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Retina Today

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THE RETINA PIPELINE

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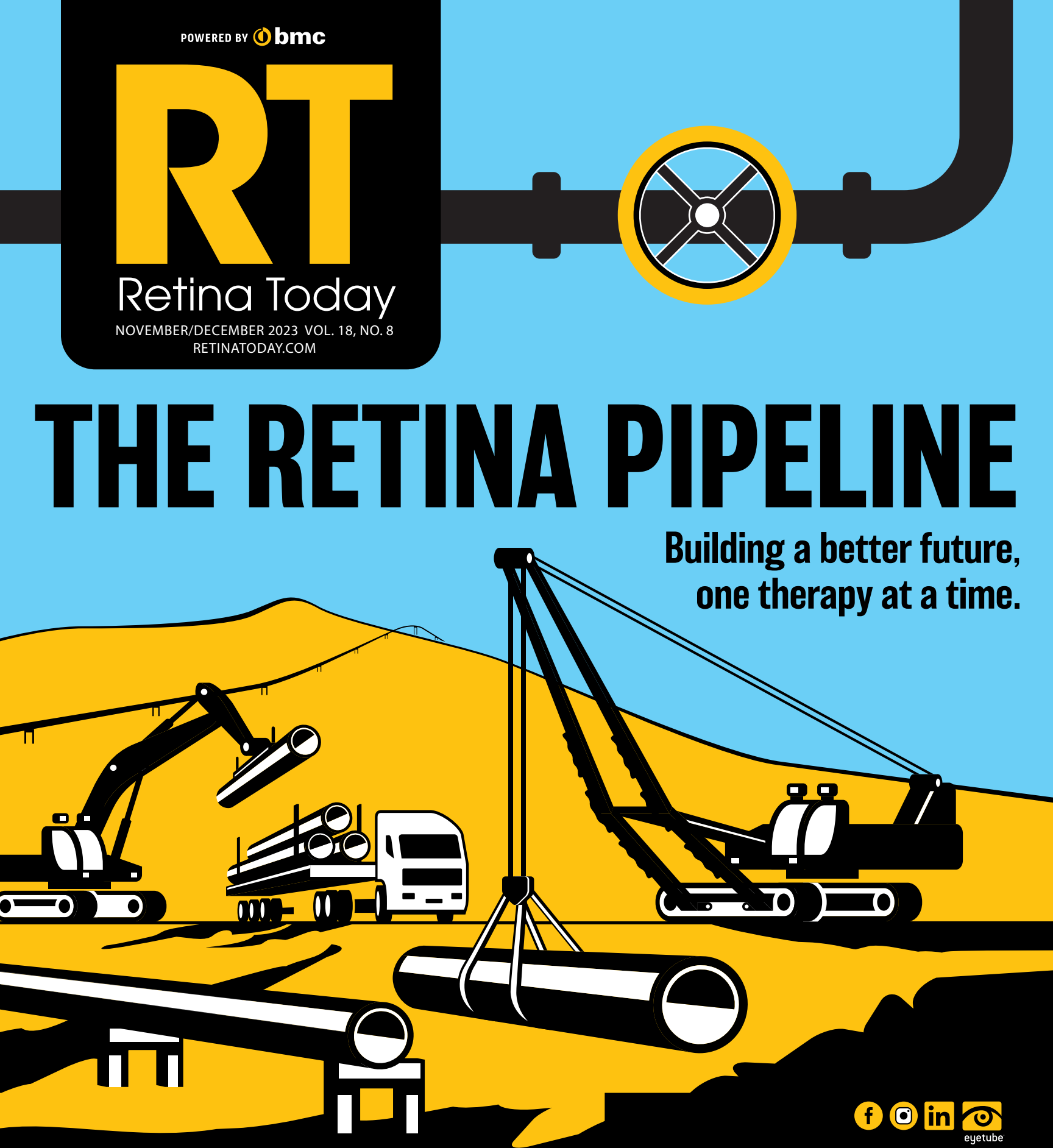


eyetube

THE FUTURE OF AMD THERAPEUTICS | ROBOTICS IN THE RETINA OR | THE DR/DME THERAPY LANDSCAPE

SUBSCRIBE FOR FREE

SYFOVRE®
(pegcetacoplan injection)
15 mg / 0.1 mL

GA unravels so much

Save retinal tissue by slowing progression[1-3]

