H. Young, MD, PhD; and vitrectomy by Thanos Papakostas, MD. The retinal detachment section concluded with the signature case panel led by Donald J. D'Amico, MD, and featuring panelists Maria H. Berrocal, MD; Steve Charles, MD; John W. Kitchens, MD; and William F. Mieler, MD.

After a lunch with views of the Boston and Cambridge skyline, the fellows shifted to more complex retinal detachment management topics, such as diabetic retinal detachments by Dr. Berrocal, proliferative vitreoretinopathy by Dr. Eliott, and trauma by Dr. Rossin. The day continued with rapid-fire talks covering the fundamentals of surgical retina, including epiretinal membranes by Katherine E. Talcott, MD; endophthalmitis by Luis J. Haddock, MD; surgical uveitis by Kareem Moussa, MD; secondary IOLs by Dr. Kitchens; and pediatric retina by Eric D. Nudleman, MD, PhD.

Other highlights included an introduction to PFO by Stanley Chang, MD, who initially described the technique, lively question-and-answer sessions, and the Founder's Lecture on vitrectomy fluidics and instrumentation by Dr. Charles. The audience was captivated by Dr. Charles' in-depth discussion of the intricacies of fluidics, as well as his quip that his retirement plan would be "asystole."

Robert B. Bhisitkul, MD, PhD, provided an introduction to ergonomics, emphasizing that macular pucker surgery is one of the highest precision surgeries that exists in all of medicine. He discussed each contributor to ergonomics (the chair, the scope height, each muscle group) and ended by reminding fellows to "keep the cornea clear—not just the patient's, but also your own!"

The day concluded with a reception, an event sponsored by YoungMD Connect, and a faculty dinner.

PRACTICE MAKES PERFECT

The hands-on teaching day took place at Mass Eye and Ear. This action-packed second day focused on putting newly learned principles into action with a wet lab, simulators, injection practice, surgical video case discussions, and small-group career mentoring (Figure 1).

The wet lab, held in the Mass Eye and Ear ORs, featured stations on vitrectomy, membrane peeling, intraocular

Images courtesy of Kevin Caldwell Photography

Figure 1. Dr. Young led a wet lab on scleral buckling (A), Dr. Houston shared vitrectomy techniques (B), and Dr. Rezende discussed Alcon's NGenuity 3D heads-up display system (C).

foreign body removal, and scleral buckling on porcine eyes. Dry lab stations showcased the latest equipment from Alcon, DORC, Oculus Surgical, Bausch + Lomb, MIRA, and Proficient Surgical. The fellows then practiced with various injectables, including the triamcinolone acetonide injectable suspension (Xipere, Bausch + Lomb), 0.18 mg and 0.19 mg fluocinolone acetonide intravitreal implants (Yutiq and Iluvien, Alimera Sciences), and the dexamethasone intravitreal implant (Ozurdex, Abbvie), and surgical simulators, such as EyeSi (Haag-Streit), Johnson & Johnson Vision's Virtual Reality Demo, and the Genentech surgical simulator. These sessions were complemented by surgical videos with faculty and focused small-group career mentoring.

Interspersed between the labs were panel discussions featuring faculty from around the country. Dr. Kitchens moderated a panel on IOLs with Dr. Talcott; Durga S. Borkar, MD, MMCi; S.K. Steven Houston III, MD; Miin Roh, MD; and Archana T. Seethala, MD, reminding fellows that secondary IOLs can be a major practice builder. The panelists also shared their lens and technique preferences. Dr. Papakostas then moderated a panel on proliferative vitreoretinopathy, retinectomies, and instruments with Xi Chen, MD, PhD; Yannek Leiderman, MD, PhD; Cynthia X. Qian, MD; Flavio A. Rezende, MD, PhD; and Francis Wu, MD. Lastly, Rishi P. Singh, MD, moderated a panel on macular holes, internal limiting membrane peeling, and instruments with Ivana K. Kim, MD; Sandra R. Montezuma, MD; Patrick R. Oellers, MD; Aleksandra Rachitskaya, MD; and Nadia K. Waheed, MD, MPH.

