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Conference Highlights: A look at interesting presentations from the Vit-Buckle Society meeting.

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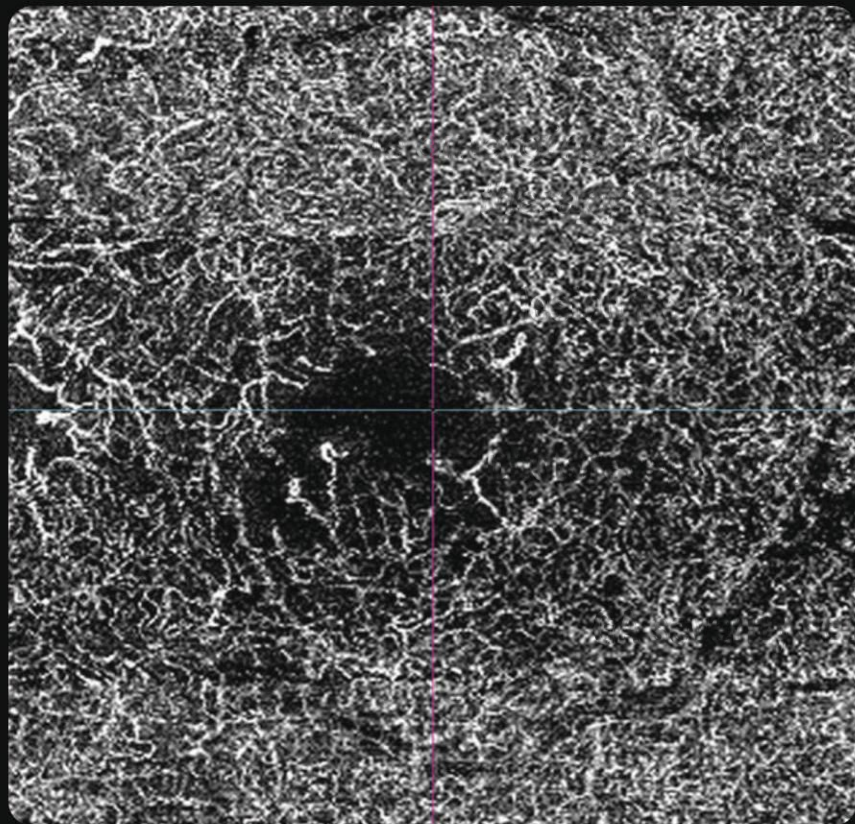
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Retina Rounds: When uveitis heralds malignancy.



lesion area

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Deep retinal plexus image of patient with diabetic retinopathy, Maestro2 OCTA scan

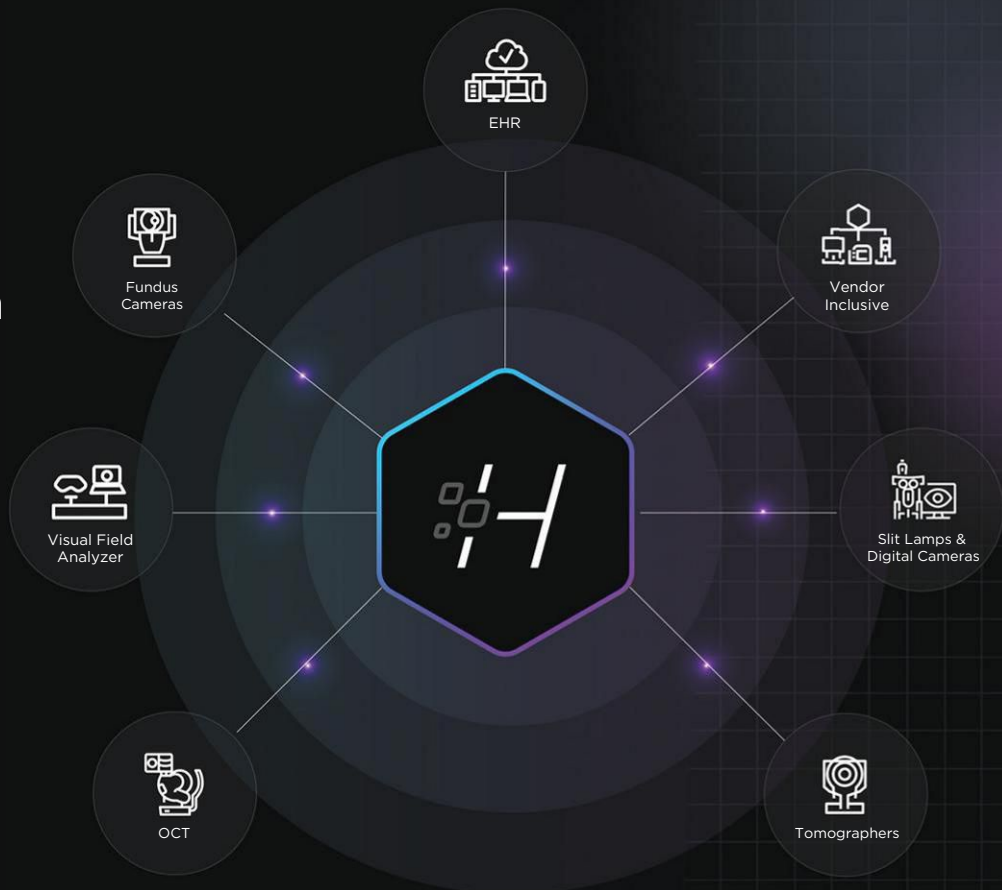


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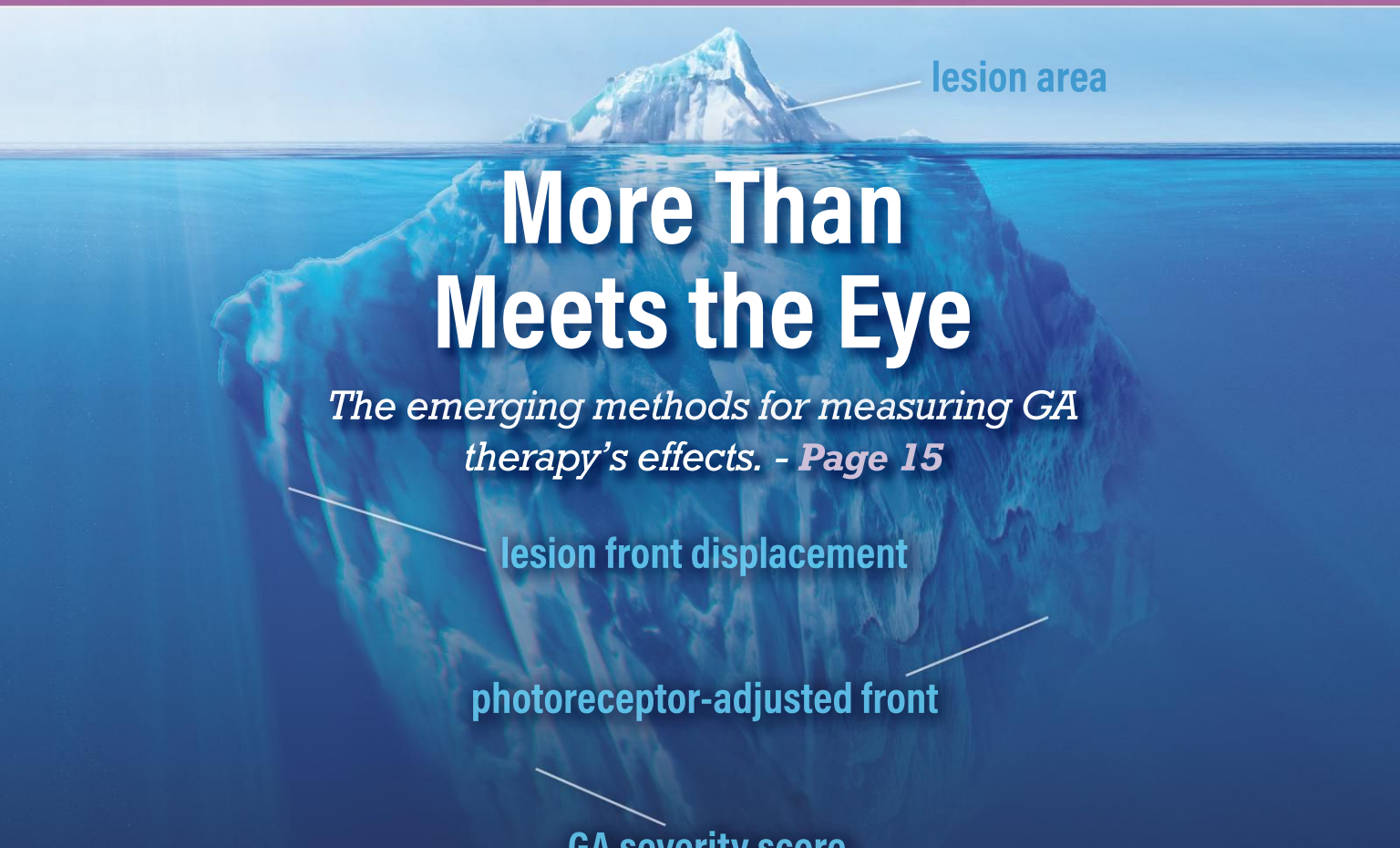
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More Than Meets the Eye

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lesion area

lesion front displacement

photoreceptor-adjusted front

GA severity score

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Online Video

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Wet AMD

EYLEA HD[®]
(aflibercept) Injection 8 mg

STRENGTH THAT ENDURES

AS SHOWN BY SIMILAR VISION OUTCOMES
WITH EYLEA HD VS AFLIBERCEPT 2 MG IN
PATIENTS WITH WET AMD (WEEK 48)^{1*}

THE FIRST AND ONLY ANTI-VEGF INJECTION
APPROVED FOR Q20W DOSING
AFTER 1 YEAR OF SUCCESSFUL
RESPONSE IN WET AMD^{1†}

SAVE THEIR VISION FOR THE FUTURE.

Delivered rapid and durable vision gains through
Week 48^{1,2**}

DOSING FLEXIBILITY. TAILOR TO YOUR PATIENTS' NEEDS.¹

*Mean change in BCVA (ETDRS letters) from baseline at
Week 48 in Wet AMD. FAS; observed values (censoring
data post ICE) at Week 48: EYLEA HD Q16W +6.2
letters (n=289), EYLEA HD Q12W +6.7 letters (n=299),
aflibercept 2 mg Q8W +7.6 letters (n=285) in PULSAR.
Following 3 initial monthly doses in all treatment groups.^{1,2}

INDICATIONS

EYLEA HD[®] (aflibercept) Injection 8 mg and EYLEA[®]
(aflibercept) Injection 2 mg are indicated for the
treatment of patients with Neovascular (Wet)
Age-Related Macular Degeneration (AMD).

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

PULSAR Study Design

Randomized, multicenter, double-masked Phase 3 clinical study in which treatment-naïve patients with Wet AMD (N=1009; age range: 50-96 years, with a mean of 74.5 years) were randomized in a 1:1:1 ratio to receive: (1) EYLEA HD Q16W (n=338); (2) EYLEA HD Q12W (n=335); or (3) aflibercept 2 mg Q8W (n=336), each following 3 initial monthly doses. In the EYLEA HD groups, patients could be treated as frequently as Q8W based on protocol-defined visual and anatomic criteria, starting at Week 16. Additionally, starting at Week 52, patient dosing intervals could be extended by 4-week increments if all protocol-defined visual and anatomic criteria were met at visits in Year 2 (ie, BCVA loss <5 letters from Week 12, no fluid in the central subfield on OCT, and no new onset foveal hemorrhage or foveal neovascularization). The primary endpoint was the mean change from baseline in BCVA at Week 48 as measured by the ETDRS letter score.^{1,3}

Recommended Dosing for Wet AMD

The recommended dose for EYLEA HD is 8 mg administered by intravitreal injection Q4W (approximately every 28 days +/- 7 days) for the first 3 doses, followed by 8 mg via intravitreal injection once every 8 to 16 weeks, +/- 1 week.¹

Some patients did not maintain a response with 8 mg once every 8 to 16 weeks, +/- 1 week, after successful response to the 3 initial monthly doses. These patients may benefit from resuming every 4-week dosing (approximately every 28 days +/- 7 days).¹

†Extended dosing intervals (8 mg once every 20 weeks, +/- 1 week) may be considered after 1 year of successful response based on visual and anatomic outcomes.¹

*Some patients saw vision improvement at Week 12 in Wet AMD (exploratory endpoint): FAS at baseline. FAS; observed values at Week 12: EYLEA HD Q16W +5.8 letters (n=330), EYLEA HD Q12W +5.5 letters (n=328), aflibercept 2 mg Q8W +6.6 letters (n=327).²

DISCOVER MORE ABOUT EYLEA HD



IMPORTANT SAFETY INFORMATION

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 (IOP) have been seen within 60 minutes of intravitreal injection, including with EYLEA HD and EYLEA. Sustained increases in IOP have also been reported after repeated intravitreal dosing with VEGF inhibitors. IOP 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 ATEs in the Wet AMD study from baseline through week 96 was 1.8% (12 out of 673) in the combined group of patients treated with EYLEA HD compared with 3.3% (11 out of 336) in patients treated with EYLEA 2 mg.
 - EYLEA: The incidence of reported ATEs 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.

ADVERSE REACTIONS

- **EYLEA HD:** The most common adverse reactions (≥3%) reported in patients receiving EYLEA HD were cataract, conjunctival hemorrhage, corneal epithelium defect, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, retinal hemorrhage, vision blurred, vitreous detachment, and vitreous floaters.
- **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.

Please see brief summary of full Prescribing Information for EYLEA HD and EYLEA on the following page.