INDICATION

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

IMPORTANT SAFETY INFORMATION

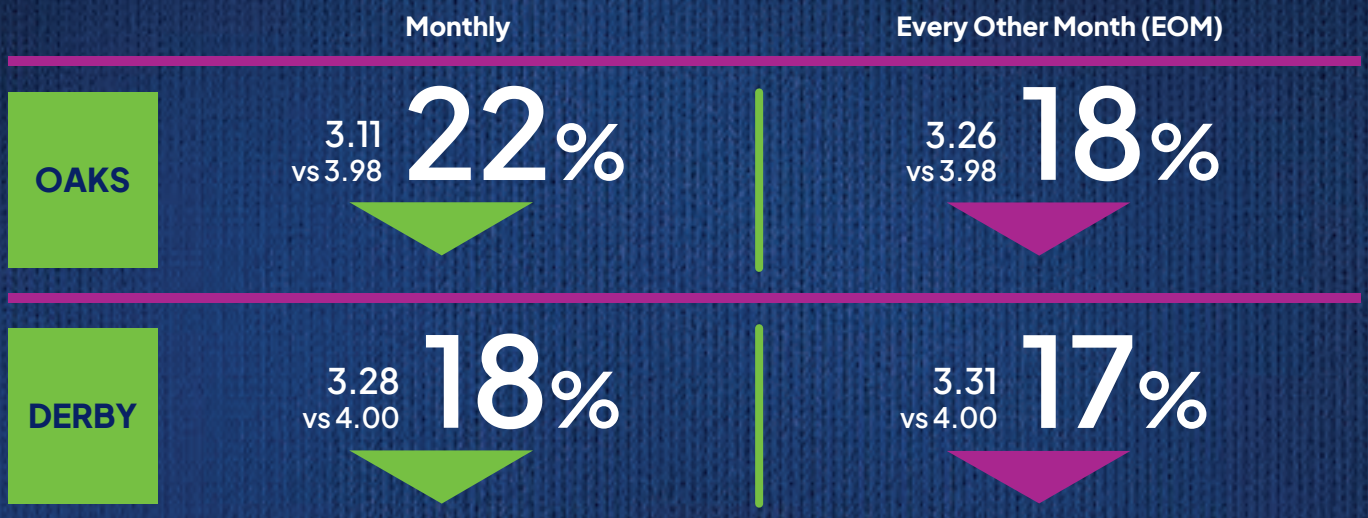
CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

SYFOVRE achieved continuous reductions in mean lesion growth rate* (mm^2) vs sham pooled from baseline to Month 24[1]



SE in trials (monthly, EOM, sham pooled): OAKS: 0.15, 0.13, 0.14; DERBY: 0.13, 0.13, 0.17.

*Slope for baseline to Month 24 is an average of slope of baseline to Month 6, Month 6 to Month 12, Month 12 to Month 18, and Month 18 to Month 24.[1]
Based on a mixed effects model for repeated measures assuming a piecewise linear trend in time with knots at Month 6, Month 12, and Month 18.[1]
GA=geographic atrophy; SE=standard error.

Explore the long-term data

IMPORTANT SAFETY INFORMATION (CONT'D)

WARNINGS AND PRECAUTIONS (CONT'D)

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

ADVERSE REACTIONS

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

Trial Design: SYFOVRE safety and efficacy were assessed in OAKS (N=637) and DERBY (N=621), multi-center, 24-month, 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 EOM, sham monthly, or sham EOM for 24 months. Change from baseline in the total area of GA lesions in the study eye (mm^2) was measured by fundus autofluorescence (FAF).[1,4]

References: 1. SYFOVRE (pegcetacoplan injection) [package insert]. Waltham, MA: Apellis Pharmaceuticals, Inc.; 2023. **2.** Pfau M, von der Emde L, de Sisternes L, et al. Progression of photoreceptor degeneration in geographic atrophy secondary to age-related macular degeneration. *JAMA Ophthalmol*. 2020;138(10):1026–1034. **3.** Bird AC, Phillips RL, Hageman GS. Geographic atrophy: a histopathological assessment. *JAMA Ophthalmol*. 2014;132(3):338–345. **4.** Data on file. Apellis Pharmaceuticals, Inc.

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

Apellis

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Ocular or Periocular Infections

SYFOVRE is contraindicated in patients with ocular or periocular infections.

Active Intraocular Inflammation

SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

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

Neovascular AMD

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

Intraocular Inflammation

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

Increased Intraocular Pressure

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

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

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

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

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:

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

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

Punctate keratitis included: punctate keratitis, keratitis

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

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

Pediatric Use

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

Geriatric Use

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

PATIENT COUNSELING INFORMATION

Advise patients that following SYFOVRE administration, patients are at risk of developing neovascular AMD, endophthalmitis, and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops any change in vision such as flashing lights, blurred vision or metamorphopsia, instruct the patient to seek immediate care from an ophthalmologist.