The preparation and understanding that is essential to achieve excellent surgical outcomes was emphasized through in-depth case discussions accompanied by surgical videos.

BEYOND THE OR

The meeting provided career mentoring through small-group discussions that shared actionable tips. In keeping with the theme of career success, the closing lecture of the course was "Top 10 Things to Keep Your Attending AND YOU Happy" by Ronald C. Gentile, MD.

In addition to the education, the vitreoretinal surgery fellowship class of 2026 had numerous opportunities to connect in small-group settings or one-on-one with leaders

Figure 2. A group photo featuring the participating fellows and faculty.

and each other (Figure 2). The relationships formed will help foster collaborations and provide a network to discuss challenging cases in the future.

The fellows left feeling prepared with foundational knowledge and skills to help them embark on their next challenge of vitreoretinal surgical fellowship training! Mark your calendars for the 15th Annual Mass Eye and Ear Vitrectomy Course, scheduled for July 11 – 12, 2025, in Boston. ■

MELISSA YUAN, MD
- Ophthalmology Resident, Retina Service, Department of Ophthalmology, Mass Eye and Ear, Boston
- Financial disclosure: None

ELIZABETH ROSSIN, MD, PHD
- Vitreoretinal Surgeon, Retina Service, Department of Ophthalmology, Mass Eye and Ear, Boston
- Financial disclosure: None

NIMESH A. PATEL, MD
- Vitreoretinal Surgeon, Retina Service, Department of Ophthalmology, Mass Eye and Ear, Boston
- Financial disclosure: Consultant (Alcon, Dutch Ophthalmic, EyePoint Pharmaceuticals, Genentech/Roche, Regeneron)

JOHN B. MILLER, MD
- Vitreoretinal Surgeon, Retina Service, Department of Ophthalmology, Mass Eye and Ear, Boston
- Financial disclosure: Consultant (Abbvie, Alcon, Carl Zeiss Meditec, Genentech/Roche, Sunovion, Topcon)

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Mark Humayun, MD, PhD
Monday, January 13
University of Southern California Ginsburg Institute for Biomedical Therapeutics

Carl Regillo, MD, FACS, FASRS
Tuesday, February 4
Wills Eye Hospital

Maria Berrocal, MD
Tuesday, March 11
Berrocal and Associates and University of Puerto Rico

Additional mentors to be announced soon!

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YMDC members engaging with retina thought leaders, Audina Berrocal, MD, and Dean Eliott, MD, during in-person events and virtual mentoring sessions.

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A CLOSER LOOK AT ELLIPSOID ZONE ATTENUATION


Could this structural finding, a newly-approved clinical trial endpoint, help us predict AMD progression? Here's what we know so far.

BY JUSTIS P. EHLERS, MD, AND CHARLES C. WYKOFF, MD, PHD

AMD is a retinal disease involving the progressive loss of photoreceptors, choriocapillaris, and retinal pigment epithelium (RPE).[1] Drusen deposits, hypertransmission observed via OCT, and changes in RPE pigmentation are often used to classify stages of early and intermediate AMD that can suggest an increased risk of photoreceptor deterioration.[2,3] Geographic atrophy (GA) is associated with significant RPE atrophy and photoreceptor loss.[3] Ongoing research aims to develop treatments administered earlier to patients with AMD with the goal of preserving visual function.

A traditional metric to assess GA is the lesion area and its changes over time, usually with fundus autofluorescence.[1] However, this metric cannot be used to assess patients at earlier stages of AMD, potentially indicating a gap in longitudinal disease biomarkers.[4] While drusen and RPE pigmentary changes can be biomarkers of disease, they may not be the first detectable changes in AMD formation; therefore, other biomarkers to identify and predict early and intermediate AMD progression to GA are needed.[5] For example, photoreceptor health may play a significant role in AMD and is a potentially valuable predictor of disease progression.