BCVA, best-corrected visual acuity; ETDRS-DRSS, Early Treatment Diabetic Retinopathy Study-Diabetic Retinopathy Severity Scale; FAS, full analysis set; ICE, intercurrent event; OCT, optical coherence tomography; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; Q16W, every 16 weeks; Q20W, every 20 weeks; VEGF, vascular endothelial growth factor.

References: 1. EYLEA HD full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. April 2026. 2. Data on file. Regeneron Pharmaceuticals, Inc. 3. Lanzetta P, Korobelnik JF, Heier JS, et al; PULSAR Study Investigators. Intravitreal aflibercept 8 mg in neovascular age-related macular degeneration (PULSAR): 48-week results from a randomised, double-masked, non-inferiority, phase 3 trial. *Lancet*. 2024;403(10432):1141-1152. doi:10.1016/S0140-6736(24)00063-1

EYLEA HD® (afibercept) Injection 8 mg, for intravitreal use AND EYLEA® (afibercept) 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 afibercept 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 afibercept 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* (2.7 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* (2.7 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 96 was 1.8% (12 out of 673) in the combined group of patients treated with EYLEA HD compared with 3.3% (11 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 96 was 6.7% (33 out of 491) in the combined group of patients treated with EYLEA HD compared with 7.2% (12 out of 167) in patients treated with EYLEA 2 mg. The incidence of reported thromboembolic events in the RVO study (QUASAR) from baseline to week 36 was 0.5% (3 out of 591) in the combined group of patients treated with EYLEA HD compared with 1.7% (5 out of 301) 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 1755 patients were treated with EYLEA HD and 804 patients were treated with EYLEA 2 mg in three clinical studies. The most common adverse reactions reported in ≥3% of patients treated with EYLEA HD were cataract, conjunctival hemorrhage, corneal epithelium defect, intraocular pressure increased, ocular discomfort/eye pain/eye irritation, retinal hemorrhage, vision blurred, vitreous detachment, and vitreous floaters.

• **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 (AMD)

EYLEA HD: The data described below reflect exposure to EYLEA HD administered every 12 weeks (HDq12). EYLEA HD administered every 16 weeks (HDq16), or EYLEA 2 mg administered every 8 weeks (2q8) in 1009 patients with Wet AMD, in 1 double-masked, controlled clinical study (PULSAR) for 96 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

Adverse Reactions	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	
	EYLEA HDq12 (n=335)	EYLEA HDq16 (n=338)	EYLEA 2q8 (n=336)	Active Control (ranibizumab) (n=1824)	Control (ranibizumab) (n=595)	EYLEA (n=1824)	Control (ranibizumab) (n=595)
Cataract ^a	10%	10%	10%	7%	7%	13%	10%
Vision blurred ^a	9%	9%	8%	2%	2%	4%	3%
Intraocular pressure increased ^a	5%	4%	3%	5%	7%	7%	11%
Conjunctival hemorrhage ^a	3%	3%	3%	25%	28%	27%	30%
Ocular discomfort/eye pain/eye irritation ^a	3%	4%	4%	-	-	-	-
Vitreous floaters ^a	2%	6%	5%	6%	7%	8%	10%
Vitreous detachment ^a	2%	4%	2%	6%	6%	8%	8%
Corneal epithelium defect ^a	3%	3%	4%	4%	5%	5%	6%
Retinal hemorrhage	5%	6%	6%	-	-	-	-
Dry eye ^a	3%	3%	5%	-	-	-	-
Intraocular inflammation ^a	2%	1%	2%	2%	3%	3%	4%
Retinal pigment epithelial tear/ epitheliopathy ^a	2%	2%	2%	-	-	-	-
Vitreous hemorrhage	<1%	1%	1%	-	-	-	-
Retinal detachment ^a	1%	1%	<1%	<1%	<1%	1%	1%
Foreign body sensation in eyes ^a	1%	2%	2%	3%	4%	4%	4%
Ocular hyperemia ^a	1%	<1%	1%	4%	8%	5%	10%
Retinal pigment epithelial detachment ^a	1%	1%	3%	-	-	-	-
Eye pain	-	-	-	9%	9%	10%	10%

Detachment of the retinal pigment epithelium	-	-	-	3%	3%	5%	5%
Injection site pain	-	-	-	3%	3%	3%	4%
Lacrimation increased	-	-	-	3%	1%	4%	2%
Retinal pigment epithelium tear	-	-	-	2%	1%	2%	2%
Injection site hemorrhage	-	-	-	1%	2%	2%	2%
Eyelid edema	-	-	-	1%	2%	2%	3%
Corneal edema	-	-	-	1%	1%	1%	1%

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

^aRepresents grouping of related terms in PULSAR

Adverse drug reactions (ADRs) reported in <1% of participants treated with EYLEA HD were lacrimation increased, eyelid edema, hypersensitivity (includes adverse events of rash, urticaria, pruritus), 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 afibercept. 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 afibercept (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).
- Scleritis.

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. Afibercept 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 afibercept) 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 afibercept [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, afibercept 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, sternalbrae, 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. Afibercept 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 afibercept 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 afibercept 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. Afibercept 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 afibercept) 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 the EYLEA HD clinical studies, approximately 66% (1156/1755) of the patients in the HD groups were 65 years of age or older and approximately 31% (543/1755) of the patients were 75 years of age or older. No overall differences in safety or effectiveness of EYLEA HD have been observed.

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 overdose, 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* (6.1)]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

REGENERON®

Manufactured by: Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road, Tarrytown, NY 10591-6707

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Musings on the outlook for bevacizumab

It's hard to believe that about 20 years ago, the anti-VEGF revolution caught fire with the rapid adoption of off-label intravitreal bevacizumab. As a fellow, I remember the excitement of seeing the dramatic response for the first time ever in wet age-related macular degeneration. Despite the passage of time, bevacizumab continues to be widely used and commonly mandated by insurers with step therapy.

On July 24, 2026, Outlook Therapeutics announced the FDA-approval of bevacizumab-vikg (Lytenava) for the treatment of wet AMD. On one hand, we now have an on-label formulation of bevacizumab that has been specifically vetted for intravitreal use. On the other hand, there are major concerns about how this will impact access to compounded bevacizumab and costs for patients, practices and the overall health-care system.

With an FDA-approved version, will compounding pharmacies be prohibited from repackaging our usual bevacizumab (Avastin, Genentech)? My guess is no, at least not in the near term.

First off, bevacizumab-vikg is only approved for wet AMD so we still need a source of bevacizumab for other retinal vascular disease indications. Secondly, there is no direct precedent where the FDA has shut down compounding in a similar situation. When there was a shortage of GLP-1 drugs, the FDA initially permitted pharmacies to compound the medication from its bulk components. Once the shortage was over, they essentially instructed pharmacies that they should no longer be producing the drug. However, in the case of bevacizumab, compounding pharmacies

aren't trying to recreate the reference product but are simply repackaging it.

The one issue that could be a threat to compounding pharmacies is that if a significant part of their business decreases due to a large portion of wet AMD patients migrating to bevacizumab-vikg, the per-syringe cost of compounded bevacizumab could go up due to decreased demand and poorer economies of scale, leading to a cycle of even less practice incentive to purchase it and further rising repackaged drug cost.

What about cost and how this will impact our patients and practice? It's possible that commercial insurers may begin to require bevacizumab-vikg instead of the compounded version, especially if it's priced competitively in relationship to the other FDA-approved alternatives. In the United Kingdom, the per-dose cost is around \$600. Similarly, if reimbursement is favorable for practices from both commercial insurers and Medicare without being more onerous for patients, then physicians may be more likely to choose it. If these conditions aren't met, I imagine the speed of adoption may be much slower.

Regardless, it will be interesting to see how bevacizumab-vikg is incorporated into our ever-growing armamentarium of treatments for retinal disease.

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cover image: Getty Images

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



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INDICATIONS AND USAGE

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

Severe Vision Loss

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

Infectious Endophthalmitis

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

Retinal Tear and Detachment

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

Vitreous Hemorrhage

Vitreous hemorrhage, which may result in temporary vision loss, has occurred following ENCELTO implantation. Patients receiving antithrombotic medication (e.g., oral anticoagulants, aspirin, nonsteroidal anti-inflammatory drugs) may be at increased risk of vitreous hemorrhage. To reduce the risk of vitreous hemorrhage, interrupt antithrombotic medications prior to the ENCELTO implantation. Vitrectomy surgery may be necessary to clear severe,

recurrent, or non-clearing vitreous hemorrhage. If the patient has a late onset vitreous hemorrhage (greater than one year following ENCELTO implantation surgery), examine the ENCELTO implantation site for possible implant extrusion. If implant extrusion has occurred, surgically reposition ENCELTO.

Implant Extrusion

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

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

Cataract Formation

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

Suture Related Complications

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

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

Delayed Dark Adaptation

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

ADVERSE REACTIONS

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

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

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



neurotech

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BRIEF SUMMARY OF PRESCRIBING INFORMATION

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

See full Prescribing Information for ENCELTO.

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

Initial U.S. Approval: 2025

INDICATIONS AND USAGE

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

DOSAGE AND ADMINISTRATION

Recommended Dose

For intravitreal implantation only

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

CONTRAINDICATIONS

ENCELTO is contraindicated in patients with:

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

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ADVERSE REACTIONS

Clinical Trials Experience

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

ADVERSE REACTIONS (cont'd)

Clinical Trials Experience (cont'd)

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

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

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

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

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

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

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Data

Animal Data

See *Risk Summary* for details on data.

Lactation

Risk Summary

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

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

Pediatric Use

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

Geriatric Use

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

Manufactured for:

Neurotech Pharmaceuticals, Inc.
Cumberland, RI 02864

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US-EO-PM-250200024 04/2025

When a social media follow becomes a boundary problem

How to handle the doctor-patient relationship in an omni-connected world.

By Jayanth Sridhar, MD



The recent story of Vaibhav Duggal, a third-year medical student who died by suicide after facing a school disciplinary process for reported unprofessional behavior, including following a patient on Instagram shortly after an encounter, is first and foremost a tragedy.¹ A young person is gone, a family is grieving, and the institutional details will likely be debated for some time. But beyond the most devastating part of the story lies a broader issue medicine must increasingly confront: What does it mean when a physician, trainee or other health professional follows a patient on social media?

For most of modern medicine, professional boundaries were easier to visualize. The clinical relationship occurred in the exam room, the hospital, the operating room or by telephone. Physicians had personal lives, but those lives weren't usually visible to patients in real time, outside of chance encounters in the community. Social media has changed that. A patient can find a doctor's Instagram account within seconds. A doctor can see a patient's public posts just as easily. A follow request, direct message, "like" or comment may feel casual online, but it doesn't necessarily feel casual within the patient-physician relationship.

That distinction matters because medicine isn't a relationship between equals in the ordinary social sense. Patients disclose intimate information, undergo physical examinations and place trust in physicians at vulnerable moments. Even when a physician's intent is innocent, the patient may experience online contact differently. A follow after a clinical encounter may be interpreted as curiosity, friendliness, marketing, flirtation, surveillance or something more intrusive. The ambiguity itself is the problem. Boundaries exist not only to prevent intentional misconduct, but also to

prevent situations where intent and perception diverge.

Professional guidance already recognizes this concern. The American College of Physicians and the Federation of State Medical Boards have advised physicians to keep professional and personal online identities separate and avoid "friending" or contacting patients through personal social media.² The AMA Code of Medical Ethics similarly emphasizes that physicians who interact with patients online must maintain appropriate boundaries and should consider separating personal and professional content.³ Medical communication, when it occurs electronically, should take place within an established patient-physician relationship, with patient consent, and in a way that can be documented in the medical record.

The practical reality, however, is becoming more complicated. Younger physicians and trainees have grown up in a world where social media is part of daily life. Patients routinely search for physicians online. Physicians use Instagram, TikTok, LinkedIn, X and other platforms for education, advocacy, recruitment, networking and practice building. The answer can't be that doctors should disappear from social media. The answer is that boundaries must be clearer.

A reasonable framework starts with basic rules: Don't initiate personal social media contact with patients; don't follow them from a personal account; don't send friend requests; and don't review their profiles without a clear clinical, legal or safety-related reason. If patients send medical questions through social media, redirect them to the patient portal, office phone or another approved clinical channel. If educational content is posted online, it should remain general rather than individualized.

(Continued on page 37)

BIO

Dr. Sridhar is an associate professor of clinical ophthalmology at Bascom Palmer Eye Institute, Miami.

DISCLOSURES

Dr. Sridhar is a consultant to Alcon, DORC, Genentech/Roche and Regeneron Pharmaceuticals.



Foreign body removal

Pearls for removing IOFBs while minimizing trauma to ocular structures.

Intraocular foreign body injuries present unique challenges that require precise and careful intervention to optimize visual outcomes and prevent complications. The goal of IOFB removal is to safely extract the foreign object while minimizing trauma to ocular structures and controlling potential complications, such as endophthalmitis or retinal detachment. Here, we present a step-by-step approach to effectively manage and remove intraocular foreign body, along with cataract extraction and IOL insertion.

Preoperative Strategies

Thorough preoperative imaging, including CT or ultrasound B-scan, is essential to determine the exact location, size and composition of the foreign body. Detailed imaging can guide the surgical plan, helping identify potential risks and inform the choice of approach and instruments. In some cases the IOFB may not be visualized on clinical examination, hence meticulous search for the IOFB is paramount intraoperatively. When there is a coexisting traumatic cataract, the preoperative and intraoperative approach

View the Video

Go to <https://vimeo.com/1215793631> or scan the QR code.



should be aimed at removal of the cataract and intraocular foreign body along with intraocular lens insertion using minimal steps, avoiding complications.

Intraoperative Strategies

1. Secure the infusion port: Ensuring a stable infusion system is critical for maintaining IOP throughout the procedure.

2. Main tunnel creation: Establish a primary tunnel for cataract removal, IOFB removal and IOL placement. Creating this entry early provides a reliable route for foreign body extraction.