Patients may experience temporary visual disturbances associated either with the intravitreal injection with SYFOVRE or the eye examination. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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

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7/23 US-PEGGA-2200163 v3.0

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TRUST THE PROCESS

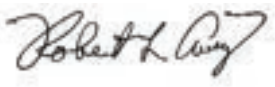

At this point, the phrase *retina pipeline* feels like a bit of a misnomer. It certainly hasn't been a smooth—or straightforward—path for many of our hopeful therapeutic candidates. But it has been long, that's for sure. This issue's cover, perhaps, better visualizes the retina pipeline of today: a constant work in progress with lots of heavy lifting by our researchers.

This year has been full of victories, failures, setbacks, and surprises. The era of geographic atrophy therapy is here with the approval of pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izervay, Iveric Bio/Astellas Pharma), but we hit a speed bump right out of the gate with cases of retinal vasculitis.[1] High-dose aflibercept (Eylea HD, Regeneron) gained FDA approval, but not before the company had to address the FDA's complete response letter (CRL).[2] Outlook Therapeutics also received a CRL for ONS-5010 (Lytenava), prompting the company to pursue another pivotal trial.[3] Kodiak Sciences paused its tarcocimab program in July after the phase 3 GLEAM and GLIMMER trials failed to meet their primary endpoints, but by early November, the program was up and running again, fueled by positive topline data from the phase 3 GLOW trial.[4] Aflibercept (Eylea, Regeneron) and faricimab (Vabysmo, Genentech/Roche) each received new indications of retinopathy of prematurity and retinal vein occlusion, respectively.[5,6]

Everyone involved in these programs deserves our heartfelt thanks—and a vacation—for pushing our field forward and improving patient care.

Beyond these well-publicized ups and downs, myriad other trials are moving along, slowly churning out data to support the viability of various novel therapies and delivery methods. The pipeline articles within this issue highlight approximately 75 clinical trials evaluating treatments for wet AMD, geographic atrophy, diabetic eye disease, and proliferative vitreoretinopathy—and this doesn't even touch the booming inherited retinal disease pipeline (see, *The Latest in Gene Therapy Clinical Trials for Inherited Retinal Disease*). It's nearly impossible to keep track of it all, and we hope these summaries (with very useful charts) help you stay on top of the data—at least until the next round of interim findings rolls out.

Like all construction projects, our pipeline is rife with delays and unexpected complications; however, Rome wasn't built in a day, and neither can we establish a full armamentarium of treatments for our varied retinal diseases without facing obstacles. We must trust the process, celebrate every victory, and learn from every failure and setback. Then we roll up our sleeves and get back to work. That's when we truly grow. ■

ALLEN C. HO, MD
CHIEF MEDICAL EDITOR

ROBERT L. AVERY, MD
ASSOCIATE MEDICAL EDITOR

1. Apellis provides updates on injection kits and rare safety events with GA drug Syfovre [press release]. Eyewire+. August 23, 2023. Accessed November 8, 2023. bit.ly/3MFvnhF
2. FDA approves Regeneron's high-dose aflibercept, Eylea HD [press release]. Eyewire+. August 19, 2023. Accessed November 8, 2023. bit.ly/49BTlnC
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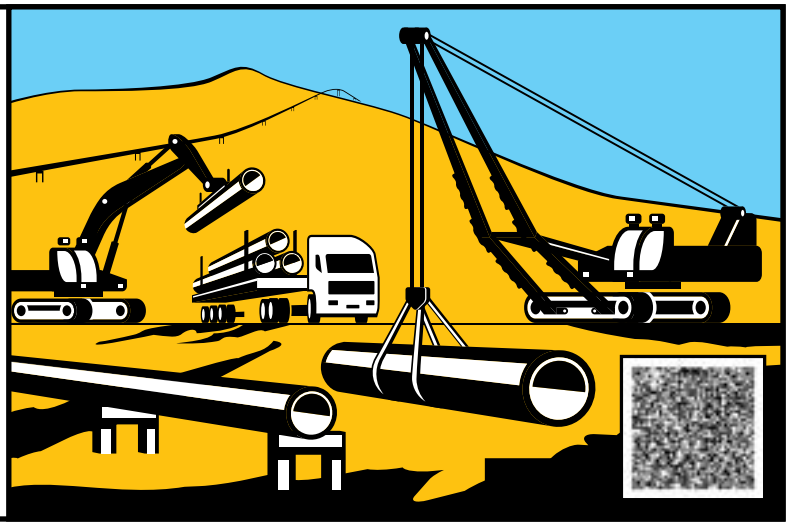
6. FDA approves Genentech's Vabysmo for the treatment of retinal vein occlusion (RVO) [press release]. Eyewire+. October 27, 2023. Accessed November 8, 2023. bit.ly/3svnggA