Evidence suggests that features such as the ellipsoid zone (EZ) are reflections of photoreceptor health and may serve as a biomarker and endpoint for AMD and GA in both clinical trials and clinical practice.[5]

ELLIPSOID ZONE INTEGRITY

Photoreceptors are highly metabolically active cells with substantial energy demands.[6] To meet these requirements, photoreceptors contain an abundance of mitochondria to produce sufficient adenosine triphosphate.[2] In healthy eyes, mitochondria account for approximately 80% of the cellular volume in cones and approximately 55% of the cellular volume in rods.[7] These mitochondria reproducibly reflect light on OCT imaging, resulting in the appearance of a consistent bright band.[7,8] Several such hyperreflective bands can be identified on OCT images of the retina (Figure 1A). The EZ, seen as the second band, comprises the outer portion of photoreceptor inner segments that appear on scans due to the dense collection of mitochondria localized to that region.[8,9]

EZ imaging analyses on OCT may capture and quantify photoreceptor degradation through measurable changes.[9,10] This may include patterns of disorder, such as discontinuity in the band, reduction in the distance between the EZ and RPE band, EZ thinning, and decreased reflectivity/brightness (Figure 1B). Common quantifiable EZ measurements by OCT include analysis of EZ-RPE thickness and EZ reflectivity.[11]

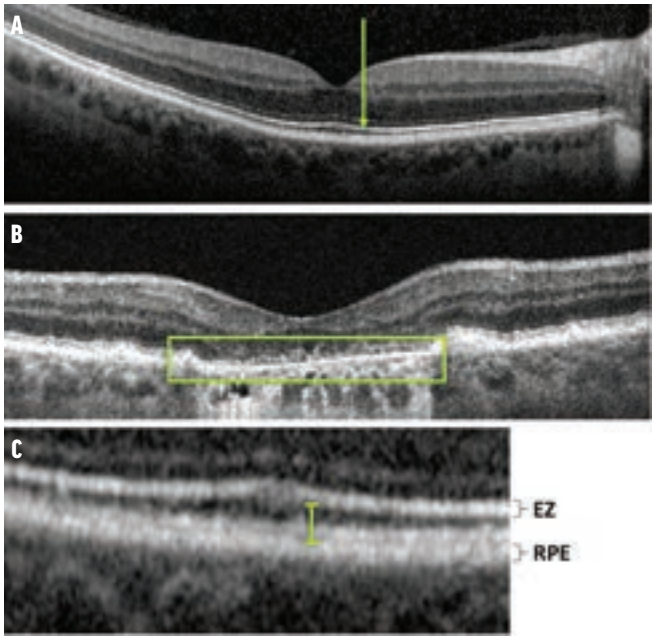

Figure 1. In a healthy retina with identifiable hyperreflective bands (A), the EZ (arrow) represents the outer portion of the inner segments of retinal photoreceptors containing large amounts of mitochondria, owing to the band's high reflectivity. In an eye with GA (B), there is total outer retinal and RPE loss in the retina. EZ-RPE thickness (C) spans the outer segments of photoreceptors and across the interdigitation zone (band directly above the RPE).

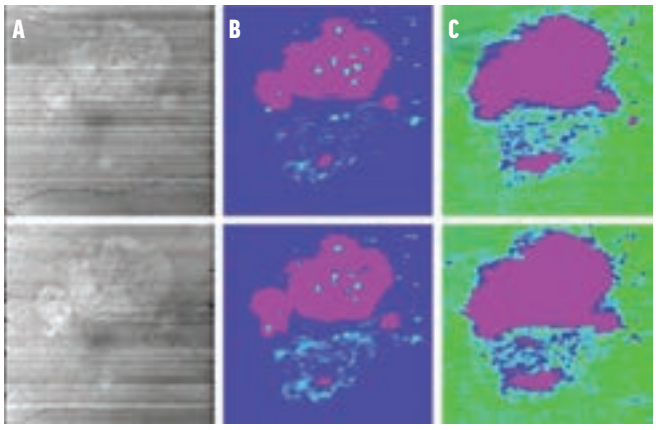

Figure 2. Longitudinal EZ integrity mapping (en face OCT) at two points 6 months apart (top and bottom, respectively) demonstrates focal areas of progressive loss (A). Note the sub-RPE compartment (B) with total RPE loss and associated GA (pink) and drusen (green). The EZ integrity map (C) demonstrates areas of normal EZ integrity (green), partial EZ attenuation (blue), and total EZ attenuation (pink).