3. Early cataract removal: If a cataract is present, it should be removed early in the procedure to enhance visualization. Care must be taken to keep the sulcus intact for subsequent IOL placement.

4. Vitrectomy and PVD induction: Perform a thorough vitrectomy with posterior vitreous detachment induction, assisted by triamcinolone acetate, to clear the vitreous and improve access.

5. Identifying the IOFB impaction site: Locating the exact site of IOFB impact is crucial; and the IOFB may be found near the site of impaction.

(Continued on page 37)

Naresh Babu Kannan, MS FNB MBA FASRS, Muthu Krishnan V, MS, and Athul Puthalath, MS



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Muthu Krishnan, V, MS



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Disclosures

The authors have no relevant disclosures.

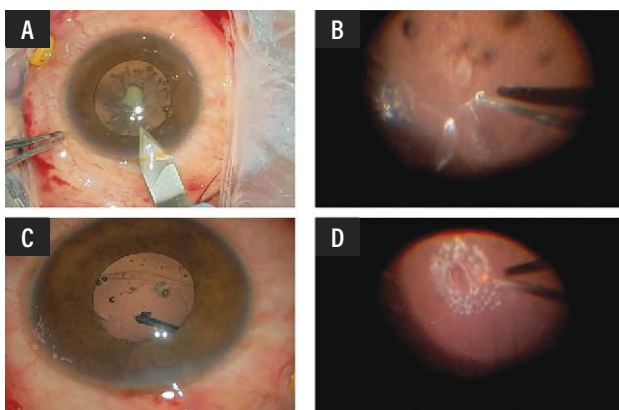


Figure 1. Main tunnel for cataract extraction, IOFB removal and IOL insertion (A). The IOFB impaction site is identified and pars plana vitrectomy is completed (B). The IOFB is then brought to the anterior chamber and removed with intraocular magnet (C). Barricade laser retinopexy is done around the impaction site (D).

Vit-Buckle Society 2026: strategies for complex cases

A roundup of this year's surgical debates and complex case session, including techniques, controversies and lessons to bring back to the OR.



Shreya
Swaminathan, MD



Ashley Zhou, MD



Vishal B.
Swaminathan, MD

By Shreya Swaminathan, MD, Ashley Zhou, MD, and Vishal B. Swaminathan, MD

The 14th Annual Vit-Buckle Society meeting brought retina specialists to Las Vegas with a “VBS in Wonderland” theme. This summary covers Session 9, which presented complex surgical cases and techniques, and Session 14, where surgeons debated controversial topics.

Session 9: Surgical Cases & Scientific Papers “Sometimes I’ve believed as many as six impossible things before breakfast.”

Moderators: Dean Elliott, MD & Gabriela Lopez Carasa, MD

Session 9 invited surgeons to present challenging cases and the techniques they used to manage them. The format highlights what worked, what didn’t, and what leaders in the field would do differently in difficult cases.

• Von Hippel-Lindau disease: capillary hemangioma–associated retinal detachment.

Lucas Zago, MD opened the session with a case of a 29-year-old woman with bilateral retinal capillary hemangiomas from Von Hippel-Lindau disease who presented with a tractional retinal detachment and hand motion vision. After treating the patient with preoperative anti-VEGF, Dr. Zago proceeded with a combined phacoemulsification and pars plana vitrectomy. He highlighted an iatrogenic break during the peeling process that prompted an extended superior retinectomy,

as well as the need for endodiathermy to control an intraoperative bleed from the tumor. Vision reached 20/80 by month two and drifted to 20/200 by month nine.

Takeaway: Dr. Zago’s case emphasizes how residual hyaloid often hides beneath tractional membranes in VHL, and finding and addressing this may prevent re-detachment of the retina.

• What a mass! Exoresection for giant choroidal melanoma.

Yu-Bai Chou, MD, PhD described a globe-sparing transscleral resection technique in a 36-year-old woman with a giant (22.5 × 11.2 × 12.5 mm) choroidal melanoma and associated retinal detachment. With the patient electing to avoid enucleation, and radiotherapy not feasible at this size, Dr. Chou performed a posterior lamellar sclerouvectomy using a partial-thickness scleral flap and controlled suprachoroidal dissection for en bloc removal of the tumor, followed by a pars plana vitrectomy with silicone oil tamponade. At four years after resection, following oil removal and cataract surgery, the patient had 20/25 vision and, more importantly, globe preservation.

Takeaway: Dr. Chou showed the audience how globe-sparing exoresection is technically demanding but a viable alternative to enucleation in select patients with giant uveal melanomas. The audience voiced concerns regarding seeding of the orbit given exposure of the tumor cells to the orbital

BIOS

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Dr. Vishal Swaminathan is a vitreoretinal surgery fellow at the University of Wisconsin-Madison.

space during resection, but at this time, no recurrence had been noted.

• ***Into the rabbit hole: Macular hole repair in complex myopic detachment.***

Aristomenis Thanos, MD presented a case of a highly myopic 62-year-old with a total macula-off retinal detachment with an inferonasal break and macular hole (VA 20/400). Dr. Thanos began the case with a combined phacoemulsification and pars plana vitrectomy, using a flex loop to help clear the adherent cortical vitreous. The posterior hyaloid was carefully addressed to release residual traction, and an amniotic membrane graft was positioned over the macular hole using preoriented markings. The retina remained stable after silicone oil removal, with graft removal planned.

Takeaway: In patients with high myopia and a macular hole with associated rhegmatogenous retinal detachment, amniotic membrane graft may be feasible to close the macular hole with concurrent RRD repair.

• ***Retinal redemption: Turning chaos into closure.***

Bruna Gil Ferreira, MD, walked the audience through a series of chronic macula-off detachments with full-thickness macular holes and severe proliferative vitreoretinopathy. Dr. Ferreira described a case of a young patient with recurrent detachment where she began the repair with dissection of pre-retinal membranes using forceps and vertical scissors to release traction and mobilize the retina. After extensive PVR removal and a retinectomy, a free autologous retinal flap was created and positioned over the macular hole. Perfluorocarbon liquid stabilized the retina and guided flap placement before fluid-air exchange. Early imaging showed flap stabilization.

Takeaway: Dr. Ferreira highlighted how free autologous flaps are a great treatment method for treatment-refractory macular holes in advanced PVR, but functional recovery remains variable in published series.

• ***Surgical management for complex***

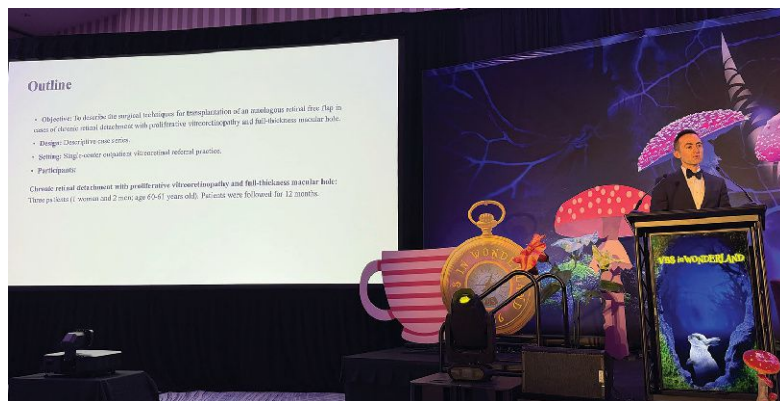


Image Credit: Matthew Starr, MD

Tarek Alasil, MD, discussed several cases pairing relaxing retinectomy with autologous retinal transplant. He found that in complex, macular hole-associated RD, tangential traction can undermine the success of the graft, underlining the need for the relaxing retinectomy.

retinal detachment with PVR and macular hole using relaxing retinectomy and autologous retinal transplantation.

Tarek Alasil, MD, presented a series of complex detachment cases pairing relaxing retinectomy with autologous retinal transplantation. He presented a case of a patient who re-detached following a prior scleral buckle, in which extensive membrane peeling was conducted before he harvested an autologous graft and positioned it under perfluorocarbon over the macular hole with a flex loop. Endolaser was used to seal the donor site and a relaxing retinectomy released persistent traction. The patient had a good outcome with visual improvement. Additional cases showed modest but meaningful functional recovery.

Takeaway: In complex macular hole-associated retinal detachments, tangential traction can undermine the success of an autologous retinal graft, emphasizing the need for relaxing retinectomies.

• ***Macular hole management without tamponade.***

Audrey Juan, MD, presented a gas-free approach to macular hole repair. After standard pars plana vitrectomy and ILM staining, she created a temporal ILM flap for large and extra-large holes. In place of gas, dispersive viscoelastic was layered over the flap at a low IOP to stabilize the flap. In her case series, six-month closure rates matched conventional gas tamponade, with faster early visual recovery in the no-gas group.

Takeaway: Viscoelastic over an ILM flap without gas may be a feasible option as more data is collected.

The prosthetic capsular bag highlights the possibility of allowing a variety of IOLs to be chosen, with flexible transscleral fixation arms that accommodate a range of axial lengths, in addition to integrated posterior vitrectomy ports.

• ***First-in-human outcomes of a sutureless, scleral-fixed, prosthetic capsular bag.***

Frank L. Brodie, MD, MBA, reported early outcomes with a sutureless scleral-fixed prosthetic capsular bag for secondary intraocular lens fixation. The device highlights the possibility of allowing a variety of IOLs to be chosen by the surgeon with flexible transscleral fixation arms that accommodate a range of axial lengths, in addition to integrated posterior vitrectomy ports. Across a 15-eye prospective series, there were no conjunctival erosions or IOL dislocations apart from a single footplate displacement in a patient with Marfan syndrome. Imaging showed stable centration with less tilt than Yamane fixation, approaching in-the-bag results.

Takeaway: A prosthetic bag may offer a more standardized solution for dislocated IOLs, with encouraging early data.

• ***Predictors of anatomic and functional success with amniotic membrane grafting for complex macular holes.***

Scott D. Walter, MD, MSc, FASRS, presented a seven-year, single-surgeon retrospective case series on complex macular hole repair. He emphasized how there's no universal approach to treatment and how intraoperative surgeon judgment should inform surgical technique. Use of silicone oil correlated with higher rates of complete and type 1 closure. Fibrin glue improved graft stability, particularly in complex or highly myopic eyes. Aggressive fluid-air exchange, by contrast, raised the risk of graft displacement.

Takeaway: For refractory holes, favor preretinal placement of amniotic membranes and use of silicone oil and fibrin glue, while avoiding aggressive fluid-air exchange that dislodges the graft.

• ***Outcomes of eyes with concurrent suprachoroidal hemorrhage and retinal detachment: A multicenter study.***

Tianyu Liu, MD, presented a two-center

retrospective study of eyes with concurrent suprachoroidal hemorrhage and retinal detachment from 2013 to 2022. At six months, visual outcomes were modest, with about 60 percent of eyes achieving reattachment overall. Rhegmatogenous cases typically required surgery for anatomic success, while some non-rhegmatogenous cases resolved without intervention. Proliferative vitreoretinopathy was consistently associated with worse anatomic and visual outcomes.

Takeaway: Dr. Liu emphasized in his talk how patients with PVR and rhegmatogenous retinal detachment may have a guarded prognosis in cases with concurrent suprachoroidal hemorrhage.

Session 14: Surgical Retina Debates “I have an excellent idea! Let's change the subject.” *Moderators: Shilpa Desai, MD & Ella Leung, MD*

The Saturday debates featured surgeons with opposing positions on clinically meaningful surgical questions, with the audience weighing in at the end of each debate.

• ***How to manage endophthalmitis: Tap-and-inject vs. immediate vitrectomy.***

Samir N. Patel, MD, argued that tap-and-inject remains a practical first-line therapy in cases of endophthalmitis, citing modern data showing visual outcomes comparable to vitrectomy with lower procedural risk and broader accessibility. Maria H. Berrocal, MD, however, made the case for early vitrectomy, emphasizing rapid clearance of organisms, toxins and inflammatory mediators, with promising results due to early surgical intervention. Tap-and-inject narrowly took the room, 51 percent to 49 percent.

Takeaway: The Endophthalmitis Vitrectomy Study still guides practice for most cases, with a recent case series suggesting a lower threshold for early vitrectomy may result in better outcomes.

• ***Who can perform pediatric surgery: Specialty centers vs. all VR surgeons.***

(Continued on page 37)

New ways of monitoring success of GA treatments

Emerging methods to help capture the effects of current and future therapies for geographic atrophy.

By Shinichiro Chujo, MD, PhD, Alberto Quarta, MD, Srinivas R. Sadda, MD, FARVO

Take-home points

- » Conventional area-based metrics don't fully capture the clinical significance of geographic atrophy progression because they ignore lesion location and direction of expansion.
- » Emerging spatial biomarkers—including lesion front displacement, photoreceptor-adjusted front, and the GA Severity Score—provide complementary information beyond lesion area alone.
- » Incorporating spatial characteristics of GA progression may improve treatment monitoring, risk stratification and personalized management in the era of complement inhibition.

Geographic atrophy is a leading cause of irreversible vision loss worldwide.^{1,2} Affecting more than 5 million individuals globally, its prevalence is expected to increase with the aging of the population.³ Though the pace can vary, GA enlarges progressively and irreversibly, ultimately causing substantial visual impairment when the lesion involves the fovea.⁴ Recent advances, including the approval of complement inhibitors and the development of gene therapies, have made slowing GA progression a realistic therapeutic goal.^{5–10}

Consequently, accurate assessment of disease progression has become increasingly important. However, many clinical trials have demonstrated only a modest association between structural outcomes, such as the rate of GA enlargement, and functional outcomes, including visual acuity.¹¹ One possible explanation is that conventional metrics, which primarily quantify GA lesion area, don't adequately account for lesion location, direction of expansion or morphological characteristics.