EZ: A BIOMARKER AND PREDICTOR OF DISEASE PROGRESSION

The prevailing feature of GA is the presence of sharply demarcated atrophic lesions due to loss of photoreceptors and RPE. Photoreceptor loss may both precede and predict the progression of AMD, including GA, before other overt signs appear.[4,12,13] In GA, areas of photoreceptor loss outside of GA lesions have been associated with lesion growth and disease advancement.[10] Quantification of EZ metrics as a related measure of photoreceptor/outer segment loss may serve as biomarkers of AMD and forecast progression.

EZ attenuation (photoreceptor degradation and/or loss), as measured by a reduction in the distance between the EZ and RPE, is a key metric of EZ integrity and, thus, photoreceptor health. Partial EZ attenuation (photoreceptor degradation) and total EZ attenuation (photoreceptor loss) describe the measured thickness between the EZ and RPE layers via OCT (EZ-RPE thickness). Normal EZ-RPE thickness is 40 µm to 50 µm (Figure 1C).[14] Total EZ attenuation represents complete loss of the EZ on OCT B-scan (Figure 2).[12] Partial EZ attenuation represents a significant decrease in the EZ-RPE thickness, defined as ≤ 20 µm, and has been found to represent significant pathologic/functional consequence in multiple retinal diseases.[12] Both partial and total EZ attenuation are significantly associated with GA progression, consistent with extensive photoreceptor loss.[15] Studies have found that baseline measurements of partial and total EZ attenuation are significantly higher in AMD patients who later develop GA and that those patients have larger rates of GA lesion growth.[12,16,17]

Several studies have demonstrated the use of relative EZ reflectivity (rEZR) as a biomarker for AMD stages. Across all stages of AMD, rEZR is significantly diminished compared with age-matched controls, and changes in intensity have been associated with functional changes in visual acuity.[2,18,19] Furthermore, decreases in rEZR correlate with AMD advancement.[5,8] In intermediate AMD, the presence of high-risk factors for disease progression and photoreceptor loss, such as large drusen, reticular pseudodrusen, and pigmentation abnormalities, have been significantly associated with reduced rEZR.[2,3,5]

Changes in the visual acuity of patients with AMD have been associated with EZ disruption, and BCVA is negatively correlated with total EZ attenuation in patients with AMD.[2,20] One analysis demonstrated that EZ-RPE thickness features were linked not only to visual acuity, but also to the risk of future loss.[21] One study in wet AMD observed a treatment-associated significant decrease in total EZ attenuation, indicating recovery of the EZ in places of prior loss.[20] Collective research supports the potential of EZ metrics as biomarkers and predictors of AMD progression.

THE VALUE OF EZ ANALYSIS IN CLINICAL TRIALS

There is an unmet need for new, reliable, and objective endpoints in AMD clinical trials. Historical primary endpoints, such as GA lesion growth rate, potentially capture only one aspect of the disease. Incorporating EZ metrics into clinical trials may aid in better capturing the entirety of the disease, both as key endpoints and as potential inclusion/exclusion criteria.

Implementation of EZ-related endpoints has already demonstrated value in AMD clinical trials. For example, the phase 2 ReCLAIM-2 clinical trial for elamipretide (Stealth BioTherapeutics) demonstrated the use of EZ attenuation as a prespecified endpoint.[22] Elamipretide treatment reduced total EZ attenuation by 43% and partial EZ attenuation by 47% over 48 weeks compared with placebo as a prespecified secondary endpoint.[22] Furthermore, higher partial and total EZ attenuation at baseline were found to be predictors of GA growth rates.[19] When observing visual outcomes, a significant correlation was established between change in low-luminance BCVA and change in total EZ attenuation at week 48.[22,23]

Analyses from other GA trials have also revealed important observations regarding EZ metrics. In a post-hoc analysis of the FILLY trial of pegcetacoplan (Syfovre, Apellis), areas of EZ attenuation were significantly reduced in treated eyes compared with sham.[24] A pooled post-hoc analysis of the GATHER1 and GATHER2 trials of avacincaptad pegol (Izervay, Astellas) demonstrated similar results, reporting a 55% reduction in partial EZ loss.[25] Additional analysis from the phase 2 ARCHER trial of ANX007 (Annexon Biosciences) showed significant reduction in progressive total EZ attenuation through 12 months (29% reduction in progression vs sham).[26] These clinical trial findings further support the evolving relation of EZ metrics as reflections of photoreceptor health and how changes in the EZ affect functional outcomes in patients.

FUTURE DIRECTIONS

As our understanding of GA and AMD continue to grow, greater efforts are being put into the development of reliable biomarkers and objective predictors of AMD progression. Evidence is accumulating to support the longitudinal utility of EZ integrity assessment toward these goals.

Applications for future research and design of clinical trials are actively evolving. In 2023, the FDA confirmed total EZ attenuation as an approvable endpoint in dry AMD studies.[27] The two phase 3 trials investigating elamipretide, ReNEW and ReGAIN, will use EZ attenuation as a primary endpoint.[28,29] Prior to this, Neurotech Pharmaceuticals reported positive data for the prespecified primary endpoint of EZ area loss in two phase 3 randomized controlled studies of revakinagene taroretcel (NT-501), a ciliary neurotropic factor-producing surgical implant, for the treatment of macular telangiectasia type 2.[30]

With EZ attenuation as an approvable endpoint, future trials may better capture the features of early disease pathogenesis and better assess critical structure-function relationships—those between photoreceptor integrity and changes in visual function.

Researchers are also working on the diagnosis and prognostication of earlier stages of AMD. Changes in photoreceptor health may precede and predict more overt signs of AMD; thus, earlier indications of the disease may improve disease monitoring, enhance personalized care delivery, and improve clinical outcomes. Collectively, research supports the use of EZ metrics as predictors of AMD progression and the recent approval of EZ-related endpoints in clinical trials for AMD. ■

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JUSTIS P. EHLERS, MD

- Norman C. and Donna L. Harbert Endowed Chair of Ophthalmic Research; Director, Tony and Leona Campane Center for Excellence in Image-Guided Surgery and Advanced Imaging Research; Vice Chair of Continuous Improvement, all at Cole Eye Institute
- Editorial Advisory Board Member, *Retina Today*
- ehlersj@ccf.org
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CHARLES C. WYKOFF, MD, PHD

- Director of Research, Retina Consultants of Texas, Houston
- Chairman of Research, Retina Consultants of America
- Deputy Chair of Ophthalmology, Blanton Eye Institute, Houston
- Professor of Clinical Ophthalmology, Houston Methodist Hospital, Houston
- Editorial Advisory Board Member, *Retina Today*
- ccwmd@houstonretina.com
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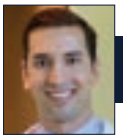

Luciano Custo Greig, MD, PhD

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

I got my start in retina as an MD-PhD student during a summer rotation investigating photoreceptor genetics and development in the laboratory of Constance Cepko, PhD, at Harvard Medical School. Although I ended up focusing on the cerebral cortex for my PhD, I remained interested in retina; when I returned to medical school, I realized that ophthalmology was the perfect fit for me, both clinically and scientifically.

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

My research mentors are Jeffrey D. Macklis, MD, DScTech, my PhD advisor at Harvard, and Jeffrey Goldberg, MD, PhD, my postdoctoral advisor at Stanford. I have grown tremendously thanks to their feedback, and I am grateful for their support and friendship.

I did my first vitrectomies as a resident at Stanford thanks to the trust of Prithvi Mruthyunjaya, MD, MHS; Steven Sanislo, MD; and Carolyn Pan, MD. During fellowship at the University of Southern California, I worked with a great group of vitreoretinal surgeons, including Andrew Moshfeghi, MD, MBA; Juan Carlos Martinez, MD; Firas M. Rahhal, MD; and Pouya N. Dayani, MD. They all have a sixth sense in the OR for when to let me figure things out and when to step in with a helpful suggestion.