For example, two eyes may exhibit the same increase in lesion area yet have markedly different effects on visual function depending on whether the lesion expands toward the fovea or into the more peripheral retina. Accordingly, increasing attention has been directed toward novel imaging biomarkers and analytical approaches that incorporate not only lesion size but also the spatial characteristics of GA progression.

Advantages of Assessing GA by Lesion Front Displacement

Traditionally, GA progression has been assessed using metrics such as total lesion area, square root-transformed lesion area and lesion perimeter.^{1,12–17} While these measures are useful for quantifying the overall extent of atrophy, they are influenced by lesion morphology and changes in lesion configuration. For example, lesions with identical rates of marginal expansion may exhibit different rates of area enlargement depending on their shape. Likewise, mergers between multiple individual atrophic foci or the emergence of new atrophic foci



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BIOS

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Dr. Quarta is a clinical and research fellow at the Doheny Eye Institute

Dr. Sadda is a professor of ophthalmology at the Doheny Eye Institute, and principal investigator for the Doheny Image Reading and Research Lab. He's the incoming chair of ophthalmology at Duke University. He consults for Apellis, Alkermes, Aavantgarde, ONL, Amgen, Abbvie, Alexion, Alnylam, Samsung Bioepis, Biogen, Boehringer Ingelheim, IvericBio/Astellas, iCare/ Centervue, Eyepoint, EyeStem, Novartis, Roche/ Genentech, Bayer, Regeneron, Pfizer, Nanoscope, Janssen, Optos, Oyster Point, Heidelberg, Ikerian, NotalVision, Topcon, Eyepoint, Surrozen, Character, Ocular Therapeutics and Neurotech.

Treat Today For Tomorrow, Tomorrow, and Tomorrow



Study design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multicenter, 2-year, Phase 3, randomized, double-masked trials. Patients with GA (atrophic nonexudative age-related macular degeneration), with or without subfoveal involvement, secondary to AMD were randomly assigned (2:2:1:1) to receive 15 mg/0.1 mL intravitreal SYFOVRE monthly, SYFOVRE every other month, sham monthly, or sham every other month for 2 years. Change from baseline in the total area of GA lesions in the study eye (mm²) was measured by FAF. SYFOVRE was also assessed in GALE, a 3-year, open-label extension study evaluating the incidence and severity of ocular and systemic AEs, and change from baseline in total area of GA lesion(s) in the study eye (mm²).^{1,3,5}

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

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INDICATION

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

IMPORTANT SAFETY INFORMATION CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

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

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

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



Start protecting your patients' tomorrows at TreatGAtoday.com

SYFOVRE[®]
(pegcetacoplan injection)
15mg / 0.1mL

- **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 $\geq 5\%$) are ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, conjunctival hemorrhage.

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



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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Ocular or Periocular Infections

SYFOVRE is contraindicated in patients with ocular or periocular infections.

Active Intraocular Inflammation

SYFOVRE is contraindicated in patients with active intraocular inflammation.

Hypersensitivity

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

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

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

Retinal Vasculitis and/or Retinal Vascular Occlusion

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

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

Increased Intraocular Pressure

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

ADVERSE REACTIONS

Clinical Trials Experience

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

A total of 839 patients with GA in two Phase 3 studies (OAKS and DERBY) were treated with intravitreal SYFOVRE, 15 mg (0.1 mL of 150 mg/mL solution). Four hundred nineteen (419) of these patients were treated in the affected eye monthly and 420 were treated in the affected eye every other month. Four hundred seventeen (417) patients were assigned to sham. The most common adverse reactions (≥5%) reported in patients receiving SYFOVRE were ocular discomfort, neovascular age-related macular degeneration, vitreous floaters, and conjunctival hemorrhage.

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

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

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:

Ocular discomfort included: eye pain, eye irritation, foreign body sensation in eyes, ocular discomfort, abnormal sensation in eye
Neovascular age-related macular degeneration included: exudative age-related macular degeneration, choroidal neovascularization
Punctate keratitis included: punctate keratitis, keratitis
Intraocular inflammation included: vitritis, vitreal cells, iridocyclitis, uveitis, anterior chamber cells, iritis, anterior chamber flare

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

Postmarketing Experience

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

Systemic exposure of SYFOVRE following ocular administration is low. Subcutaneous administration of pegcetacoplan to pregnant monkeys from the mid gestation period through birth resulted in increased incidences of abortions and stillbirths at systemic exposures 1040-fold higher than that observed in humans at the maximum recommended human ophthalmic dose (MRHD) 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 MRHD.

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.

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can alter lesion perimeter, complicating the interpretation of growth rates.^{18,19}

To address these limitations, our group proposed a novel metric, termed the GA lesion front displacement.²⁰ Rather than quantifying changes in lesion area, this approach directly measures the distance that the atrophic border advances over time. Similar to measuring the retreat of a coastline, lesion front displacement focuses on the movement of the lesion margin itself rather than the total area affected (*Figure 1*).

This approach offers several potential advantages. First, because it directly measures border advancement, it's less dependent on lesion shape and is therefore more robust in the presence of merging multifocal lesions or changes in lesion morphology. Second, it enables localized assessment of disease progression, allowing regional differences in lesion expansion to be quantified rather than averaged across the entire lesion. Finally, it allows for the expansion of the lesion to be more easily adjusted for location of the border and the direction of expansion. Importantly, by evaluating progression at the lesion border, lesion front displacement may provide a more sensitive metric for assessing treatment response in individual patients. Taken together, lesion front displacement complements conventional area-based metrics and represents a more direct, morphology-independent approach to quantifying GA progression.

A Photoreceptor Density-Based Approach to Evaluating Geographic Atrophy Progression

The value of lesion front displacement extends beyond quantifying the rate of lesion enlargement. By analyzing the direction of lesion expansion and the retinal region into which the lesion advances, this approach may provide insights into the biological mechanisms underlying GA progression. Previous studies have demonstrated that GA tends to progress more rapidly toward the peripheral retina than toward the fovea, and that eyes with foveal-sparing

GA preferentially exhibit peripheral expansion.²¹ However, the biological basis for this directional pattern remains poorly understood. To investigate this question, our group recently examined the relationship between GA progression and the spatial distribution of retinal photoreceptors.²² In the human retina, cone photoreceptors are most densely concentrated at the fovea, whereas rod photoreceptors reach peak density in the parafoveal region. As a result, total photoreceptor density exhibits a characteristic topographic distribution across the macula.

Based on histological photoreceptor density data, we generated a theoretical photoreceptor density map (*Figure 2*) and developed a novel metric, termed photoreceptor-adjusted front, in which lesion front displacement is normalized according to the local photoreceptor density.

Using the conventional front displacement metric, lesion expansion appeared to occur preferentially toward the peripheral retina. However, after adjustment for photoreceptor density, this directional difference was markedly attenuated. Furthermore, the directional variability of lesion

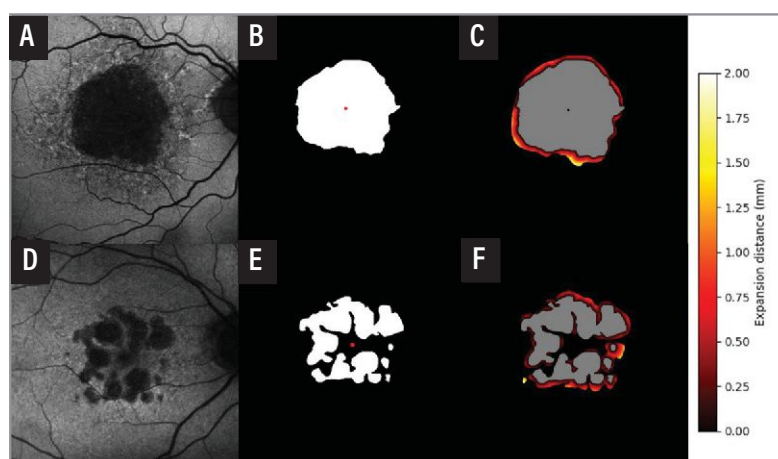


Figure 1. Workflow for calculating geographic atrophy lesion front displacement. Original fundus autofluorescence image (A). Binary GA lesion mask generated using the Spectralis Region Finder (B). Heatmap of lesion margin expansion generated using a Euclidean distance map (C). In eyes with multifocal GA, each lesion was segmented and divided into 12 clock-hour sectors, allowing quantification of the overall directional pattern of lesion expansion (D-F). Adapted from: Chujo et al. *Ophthalmol Sci.* 2026;6(7):101198.

progression was also reduced, suggesting that at least part of the apparent directional preference of GA expansion may be explained by the nonuniform spatial distribution of retinal photoreceptors. These findings demonstrate that incorporating retinal cellular architecture into structural imaging analyses may provide new biological insights into GA progression and may complement conventional approaches based solely on lesion enlargement.

A Severity Score Beyond Lesion Area

Lesion area remains the most widely used metric for assessing GA progression. However, the clinical significance of lesion enlargement isn't determined solely by its size. Two eyes may exhibit the same increase in lesion area yet have markedly different functional consequences depending on where the lesion expands. For example, enlargement toward the peripheral retina is likely to have a different impact on visual function than enlargement toward the fovea. Nevertheless, conventional area-based metrics treat both scenarios as an equivalent increase in lesion size. To address this

limitation, our group recently proposed a novel GA Severity Score inspired by the concept of the Hill of Vision (HOV) (*Figure 3*).²³

Rather than evaluating lesion area alone, this approach incorporates the spatial relationship between the lesion and the fovea by assigning greater weight to atrophy occurring closer to the foveal center. Importantly, the GA Severity Score isn't a direct measure of visual function. Instead, it provides a spatially-weighted structural assessment that captures aspects of disease severity not reflected by lesion area alone. By incorporating lesion location into the evaluation of GA progression, this metric may better represent the potential functional impact of lesion enlargement. Although further validation against visual acuity, microperimetry and other functional outcomes is needed, the GA Severity Score may serve as a valuable complementary biomarker for monitoring disease progression and evaluating treatment response.

Future Perspectives for GA Management

The introduction of complement inhibitors has marked a major turning point in the management of GA. Rather than simply documenting lesion enlargement, clinicians are now increasingly required to determine which patients are most likely to benefit from treatment and whether therapy is effectively altering the course of disease.

Meeting these challenges will require more than conventional area-based measurements. Evaluating where the lesion is expanding and which retinal regions are being affected may provide clinically meaningful information beyond lesion size alone. Lesion front displacement quantifies the direction and rate of lesion expansion, photoreceptor-adjusted front incorporates the underlying retinal cellular architecture and the GA Severity Score reflects the spatial importance of lesion location relative to the fovea. Together, these complementary

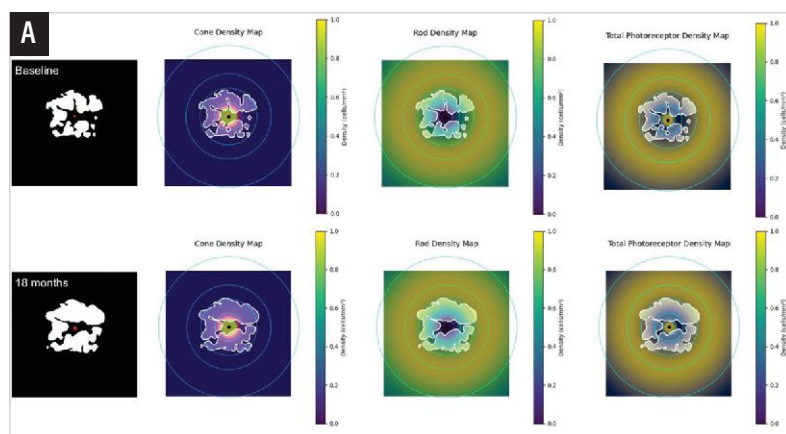


Figure 2. Spatial assessment of geographic atrophy progression using photoreceptor density maps. Cone, rod and total photoreceptor density maps generated from published histological data were overlaid with baseline and 18-month GA lesion masks. The red dot indicates the foveal center. Lesion expansion was quantified according to the underlying photoreceptor density distribution by measuring both Δ photoreceptor loss and Δ GA area within concentric rings centered on the fovea. This approach enables evaluation of GA progression based not only on lesion enlargement but also on the retinal cellular environment into which the lesion expands. Adapted from: Chujo et al. *Ophthalmol Sci.* 2026;6(7):101198.



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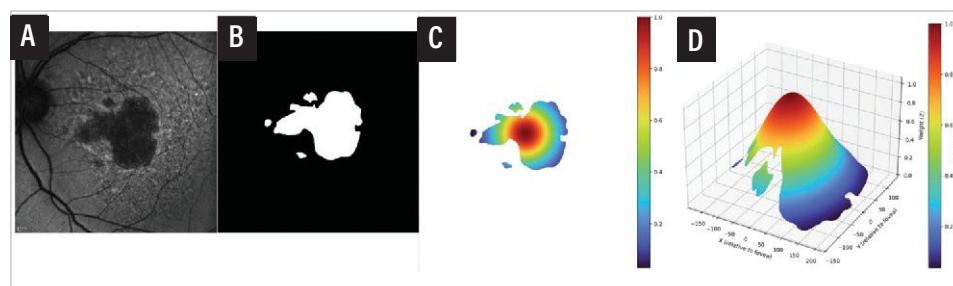


Figure 3. Generation of hill of vision-inspired severity maps from fundus autofluorescence images of geographic atrophy. Fundus autofluorescence image (A). Binary GA lesion mask (B). Two-dimensional severity heatmap generated by Gaussian weighting of GA lesion pixels (C). Three-dimensional visualization of the GA Severity Score (D). Warmer colors indicate greater lesion severity. Adapted from: Chujo S, et al. *Graefes Arch Clin Exp Ophthalmol*. 2026.

approaches have the potential to improve assessment of disease progression and treatment response by capturing information that's not reflected in lesion area alone.