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

The highlight of training has been working at Los Angeles County Hospital. Taking care of patients with diabetic retinal pathology has been challenging but rewarding. As an immigrant from Argentina, I have particularly enjoyed providing medical care in Spanish. Patients are thrilled to have a doctor who can communicate in their language, and I am grateful for the special rapport this has established with them.

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

While running a research laboratory dedicated to retinal gene therapy and regeneration, I plan to apply my knowledge of surgical techniques, virology, genetics, and retina development to formulate new therapeutic approaches for inherited retinal disease and advanced degenerative retinal pathologies.

FIRST CAREER MILESTONE

Dr. Greig has joined UCSF's Department of Ophthalmology as an assistant professor.

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

Vitreoretinal surgery is a competitive field, and a few difficult interactions can scare residents away. However, some of the most dedicated, compassionate, and brilliant doctors are retina specialists. If you find the right environment and mentors, vitreoretinal surgery is hard to beat in terms of the diversity of pathology, complexity of surgical approaches, and cutting-edge innovation. ■

LUCIANO CUSTO GREIG, MD, PHD
- Former Vitreoretinal Surgery Fellow, University of Southern California, Los Angeles
- luciano.greig@ucsf.edu
- Financial disclosure: None

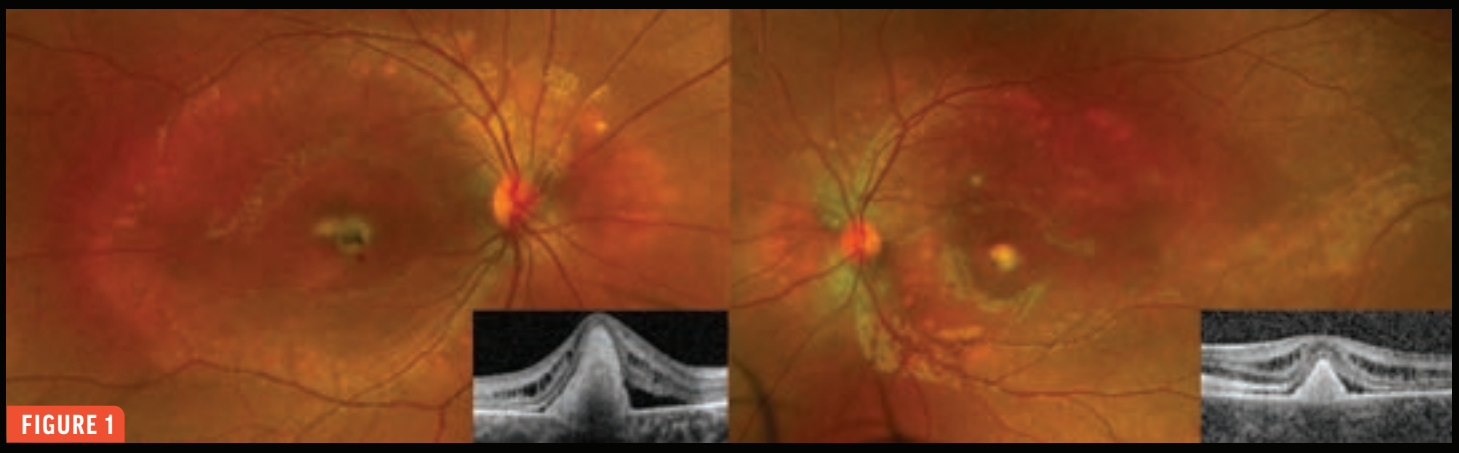

FIGURE 1

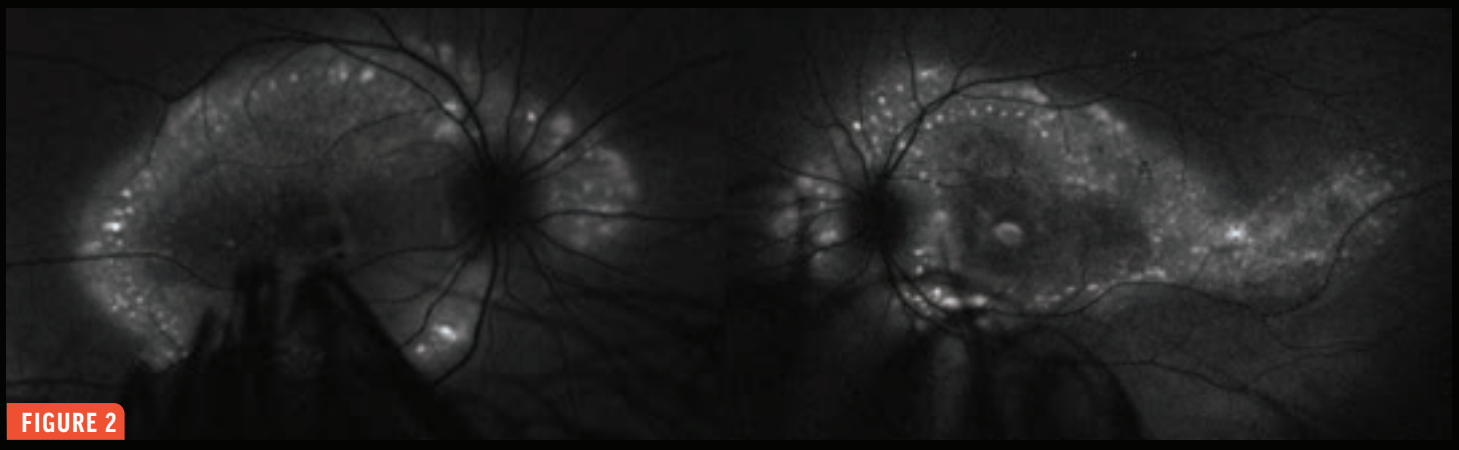

FIGURE 2

MULTIGENERATIONAL AUTOSOMAL RECESSIVE BEST DISEASE

Retinal findings raised suspicion for this inherited retinal disease, confirmed with genetic testing.

BY SAYENA JABBEHDARI, MD, MPH, MBA; FLORIN GRIGORIAN, MD; AND MICHALIS GEORGIOU, MD, PHD