Looking ahead, integration of these imaging biomarkers with artificial intelligence-based prediction models may enable more accurate risk stratification, individualized treatment planning and earlier identification of eyes at greatest risk for vision loss. Although these methods remain investigational and require further clinical validation, they highlight an important shift in the evaluation of GA—from measuring how much atrophy has developed to understanding where and how it's progressing. This spatially informed approach may ultimately contribute to more personalized and clinically meaningful management of patients with GA. ^{RS}

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Stem cell therapies for retinal diseases: Recent trials

A look at the approaches in the research pipeline for protecting the retina or replacing damaged cells.

By Thomas Su, BS, Michael Pan, BS,
Juliette E. McGregor, PhD, and Amir H. Kashani, MD, PhD

Take-home points

- » Currently, there's no way to restore tissue lost to retinal degenerative diseases, so treatment primarily aims to slow progression; stem cell therapy is being explored as a way to replace damaged cells and slow progression.
- » Clinical studies suggest that RPE transplantation is generally safe and feasible, with cell suspensions and RPE sheets/scaffolds showing signs of anatomical survival and occasional visual improvement, though the exact mechanism and durability of benefit remain uncertain.
- » Photoreceptor replacement is very early in development but is progressing through preclinical work and early trials; overall, the field is promising, but larger randomized studies with longer follow-up are needed.

Retinal degenerative diseases such as dry age-related macular degeneration, retinitis pigmentosa and Stargardt macular dystrophy are characterized by retinal pigment epithelium atrophy and photoreceptor loss.¹ Current strategies for the treatment of these conditions focus on preserving existing vision and slowing disease progression. While conservative strategies such as nutritional supplementation and optimization of lifestyle factors remain the cornerstone of management in many cases, there are a number of emerging pharmacologic therapies such as complement inhibitors for AMD which have shown promising results.²⁻⁶ However, there are no effective treatments that can restore vision in patients with advanced disease who have already lost retinal tissue that supports vision.

Stem cell therapy is one promising option being explored for the treatment of such late-stage disease, with the intent of either protecting residual tissues via the release of trophic factors or replacing damaged cells.^{7,8} In this review, we'll discuss the de-

velopment of various stem cell therapies for retinal degenerative diseases (*Figure 1*) with a focus on clinical trials.

Background on cell therapy

Stem cells have the ability to self-renew indefinitely and to differentiate into multiple lineages. There are several potential sources of stem cells, including embryonic, fetal, and adult somatic cells.⁶ Human embryonic stem cells (hESCs) and fetal stem cells can be harvested from blastocysts and fetal tissue, respectively, but there are legal and ethical issues surrounding this process as well as a practical supply-demand problem.^{9,10} Stem cells have also been identified in other reservoirs in adults, such as the bone marrow (BM) or the umbilical cord (UC). These cell populations are more heterogeneous, but cells with specific identities can be isolated and expanded in culture.¹¹ Another possibility surfaced with discovery in the early 2000s that the introduction of a specific set of transcription factors could restore differentiation potential to terminal adult somatic cells. These induced pluripo-



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Stem Cell Therapies for Retinal Degenerative Diseases

Current strategies, clinical progress, and future directions

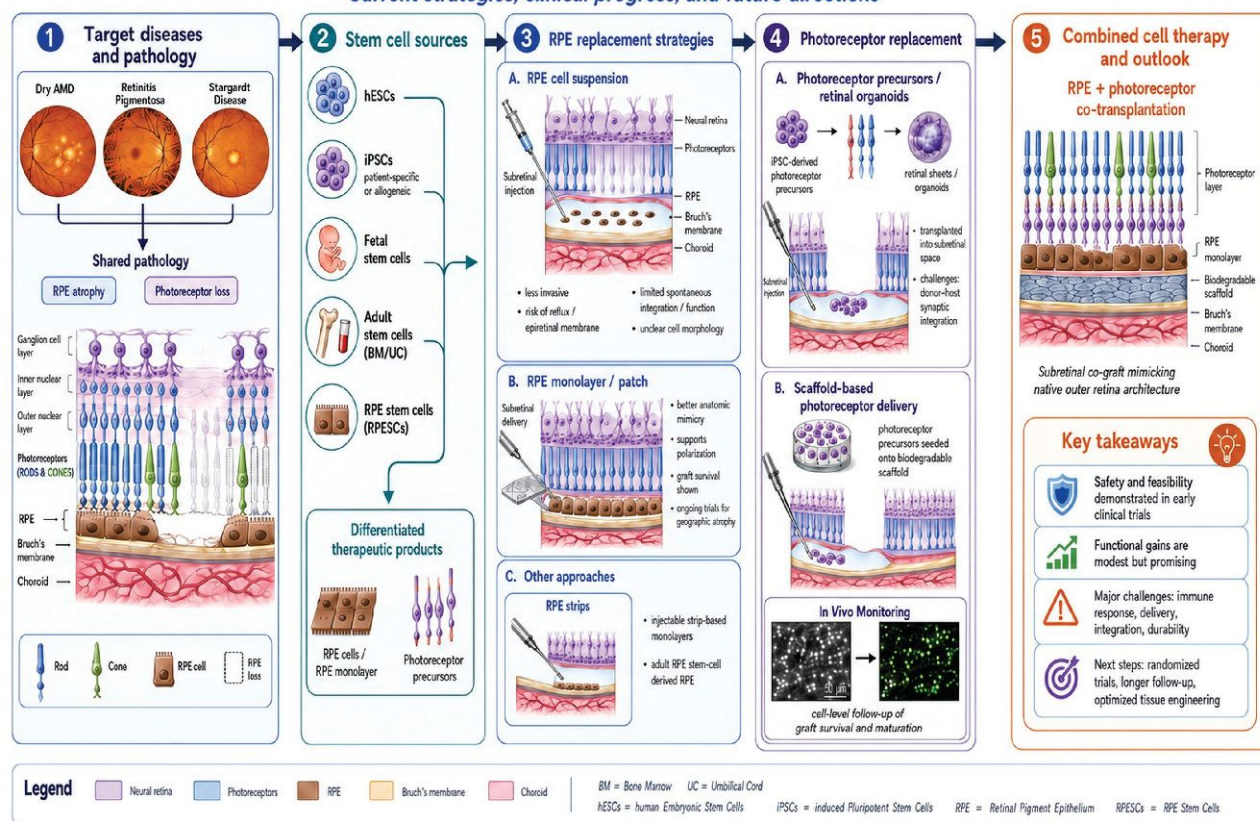


Figure 1. Summary of common sources, products and delivery methods used for stem cell therapies. Cell products include suspensions of specific expanded cell populations, discrete monolayers of retinal tissue (RPE and/or PRs) to mimic native anatomy and whole slabs of retinal organoid consisting of PRs with connected interneurons. (Created with assistance from ChatGPT-5.5.)

tent stem cells (iPSCs), typically generated from skin fibroblasts or blood cells, have become a less invasive and more accessible means of creating specific cell products for research and therapy.¹² Lastly, there's a subpopulation of RPE cells which are capable of self-renewal, termed RPE stem cells; these RPESCs can be directly expanded to generate RPE progeny without first undergoing induced de- and re-differentiation. This approach theoretically bypasses limitations of induction, including low efficiency rate and tumorigenic potential.^{13,14}

RPE transplantation

By way of a quick review, the RPE serves to maintain the blood-retinal barrier and support photoreceptor function by phagocytosing used outer segments and recycling photopigment.¹⁵ The RPE has been a pri-

mary focus of cell replacement strategies due to its laminar structure and importance in defining the retinal architecture and metabolism.⁶ There are two main methods by which therapeutic RPE cells may be introduced to the subretinal space: injection of a cell suspension or transplantation of a cellular monolayer (with or without an artificial scaffold). The former approach is less invasive and requires a smaller retinotomy, but several clinical trials have shown that RPE cell suspensions don't spontaneously form a normal monolayer in the subretinal space, and there's a greater risk of reflux into the vitreous cavity. In addition, RPE cells require adhesion to a substrate to fully polarize and differentiate. Therefore, the functional status of RPE cells in suspension is unclear. Implantation of an RPE monolayer requires a more involved surgical pro-

cedure but the results more closely mimic the anatomy and physiology of the tissue to be replaced.⁴⁻⁶ This approach has been used in several clinical trials as well. Next, we review the results of the most recent such studies focusing on studies that have been published over the past six years. We refer the reader to our previous reviews for more comprehensive discussion of earlier landmark studies.⁴⁻⁶

• **RPE cell suspensions.** In 2012 a Phase I/IIa study of subretinal injection of allogeneic hESC-RPE suspensions for treatment of advanced dry AMD and Stargardts was published.¹⁶ The four-year follow-up results for 18 patients demonstrated safety and possible efficacy in half of them.¹⁷ Since that time, several studies using hESC-RPE suspensions have reported similar results.

In 2020, a paper reported one-year results of subretinal injection of HLA-matched allogeneic iPSC-RPE cell suspension without systemic immunosuppressive medications in five patients with exudative AMD.¹⁸ There were two instances of suspected mild rejection which resolved with local administration of steroids, and all five patients developed epiretinal membranes thought to be caused by the reflux of graft cells into the vitreous space. However, the RPE graft survived in all cases, demonstrating the short-term feasibility of conservative management of a potential post-engraftment immune responses. There was neither a notable increase nor decrease in vision one year after the procedure.

In 2021, a paper reported a three-year assessment of a Phase I trial involving subretinal injection of hESC-RPE cells in three patients with SMD.¹⁹ No unexpected serious adverse events were noted during this period, and there was no evidence of abnormal proliferation or immune rejection. The rates of progression in the area of decreased autofluorescence remained within expectations of the natural course of SMD, and best corrected visual acuity improved in one patient and remained stable in the other two. Similarly, researchers reported

five-year results from seven patients with SMD who underwent subretinal injection of hESC-RPE cells with no unexpected local or systemic adverse reactions.²⁰ On average, the seven treated eyes had similar visual function and retinal sensitivity compared to the fellow eyes at five years.

A 2023 report performed a 12-month follow-up of 12 patients with advanced SMD who received hESC-RPE cells in suspension via subretinal injection.²¹ No unexpected surgery-related or transplantation-related adverse events occurred over this period, and interestingly, all patients had better final BCVA in operated eyes as compared to baseline.

These promising results have been tem-

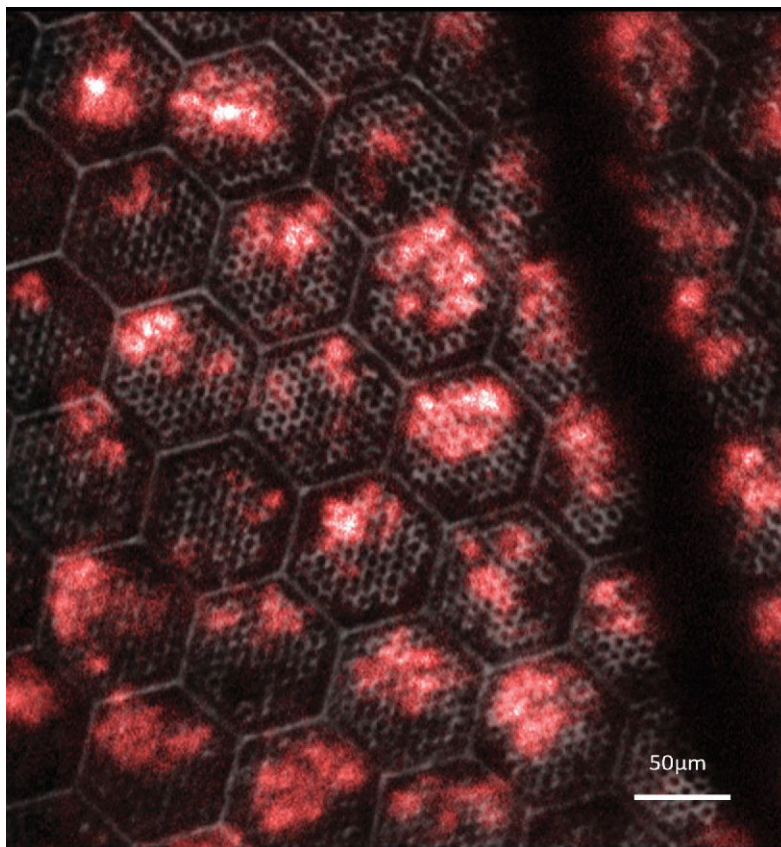


Figure 2. Adaptive optics scanning light ophthalmoscope image of a honeycomb scaffold seeded with photoreceptor precursors (red) in the subretinal space of a non-human primate model *in vivo*. Infrared reflectance image of the scaffold microstructure is overlaid with the false-colored fluorescence image of photoreceptor precursors expressing tdTomato.

pered by several observations. First, the subretinal blebs in these cases often don't cover the area of RPE atrophy. Second, signs of RPE reconstitution have been limited to very small regions (compared to overall bleb size) where hyper-reflective bands on OCT seem to suggest engrafted RPE. Therefore, while these studies show at least some vision improvement, the mechanisms by which subretinal injection of RPE cell suspensions work aren't clear and is unlikely to represent direct RPE-photoreceptor mediated vision restoration.

- **RPE sheets.** In 2017, investigators reported the first use of an autologous iPSC-RPE monolayer after surgical removal of choroidal neovascular membrane for treatment of neovascular AMD²² and subsequent four years of follow-up²³ without unexpected serious adverse events. They found that the sheet had survived in place with slight expansion of the pigmented boundaries and there was no evidence of graft rejection. Further, the thickness of the photoreceptor layer and the choroidal volume were subjectively better at the transplant site compared to non-covered areas. Visual acuity remained stable at around 20/200 over the entire duration of follow-up. Since that time, several studies using monolayers of RPE in various formations have been reported.