A 6-year-old boy with a positive family history of Best disease was referred to our pediatric retina clinic for evaluation due to decreased vision. His VA was 20/200 OD and 20/30 OS at presentation. Widefield pseudocolor images showed multifocal vitelliform material in each eye, along with choroidal neovascular membrane in his right eye (Figure 1).

OCT showed well-defined subretinal hyperreflective material in each eye with a subretinal hemorrhage in the right eye (Inset). Fundus autofluorescence images of each eye showed marked hyperautofluorescence corresponding to the subretinal vitelliform material (Figure 2).

The patient underwent monthly injections of an anti-VEGF agent in the right eye for treatment of the choroidal

THE PATIENT HAD A FAMILY HISTORY OF AUTOSOMAL RECESSIVE BESTROPHINOPATHY IN HIS SIBLINGS, COUSIN, AND UNCLE, AND HIS IMAGING FINDINGS WERE CONSISTENT WITH THIS CONDITION.

neovascular membrane. At the most recent visit, his VA had improved to 20/60 OD.

GENETIC EVALUATION

The patient had a family history of autosomal recessive bestrophinopathy in his siblings, cousin, and uncle, and his imaging findings were consistent with this condition. With genetic testing, the patient was found to be homozygous for the c.653G>A, p.(Arg218His) *BEST1* variant, which was segregated to both parents. ■

MICHALIS GEORGIOU, MD, PHD
- Medical Retina Fellow, Department of Ophthalmology, Duke University, Durham, North Carolina
- Financial disclosure: None

FLORIN GRIGORIAN, MD
- Pediatric Ophthalmologist and Vitreoretinal Surgeon, Jones Eye Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas
- Financial disclosure: None

SAYENA JABBEHDARI, MD, MPH, MBA
- Ophthalmology Resident, Jones Eye Institute, University of Arkansas for Medical Sciences, Little Rock, Arkansas
- jabbehdarisayena@gmail.com
- Financial disclosure: None

If you have images you would like to share, email Manish Nagpal, MS, FRCS, FASRS, at drmanishnagpal@yahoo.com.

Note: Photos should be 400 dpi or higher and at least 10 inches wide.

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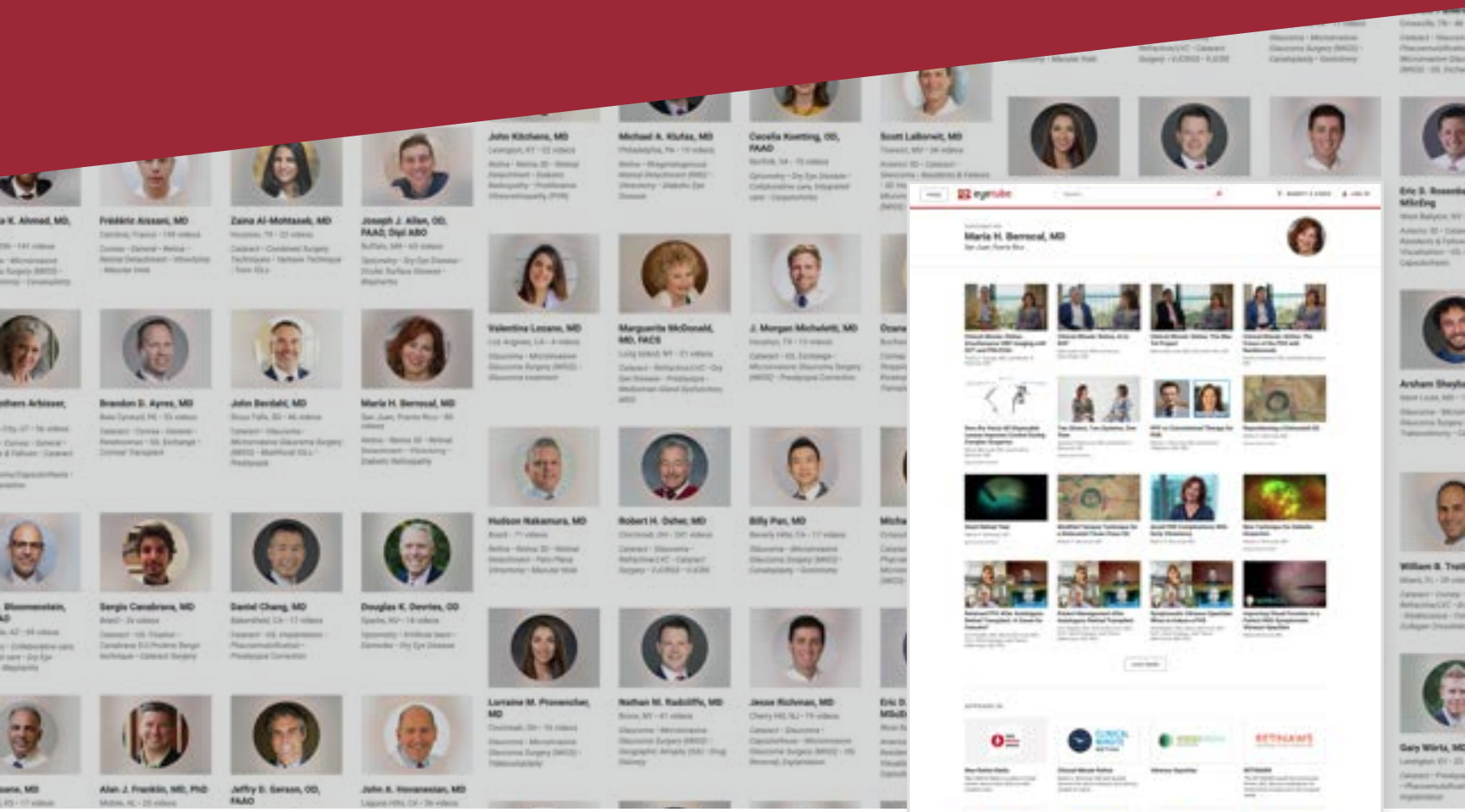

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