In 2018, one of this article's authors (AHK) and co-workers reported preliminary results on five patients from a Phase I/IIa trial of an allogeneic, HLA-mismatched hESC-RPE sheet on a synthetic scaffold with subsequent follow up on 16 patients at one and three years.^{24,25} None of the subjects had unexpected serious adverse events.²⁴ At three years, implanted eyes were more likely than non-implanted eyes to gain >5 Early Treatment Diabetic Retinopathy Study letters of BCVA and were less likely than non-implanted eyes to lose >5 letters, although this signal wasn't statistically significant. There was no significant difference in fixation ability of either the implanted or the non-implanted eyes at this time point,

but one patient demonstrated improvement in retinal sensitivity within and surrounding the area of the implant. One subject in the study passed away two years after implantation from natural causes. Histopathologic analysis of the implanted eye demonstrated survival of the graft in the subretinal space, no evidence of immune response directed at the implant, and expression of rhodopsin in the area of neurosensory retina overlying the implant.²⁶ There were no unanticipated severe implant-related adverse events throughout the study.²⁵

In 2024, an analysis reported a five-year follow-up of scaffold-based hESC-RPE transplantation in two patients with advanced neovascular AMD and acute subretinal hemorrhage.²⁷ Both subjects had some extension of pigmentation beyond the original graft area and no evidence of uncontrolled RPE proliferation or immune rejection. Both subjects also had initial improvements in BCVA, fixation and retinal sensitivity, but these improvements were only sustained in one subject.

These studies suggest that surgical implantation of RPE monolayers more closely mimic the natural RPE appearance *in vivo*. In all these studies, the pigmentation of the implanted RPE was maintained and the OCT appearance of the implanted cells was consistent with that of RPE. One limitation of these studies is that the patient population had very advanced disease that likely put a ceiling on the potential for visual improvement. Nevertheless, both these studies and those using cell suspensions suggest that RPE transplantation is safe and feasible thereby opening the path for additional studies.

There are at least two promising ongoing studies using RPE monolayer approaches. The first is a Phase I/IIa study of induced pluripotent stem cell derived RPE on a biodegradable scaffold for geographic atrophy that's ongoing at the National Eye Institute. Another is a Phase IIb study using human embryonic stem cell derived RPE for GA that's sponsored by Regenerative



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The monocular patient who has lost central vision in one eye to either nAMD or GA, and is looking to preserve vision in their better eye, may be motivated to seek treatment.

Patch Technologies.

• **Other RPE replacement strategies.**

An alternative, intermediate approach between suspensions and sheets involves RPE cells grown in monolayers within narrow grooves. These “RPE strips” were successfully injected into the subretinal space of three patients (one with advanced dry AMD and two with RP) using a 31G cannula. A paper described safety and efficacy outcomes of this Phase I/II trial in 2025.²⁸ No unexpected serious adverse events were noted, but a suspected immune reaction and epiretinal membrane formation were observed in one patient each. At the one-year mark, there was a reduction in the abnormal area in all three patients, with one patient also reporting significant vision-related quality of life improvement.

Another option being explored in RPE transplantation is the direct use of adult RPE stem cells isolated from post-mortem tissue and expanded in culture. A 2025 paper reported interim results from the first-in-human study of RPESC-RPE cells delivered as a suspension via subretinal injection in six patients with dry AMD.²⁹ The treatment was well-tolerated with no cell-product-related severe adverse events. Treated eyes had improvements in BCVA, whereas untreated eyes had reduced visual acuity compared to baseline consistent with the natural history of GA. These results suggest that there may be advantages to using this cell type although this method would have all the limitations of cell suspension methods listed above.

Photoreceptor transplantation

The results of RPE transplantation studies described above raise the obvious question of whether a similar approach is viable for photoreceptors as well. Photoreceptor transplantation faces many of the same challenges as RPE transplantation, such as stringent organization and polarity demands. Photoreceptors come in varied types, and they must also functionally integrate with host tissue for proper transduction of visual

signals.³⁰ Photoreceptor replacement is still being optimized at the pre-clinical stage. One line of investigation in photoreceptor transplantation is based on human pluripotent stem cell-derived photoreceptor precursors (hPSC-PRPs). These cells are produced within three-dimensional retinal organoids that recapitulate human retinogenesis. Within this category, two main products have shown promise: iPSC-derived retinal sheets^{31,32} and suspensions of photoreceptor precursors.^{33,34}

In similar fashion to RPE suspensions, direct subretinal injections of purified photoreceptor precursor cells have been associated with inconsistent delivery and reflux into the vitreous cavity, but without the prevalence of epiretinal membrane formation. Better anatomic success has been seen with the use of structured retinal sheets, but synaptic connection has remained limited due to the presence of interneurons and the formation of rosettes. Efforts are underway to use genome editing to optimize donor-host connectivity by depleting the interneurons.³⁵

Another method being explored by one of this article’s authors (JEM) is the use of synthetic scaffolds seeded with isolated PRPs.³⁶ To track the survival, distribution, and morphology of transplanted photoreceptors in animal models *in vivo*, hPSC-PRPs can be genetically engineered to express fluorescent reporter proteins. Pairing this approach with adaptive optics scanning laser ophthalmoscopy, it’s possible to assess both the microstructure of the scaffold and the survival and maturation of the photoreceptor transplant at a cellular level in the living eye (*Figure 2*).

Photoreceptor cell replacement therapies are now being evaluated in a small number of clinical trials. In 2023, two-year results from the first in-human study of retinal organoid transplantation were published.³⁷ Two subjects with RP were implanted with allogeneic iPSC-derived retinal organoids, which survived with neither immune rejection nor unexpected overgrowth. Visual

acuity and visual field both remained stable, but retinal sensitivity decreased across the entire measurement area, including at the points overlying the local transplant site.

Adaptive optics optical computed tomography was performed on one patient who received retinal organoid transplantation.³⁸ It was observed that the implanted region had outer plexiform layer-like lines and reflective particles consistent in appearance with outer segment discs, suggesting that the graft may have developed functional morphology. Another clinical trial which is now underway is the Phase I/IIa CLARICO trial for OpCT-001, the first iPSC-derived cell therapy for primary photoreceptor diseases.

Because of the inherent interdependence of RPE and photoreceptor cells and their concomitant loss in advanced disease, researchers are also investigating co-transplantation of both cell types.³⁹ In a proof-of-concept study involving an immunodeficient laser induced rat model of advanced retinal degeneration researchers demonstrated safe transplantation of a co-graft consisting of a retinal organoid plus a polarized RPE monolayer on a parylene scaffold.⁴⁰ Immunohistochemistry revealed that these co-grafts generated photoreceptors and developed neuronal processes which migrated into the host retina. Visual function assessments using optokinetic nystagmus showed improvement in the implanted animals compared to controls. Further optimization of the co-grafting process is still required, but these results support the translational potential of this technique.

Conclusions and future directions

These recent clinical trials contribute to a growing body of evidence pointing to the safety and feasibility of stem cell therapies when performed with appropriate oversight, expertise and expectation. Overall, well-performed cell-based interventions have been associated with reasonable serious adverse event rates for clinical implementation. Continued research into alternative immunosuppression regimens and modes of delivery may further help reduce

risks. Functional improvement has been difficult to demonstrate, partially owing to an inherent limitation of early phase studies in a relatively small sample size and often advanced disease. Efficacy analysis is further complicated by significant heterogeneity in control groups and outcome measures.

However, improvements in visual acuity, visual field and retinal sensitivity have been noted in preliminary studies, especially those implementing careful patient selection. Further, a recent meta-analysis found that, across a total of 18 studies describing quantitative data from 224 eyes, cell therapy was associated with significantly improved BCVA in AMD, RP and SMD.⁴¹

Ultimately, randomized controlled trials with longer follow-up will be critical to establish definitive therapeutic benefit, assess treatment durability and monitor for late-onset or rare adverse effects. It's clear that, with continued optimization of tissue engineering and graft delivery, stem cells hold tremendous therapeutic potential in retinal degenerative diseases. It's important to note that poorly done studies (often prematurely claiming effectiveness) have had catastrophic results and we encourage readers to review an *NEJM* article summarizing these events.⁴² Physicians and patients should exercise caution when considering enrolling in clinical trials that seem to promise or exaggerate positive results, especially if payment for participation is required.⁴² 

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(Continued on p. 36)

Tips and techniques for managing pediatric detachments

It's important to remember that children aren't just little adults, and require specific strategies for their detachments.

By Tadashi Yokoi, MD, PhD



Tadashi Yokoi,
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Take-home points

- » In pediatric RRD, especially phakic eyes with anterior pathology, consider scleral buckling first.
- » In pediatric TRD, the goal is selective traction release, not complete membrane removal. Avoid forced PVD induction and iatrogenic breaks.
- » Pediatric RD surgery starts with setup: disease-specific port placement, direct scleral visualization in infants, and stable infusion. Smaller-footprint viewing systems and short instrumentation can improve maneuverability, particularly in neonatal and infant eyes.

Managing pediatric retinal detachment requires a disease- and anatomy-specific strategy rather than a scaled-down application of adult retinal detachment surgery. The pediatric eye has a developing pars plana, a proportionally large crystalline lens, a formed and often firmly adherent vitreous, and a higher likelihood of developmental or inherited vitreoretinal disease.^{1,2} In rhegmatogenous retinal detachment, particularly in phakic children with anterior pathology, scleral buckling should be considered as a primary procedure.³⁻⁵ In tractional retinal detachment, the priority is controlled release of clinically significant traction while avoiding maneuvers that may create iatrogenic breaks,^{1,2,5} an approach that embodies the “Less is more” philosophy.

Examination under anesthesia and setting up the case

Examination under anesthesia is often part of the operation rather than a separate diagnostic step. The surgeon should document the retina with scleral depression,

examine the fellow eye, obtain OCT or ultrasonography when useful, and perform widefield fluorescein angiography when FEVR, ROP or peripheral ischemia is suspected. Before placing a trocar for vitrectomy, the entry site should be selected for that child. Craig A. Lemley, MD, and Dennis P. Han, MD, proposed 1.5 mm posterior to the limbus at 1 to 6 months, 2 mm at 6 to 12 months, 2.5 mm at 1 to 2 years, 3 mm at 2 to 6 years, and 3.5 mm at 6 to 18 years. Lauren Wright, MD, and colleagues later emphasized that disease-specific anatomy, including ROP, PFV, coloboma and high myopia, can modify these distances.^{6,7}

Infant trocar placement shouldn't be performed like routine adult transconjunctival entry. After conjunctival cutdown, the intended sclerotomy site should be stabilized by grasping the adjacent sclera with forceps, allowing controlled trocar penetration despite the extremely soft sclera. A small pre-incision with a sharp blade, such as a V-lance, may further improve control in selected cases. The trocar should be directed more vertically, while carefully avoiding the lens. At the end of surgery,

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ports should be sutured liberally in neonates, infants, young children, hypotonous eyes or children likely to rub the eye postoperatively.

Visualization is a working-space issue as much as an optical issue. In infants, narrow fissures and small globes with shorter pars plana may cause a standard round noncontact lens to interfere with instrument movement. Smaller-footprint Resight-compatible front lenses can be useful, including the Oculus Versa HD Disposable LenZ for Zeiss Resight and Picture Technology's PT-S133 in Japan.

Shorter instruments can be considered, especially for the neonate and infant cases. Commercially available short-shaft systems, such as the Constellation 25+ Short Ultravit Vitrectomy Probe with compatible short-pak instrumentation (Alcon) or ultra-short vitrectomy kits from DORC, may be useful, particularly in neonatal and infant eyes. These instruments, with an approximately 18-mm shaft, can improve maneuverability and reduce the risk of excessive intraocular entry.

RRD: Consider buckling first

Many pediatric RRDs begin anteriorly: dialysis; ora breaks; lattice holes; traumatic tears; Stickler-related vitreous-base abnormalities; or FEVR-associated peripheral breaks. In these eyes, scleral buckling should be actively considered before primary vitrectomy, even in the presence of subretinal PVR, as illustrated by the representative case shown in Figure 1. Pediatric RRD series support primary scleral buckling, and primary vitrectomy alone may be less favorable than scleral buckle or combined buckle-vitrectomy in selected children.³⁻⁵ A segmental buckle is appropriate for the RD due to a localized lattice hole(s). Because many pediatric vitreoretinal diseases involve broad circumferential peripheral pathology, an encircling buckle should be considered for multiple holes, inferior pathology, high myopia, Stickler syndrome without a giant retinal tear,

FEVR or trauma.

Vitrectomy is often unavoidable for giant retinal tear, posterior break, dense vitreous hemorrhage, severe PVR, especially with severe preretinal proliferation; traumatic incarceration, breaks with highly liquefied vitreous or failed buckle.^{3,8} Although complete PVD induction may be desirable, it shouldn't be forced when anomalous, firm vitreoretinal adhesion makes the posterior hyaloid inseparable. Careful shaving, traction segmentation and external support may be safer than aggressive posterior hyaloid separation.^{1,2} In pediatric giant retinal tear, stabilize the posterior flap with perfluorocarbon liquid, meticulously trim anterior flap traction, and strongly consider encircling buckling in young children, syndromic eyes or eyes with inferior pathology.⁸ Gas may be appropriate for an older cooperative child with superior breaks. Silicone oil is often more practical in young children, in eyes with inferior pathology, PVR, giant retinal tears, or combined TRD/RRD, and when reliable postoperative positioning is unlikely.

In Stickler syndrome, Cambridge cryotherapy and Manchester 360-degree laser

prophylaxis have both reported substantial reduction in detachment risk, and established detachments may require multiple procedures with combinations of buckle, vitrectomy, retinopexy and silicone oil.⁹⁻¹¹ During vitrectomy, a thin resid-



Figure 1. An 11-year-old girl with subretinal PVR in the left eye caused by a peripheral retinal break at 3 o'clock associated with FEVR. The left panels show the preoperative pseudocolor fundus photograph and OCT image. BCVA was 20/200, and both the fundus photograph and OCT findings indicated that the detachment was longstanding. Encircling scleral buckling was performed using a #506 sponge. The right panels show successful retinal reattachment and improvement of BCVA to 20/60 at one month postop. This case illustrates the importance of scleral buckling, even in a complicated case with subretinal PVR.

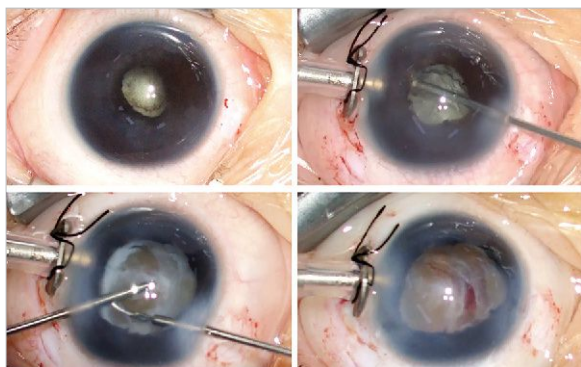


Figure 2. An 11-month-old boy with stage 5 FEVR in the left eye, shown from the surgeon's view. The corneal diameter was 9 mm, slightly smaller than normal. The iris was partially adherent to the cornea superiorly, laterally, and inferiorly, with mild corneal opacity in these areas. Preoperatively, a retrolental fibrovascular plaque pushed the lens anteriorly, with 360-degree posterior synechiae and an extremely shallow anterior chamber (top left). A specially designed 2.5-mm infusion cannula was placed through the limbus and sutured, and lensectomy was performed after dissection of the iridocorneal adhesions and sphincterectomy (top right). The retrolental fibrous tissue was dissected and resected (bottom left), and the completely closed funnel was opened toward the optic nerve head. A certain amount of preretinal fibrous membrane was intentionally left in place to avoid iatrogenic breaks, consistent with the "less is more" philosophy.

or hyaloid may persist despite extensive vitreous liquefaction. Its identification and removal are often critical to success. Careful shaving of the thick peripheral vitreous over areas of characteristic radial perivascular degeneration is also important.

FEVR can produce RRD, TRD, or a combined detachment. Avascular peripheral retina and anomalous vascular development should be assessed with

widefield imaging.¹² If peripheral holes and anterior contraction dominate, encircling buckling should be considered first, together with treatment of ischemic retina when indicated.¹³ When traction around the causative break is substantial, combined scleral buckling and vitrectomy is often required. In FEVR-associated RRD, prognosis depends largely on the break location and the surrounding traction. Breaks located beneath or adjacent to retinal folds make surgical repair considerably more complex and the visual prognosis more guarded.

RD in morning glory disc anomaly and chorioretinal coloboma often require vitrectomy, because the pathologic communication and causative break may lie at the disc anomaly, intercalary membrane or coloboma margin. Around anomalous optic discs, the posterior hyaloid is often abnormal and tightly adherent. Complete PVD induction is frequently impossible; therefore, anomalous vitreous should be removed

conservatively rather than by forceful hyaloid separation.¹⁴⁻¹⁶ In coloboma-associated RD, search carefully for breaks in the intercalary membrane and at the coloboma margin, apply laser to identified breaks if possible, and the coloboma edge, and use long-acting tamponade in unstable eyes.^{15,16} In morning glory anomaly, peripapillary communication and abnormal disc tissue can make reattachment slow and recurrence possible; surgery often requires careful vitrectomy, cautious peripapillary laser, and silicone oil in highly complex cases.¹⁴ Because the use of silicone oil in eyes with chorioretinal coloboma or morning glory anomaly remains controversial owing to the potential risk of intracranial migration, explicit preoperative discussion with the parents is essential.

TRD: Selective release rather than exhaustive peeling

Pediatric TRD surgery is controlled traction release. In ROP, FEVR and PFV, the goal isn't to remove every membrane but to reduce the traction that threatens or distorts the macula. Firmly adherent tissue may be left in place when peeling would create a retinal break. Once an iatrogenic break is created, visual outcomes become less favorable; therefore, each maneuver should be judged by whether it safely improves the retinal configuration and visual potential.⁵

In ROP, stage 4A is the most favorable surgical window: The macula is still attached, and lens-sparing vitrectomy can relax ridge traction before the eye progresses to a funnel configuration.^{17,18} PVD induction isn't required. Traction should be segmented along ridge-to-ora, ridge-to-lens and circumferential vectors. Because laser photocoagulation of the far peripheral retina can be difficult during lens-sparing vitrectomy, preoperative external laser treatment should be considered when indicated. If anti-VEGF has been used, vascular activity may decrease while fibrotic contraction continues or even accelerates;

timing should be guided by the tractional course and retinal configuration rather than the injection date alone.¹⁷

Stage 5 ROP and FEVR shift the surgical access problem. When anterior traction, retrolental fibroplasia, or a closed funnel prevents safe pars plicata work, an anterior lensectomy-vitreotomy approach, or limbal approach, may provide a far safer surgical corridor than pars plicata trocar placement.¹⁹ The aim is to open the funnel and free the posterior pole when possible. A partially relaxed posterior pole without iatrogenic breaks may be a better endpoint (*Figure 2*) than an extensive dissection that converts TRD into combined TRD/RRD.

FEVR-TRD is age dependent. Younger children may have more vascularly active proliferation, whereas older children often have more fibrotic folds. Ischemic retina with neovascular components should be treated with laser when accessible, buckle support should be considered for peripheral contraction, and vitrectomy should be used for posterior tractional maculopathy. The appropriate endpoint is reduction of macular distortion, not complete removal of every peripheral membrane.²⁰ Most importantly, adequate laser photocoagulation of ischemic retina is fundamental to controlling vascular activity and achieving long-term success in this disease.

PFV is caused by abnormal persistence of the fetal hyaloid vascular system. The retrolental plaque, stalk, ciliary processes, anterior retina and posterior pole may be connected. Early surgery can help selected posterior PFV eyes with tractional detachment and tractional maculopathy, but microphthalmia, glaucoma, cataract and macular aplasia or dysplasia limit prognosis.²¹⁻²³ If anterior displacement of the retina or dense retrolental tissue obscures the route, limbal access may be safer than pars plana entry.²² Lens preservation is valuable only when it still permits meaningful release of stalk and macular traction. For isolated anterior PFV, early surgery is often favored by analogy with the timing

principles of unilateral congenital cataract surgery. In contrast, vitrectomy for posterior or combined anterior-posterior PFV is indicated more selectively, depending primarily on macular involvement.

In conclusion, successful pediatric retinal detachment surgery begins with understanding the pediatric vitreous, the developing retina and the disease-specific mechanisms that shape each detachment. 

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Once an iatrogenic break is created, visual outcomes become less favorable; therefore, each maneuver should be judged by whether it safely improves the retinal configuration and visual potential.



When uveitis heralds malignancy

Paraneoplastic uveitis as a presenting sign for metastatic melanoma.

By **Emma Stenz, MD,**
Alex Tseng, MD, and
Nathan Agi, MD



Emma Stenz, MD



Alex Tseng, MD



Nathan Agi, MD

A 63-year-old man presented with three weeks of painless blurred vision and floaters in the right eye after being struck by a branch in the forehead and developing a pustule. He was initiated on topical steroids a week after the injury. Several weeks later, he was referred to the emergency department at an academic medical center. He denied any new systemic symptoms.

His medical history was notable for stage pT2b malignant melanoma of the upper back diagnosed five years prior to presentation. He underwent wide local excision with negative margins and sentinel lymph node biopsy which was negative for metastasis. Therefore, no adjuvant chemotherapy or immunotherapy was pursued.

Initial examination findings

Examination showed best-corrected visual acuity of 20/30 in the right eye and 20/20 in the left. Intraocular pressure and pupillary responses were normal. Slit lamp examination revealed 2+ cell and 1+ flare in the anterior chamber in the right eye, without apparent inflammation in the left eye. Dilated examination of the right eye revealed scattered intraretinal hemorrhages involving the macula and periphery, as well as filamentary vitritis overlying the optic nerve (*Figure 1*).

Fundus examination of the left eye was unremarkable.

Initial workup and management

The patient was admitted to the hospital for a broad infectious and inflammatory workup, including chest X-ray, complete blood count, comprehensive metabolic panel, urinalysis, HIV serologies, syphilis IgG and rapid plasma reagin (RPR), QuantiFERON Gold, Toxoplasmosis IgG, and hepatitis C serologies, all of which were unremarkable. His bacterial and fungal blood cultures were additionally negative. He underwent vitreous tap and injection of voriconazole, ceftazidime and vancomycin, and the vitreous fluid was negative for bacterial and fungal culture and PCR, as well as viral (CMV, HSV and VZV) PCR. Gram stain of the vitreous fluid was notable for 3+ mononuclear cells. MRI orbits with and without contrast demonstrated unremarkable orbital findings. Our service obtained optical coherence tomography of the retina which didn't demonstrate intraretinal or subretinal fluid in either eye.

Following discharge, he remained stable on topical steroids and atropine. Given the diagnostic uncertainty, he underwent diagnostic pars plana vitrectomy a month later. Flow cytometry, cytology, as well as bacterial and



Figure 1. Optos pseudocolor fundus photograph of the right eye (A) demonstrating presence of scattered retinal hemorrhages and vitritis. The left eye (B) has unremarkable findings.

BIOS

Dr. Agi is an assistant professor of ophthalmology at the University of Washington in Seattle where **Dr. Stenz** is an ophthalmology resident and **Dr. Tseng** is a vitreoretinal surgery fellow.

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fungal culture and PCR were unremarkable. Pathology revealed scattered lymphocytes and histiocytes without findings consistent with malignancy.

Additional exam findings and workup completion

Two months following his initial PPV, he developed new floaters and blurred vision in the left eye. BCVA was 20/30 in the right eye and 20/50 in the left. Slit lamp and dilated fundus examination was unremarkable in the right eye, but revealed 1+ mixed anterior chamber cell, small keratic precipitates and 2+ clumped vitritis in the left eye (*Figure 2*). He subsequently underwent a diagnostic PPV of the left eye which similarly had unremarkable microbial studies, flow cytometry and cytology.

In consultation with medical oncology, we obtained computed tomography scans of his chest, abdomen and pelvis, which were notable for multiple pulmonary nodules, retroperitoneal soft tissue nodules and radiolucent bone lesions. PET CT F-18 FDG whole body also demonstrated avid FDG uptake in the right supraclavicular lymph nodes and abdominal lymph nodes. Cytology from a retroperitoneal lymph node biopsy found monotonous round cells without specific immunologic differentiation markers, and flow cytometry was negative for abnormal B or T lymphoid cell populations, suggestive of dedifferentiated melanoma.

Diagnosis and management

He was diagnosed with bilateral paraneoplastic anterior and intermediate uveitis in the setting of stage IV metastatic dedifferentiated melanoma. His intraocular inflammation remained quiescent following his surgeries and he was started on palliative combination immunotherapy (anti-PD-1 plus anti-CTLA-4) for his systemic metastatic burden by oncology.

Discussion

Ocular paraneoplastic syndromes (OPS) are rare disorders that occur secondary to either immune-mediated cross-reactivity involving tumor antigens or ectopic production of hormones or growth factors by cancer cells.¹ These syndromes may precede or accompany a recurrence in malignancy, highlighting their potential value as early warning signs. The estimated incidence of OPS in cancer patients is about 0.01 percent.² While numerous malignancies are associated with OPS, the most common etiologies include small cell lung cancer, genitourinary malignancies such as endometrial and ovarian cancer, neuroendocrine tumors, lymphoma and malignant melanoma.³

Melanoma is associated with several systemic and ocular paraneoplastic syndromes. In a review of 59 cases, melanoma-associated retinopathy was the most common manifestation, while paraneoplastic encephalitis and cerebellar degeneration were less frequent.⁴

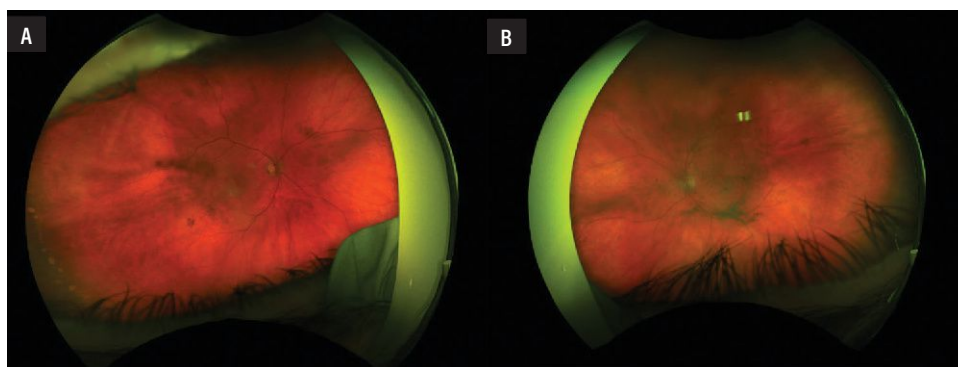


Figure 2. Optos pseudocolor fundus photograph of the right eye demonstrates continued resolution of vitreous cell (A), while the photograph of the left eye shows new vitreous cell and haze partly obscuring details of the macula and optic nerve (B).

More rarely, melanoma-associated paraneoplastic vitelliform retinopathy has been described, characterized by serous macular detachment and nummular vitelliform retinal lesions.⁵

Paraneoplastic uveitis is a rare subtype of OPS. In a review of cases reported between 2010 and 2023, there were 11 cases of paraneoplastic uveitis associated with pulmonary malignancies and lymphoma identified, including three cases each of anterior, intermediate and posterior uveitis, and two cases of panuveitis.⁶ Other reports include bilateral hypopyon and vitritis as the initial manifestation of metastatic peritoneal carcinomatosis,⁷ and bilateral paraneoplastic vitritis without other fundus abnormalities in a patient with ocular small-cell lung carcinoma.⁸ An additional report described eight cases of granulomatous paraneoplastic vitritis, three of which led to a new cancer diagnosis and five of which signaled disease recurrence.⁹ Although the underlying malignancies were heterogeneous, none were associated with melanoma. This case represents one of the first reported cases of a paraneoplastic anterior and intermediate uveitis associated with malignant melanoma.

Metastatic melanoma portends a poor prognosis, with five-year survival rates estimated at about 35 percent for patients with distant metastases.¹⁰ Systemic treatments that can prolong life expectancy include checkpoint inhibitors such as anti-PD-1 and anti-CTLA-4 antibodies, which act to enhance the body's T-cell ability to recognize and kill malignant cells. In our case, additional local therapy such as topical, intravitreal, or systemic steroids weren't necessary in preventing recurrence of intraocular inflammation following PPV.

Bottom line

This case represents a unique presentation of metastatic melanoma presenting initially as an anterior and intermediate paraneoplastic uveitis. Clinicians should be aware of the malignancy-associated paraneoplastic syndromes, which facilitates earlier diagnosis and treatment. 

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FEATURE

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(Continued from p. 29)

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6. Ample vitrectomy around the impaction site: Carefully complete the vitrectomy around any retinal break due to IOFB impaction to reduce traction and prevent further retinal damage.

7. Locating and isolating the IOFB: Conduct a meticulous search for the IOFB, typically near the impaction site, and perform a complete vitrectomy around it to ensure safe retrieval (Figure 1).

8. Retrieving the IOFB: Using intraocular forceps (or a magnet if appropriate), gently grasp and guide the IOFB into the anterior chamber for controlled removal.

9. Exteriorizing the IOFB: Carefully extract the IOFB through the main tunnel using an intraocular magnet, maintaining control to avoid additional ocular trauma.

10. IOL placement: Once the foreign body is removed, place an IOL in the sulcus.

11. Wound closure: Securely close the main tunnel with sutures to maintain ocular integrity.

12. Endolaser barricade: Adequate laser around the impaction site to fortify the retina is paramount.

Administer antibiotics and steroids postoperatively to manage inflammation and infection risk, and follow up with imaging to monitor for complications such as retinal detachment.

This structured approach and adherence to these intraoperative strategies help to maximize safety and outcomes in IOFB cases. ^{RS}

Social Media Specialist

(Continued from page 10)

Institutions also need to teach this explicitly. “Be careful online” is not enough. Trainees need concrete guidance for common scenarios: a patient follows them; sends a message; comments on a post; appears on a dating app; or overlaps with their local community. These are no longer rare hypotheticals.

The simplest test remains useful: Would the same interaction feel appropriate if it occurred in person immediately after the clinic visit, with the patient fully aware of the power differential? If not, it probably doesn’t belong on personal social media either. A follow is not always “just a follow.” In medicine, it can carry meaning beyond what the physician intended. ^{RS}

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Vit-Buckle Society highlights

(Continued from page 14)

Nimesh A. Patel, MD, argued that pediatric vitreoretinal surgery belongs in dedicated children’s hospitals with the supporting infrastructure, such as pediatric anesthesia, child life services and coordinated perioperative care. Safa Rahmani, MD, on the other hand, countered that all VR surgeons should be prepared to handle at least some pediatric pathology, particularly trauma and retinal dialysis, given how limited specialty access can be for many families. The audience favored the points of Dr. Rahmani, agreeing there should be broader participation in pediatric retina surgery with a vote of 72 percent to 28 percent.

Takeaway: General VR surgeons should be comfortable managing pediatric trauma and retinal dialysis, however a referral to a dedicated pediatric hospital may be warranted in cases with complex pathology.

• How to manage RD: PPV alone vs. SB/PPV.

R. Ross Lakhanpal, MD, argued that small-gauge vitrectomy, wide-angle viewing, modern fluidics and improved illumination have reduced the need for scleral buckle procedures in primary retinal detachments, with faster recovery and fewer buckle-related complications. Talia R. Kaden, MD, made the case for the buckle in complex surgical scenarios, such as young phakic patients, cases with inferior pathology, and PVR or high-PVR-risk eyes. Dr. Kaden won, with 87 percent of the vote.

Takeaway: The Primary Retinal Detachment Outcomes Study data supports SB or combined PPV/SB over PPV alone in phakic eyes (91 to 92 percent vs. 83 percent single surgery anatomic success), especially with inferior breaks or PVR risk.

• Optimal timing for mac off RRD: The sooner, the better vs. there’s no urgency.

Ferhina S. Ali, MD, argued for earlier repair of macula-off retina detachments, citing meta-analyses showing improved outcomes with repair within three days of onset. Akshay S. Thomas, MD, MS, FASRS, pushed back and argued that repair should be timely, but most macula-off detachments don’t require overnight surgery and can be safely deferred several days. He emphasized how OR access, scheduling and patient expectations are all factors to consider. Dr. Thomas’ position in the debate carried the debate with a 87 percent vs. 13 percent.

Takeaway: Recent meta-analyses show better VA outcomes with repair within two to three days, but in the real world, pragmatic factors such as OR access, staffing and preoperative planning mean time and patience may allow for more optimal surgical preparation. ^{RS}

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

1 INDICATIONS AND USAGE

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

2 DOSAGE AND ADMINISTRATION

2.1 General Dosing Information

IZERVAY must be administered by a qualified physician.

2.2 Recommended Dosage

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

4 CONTRAINDICATIONS

4.1 Ocular or Periorcular Infections

IZERVAY is contraindicated in patients with ocular or periorcular infections.

4.2 Active Intraocular Inflammation

IZERVAY is contraindicated in patients with active intraocular inflammation.

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments

Intravitreal injections may be associated with endophthalmitis and retinal detachments. Proper aseptic injection techniques must always be used when administering IZERVAY in order to minimize the risk of endophthalmitis. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay, to permit prompt and appropriate management.

5.2 Neovascular AMD

In the GATHER1 and GATHER2 clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Over 24 months, the rate of neovascular (wet) AMD or choroidal neovascularization in the GATHER2 trial was 12% in the IZERVAY group and 9% in the sham group. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

5.3 Increase in Intraocular Pressure

Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

6 ADVERSE REACTIONS

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

- Ocular and periorcular infections
- Active intraocular inflammation
- Endophthalmitis and retinal detachments
- Neovascular AMD
- Increase in intraocular pressure

6.1 Clinical Trials Experience

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

The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham. Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY for up to 12 months pooled across the GATHER1 and GATHER2 studies are listed below in Table 1.

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

Adverse Drug Reactions	IZERVAY N=292	Sham N=332
Conjunctival hemorrhage	13%	9%
Increased IOP	9%	1%
Blurred Vision*	8%	5%
Choroidal neovascularization	7%	4%
Eye pain	4%	3%
Vitreous floaters	2%	<1%
Blepharitis	2%	<1%

* Blurred vision includes visual impairment, vision blurred, visual acuity reduced, visual acuity reduced transiently.

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

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

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

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

² Punctate keratitis includes punctate keratitis and keratitis. Photopsia, optic ischemic neuropathy, vitreous hemorrhage, vitreal cells, vitritis, and endophthalmitis were each reported in ≤ 1% of patients treated with IZERVAY for up to 24 months across the GATHER1 and GATHER2 studies.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy Risk Summary

There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits. Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.5 times and 3.4 times the human exposure, respectively, based on Area Under the Curve (AUC), following a single 2 mg intravitreal (IVT) dose (see Animal Data). In the U.S. general population, the estimated background risks of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15%-20%, respectively.

Animal Data

An embryo fetal developmental toxicity study was conducted with pregnant rats. Pregnant rats received daily IV injections of avacincaptad pegol from day 6 to day 17 of gestation at 0.1, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. An increase in the incidence of a non-adverse skeletal variation, described as short thoracolumbar (ossification site without distal cartilage) supernumerary ribs, was observed at all doses evaluated. The clinical relevance of this finding is unknown. Plasma exposures at the high dose were 5.5 times the human AUC of 999 ng-day/mL (23976 ng-hr/mL) following a single 2 mg IVT dose. An embryo fetal developmental toxicity study was conducted with pregnant rabbits. Pregnant rabbits received daily IV injections of avacincaptad pegol from day 7 to day 19 of gestation at 0.12, 0.4, 1.2 mg/kg/day. No maternal or embryofetal adverse effects were observed at any dose evaluated. Plasma exposure in pregnant rabbits at the highest dose of 1.2 mg/kg/day was 3.4 times the human AUC of 999 ng-day/mL (23976 ng-hr/mL) following a single 2 mg IVT dose.

8.2 Lactation

There is no information regarding the presence of avacincaptad pegol in human milk, or the effects of the drug on the breastfed infant or on milk production. Many drugs are transferred in human milk with the potential for absorption and adverse reactions in the breastfed child. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for IZERVAY and any potential adverse effects on the breastfed infant from IZERVAY.

8.4 Pediatric Use

Safety and effectiveness of IZERVAY in pediatric patients have not been established.

8.5 Geriatric Use

Of the total number of patients who received IZERVAY in the two clinical trials, 90% (263/292) were ≥65 years and 61% (178/292) were ≥75 years of age. No significant differences in efficacy or safety of avacincaptad pegol were seen with increasing age in these studies. No dose adjustment is required in patients 65 years and above.

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MAT-US-IZE-2026-00121 02/26



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

Moments like this deserve your protection.

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

**Protect healthy retinal cells for longer
with IZERVAY^{1,2*}**

Scan to explore IZERVAY: The #1 prescribed
FDA-approved treatment for new GA patients^{3†}



izervay
(avacincaptad pegol
intravitreal solution) 2 mg

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

†Based on Symphony data from 3/24-12/25. May not represent entire patient population.
Dr. Arshad Khanani is a compensated physician.

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

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

Neovascular AMD

- In the GATHER1 and GATHER2 clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly

and 4% in the sham group) by Month 12. Over 24 months, the rate of neovascular (wet) AMD or choroidal neovascularization in the GATHER2 trial was 12% in the IZERVAY group and 9% in the sham group. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

Increase in Intraocular Pressure

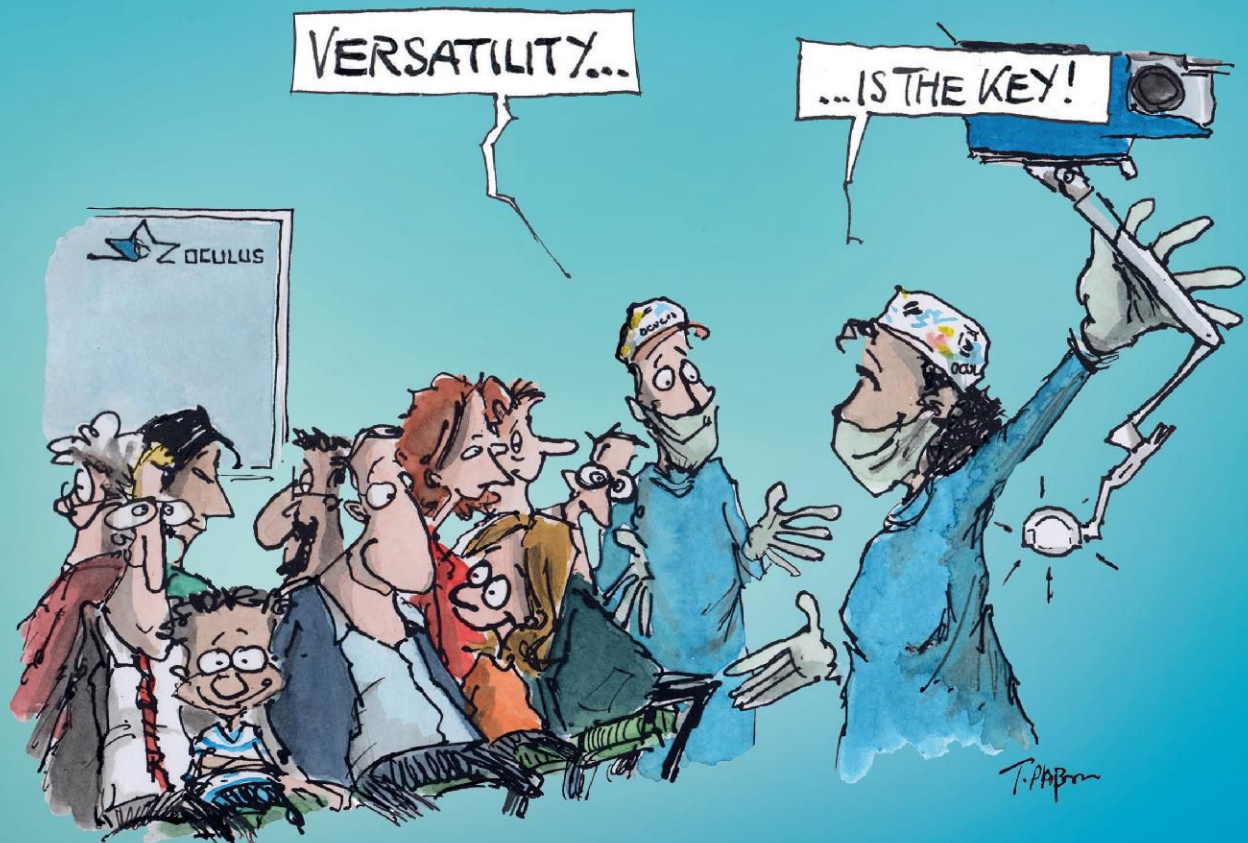
- Transient increases in intraocular pressure (IOP) have been observed after an intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed as needed.

ADVERSE REACTIONS

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

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

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



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