THE LATEST IN GENE THERAPY CLINICAL TRIALS FOR INHERITED RETINAL DISEASE



0.18 mg
YUTIQ®
(fluocinolone acetonide intravitreal implant) 0.18 mg

Discover CONTINUOUS CALM™ in uveitis[1]

YUTIQ is designed to deliver a sustained release of fluocinolone for up to 36 months for patients with chronic non-infectious uveitis affecting the posterior segment of the eye.[1]

- Proven to reduce uveitis recurrence at 6 and 12 months[1,*]
  At 6 months–18% for YUTIQ and 79% for sham for Study 1 and 22% for YUTIQ and 54% for sham for Study 2 (p<0.01). At 12 months–28% for YUTIQ and 86% for sham for Study 1 and 33% for YUTIQ and 60% for sham for Study 2.
- Extended median time to first recurrence of uveitis[1,2]
  At 12 months–NE[†] for YUTIQ/92 days for sham in Study 1; NE for YUTIQ/187 days for sham in Study 2.
- Mean intraocular pressure (IOP) increase was comparable to sham[1,3]
  Study was not sized to detect statistically significant differences in mean IOP.

*Study design: The efficacy of YUTIQ was assessed in 2 randomized, multicenter, sham-controlled, double-masked, Phase 3 studies in adult patients (N=282) with non-infectious uveitis affecting the posterior segment of the eye. The primary endpoint in both studies was the proportion of patients who experienced recurrence of uveitis in the study eye within 6 months of follow-up; recurrence was also assessed at 12 months. Recurrence was defined as either deterioration in visual acuity, vitreous haze attributable to non-infectious uveitis, or the need for rescue medications.

[†]NE=non-evaluable due to the low number of recurrences in the YUTIQ group.

For more information, visit
HCP.YUTIQ.com

INDICATIONS AND USAGE

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

Ocular or Periocular Infections: YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases.

Hypersensitivity: YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

WARNINGS AND PRECAUTIONS

Intravitreal Injection-related Effects: Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection.

Steroid-related Effects: Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection.

Risk of Implant Migration: Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

ADVERSE REACTIONS

In controlled studies, the most common adverse reactions reported were cataract development and increases in intraocular pressure.

Please see brief summary of full Prescribing Information on adjacent page.

References: 1. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg full US Prescribing Information. EyePoint Pharmaceuticals, Inc. February 2022. **2.** Data on file. Alimera Sciences, Inc. MI-DOF-YUT-001. 3. Data on file. Alimera Sciences, Inc. MI-DOF-YUT-002.

Alimera

1-844-445-8843. US-YTQ-MMM-0006-02 10/2023

YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg, for intravitreal injection
Initial U.S. Approval: 1963

BRIEF SUMMARY: Please see package insert for full prescribing information.

1. INDICATIONS AND USAGE. YUTIQ® (fluocinolone acetonide intravitreal implant) 0.18 mg is indicated for the treatment of chronic non-infectious uveitis affecting the posterior segment of the eye.

4. CONTRAINDICATIONS. 4.1. Ocular or Periocular Infections. YUTIQ is contraindicated in patients with active or suspected ocular or periocular infections including most viral disease of the cornea and conjunctiva including active epithelial herpes simplex keratitis (dendritic keratitis), vaccinia, varicella, mycobacterial infections and fungal diseases. **4.2. Hypersensitivity.** YUTIQ is contraindicated in patients with known hypersensitivity to any components of this product.

5. WARNINGS AND PRECAUTIONS. 5.1. Intravitreal Injection-related Effects. Intravitreal injections, including those with YUTIQ, have been associated with endophthalmitis, eye inflammation, increased or decreased intraocular pressure, and choroidal or retinal detachments. Hypotony has been observed within 24 hours of injection and has resolved within 2 weeks. Patients should be monitored following the intravitreal injection *[see Patient Counseling Information (17) in the full prescribing information]*. **5.2. Steroid-related Effects.** Use of corticosteroids including YUTIQ may produce posterior subcapsular cataracts, increased intraocular pressure and glaucoma. Use of corticosteroids may enhance the establishment of secondary ocular infections due to bacteria, fungi, or viruses. Corticosteroids are not recommended to be used in patients with a history of ocular herpes simplex because of the potential for reactivation of the viral infection. **5.3. Risk of Implant Migration.** Patients in whom the posterior capsule of the lens is absent or has a tear are at risk of implant migration into the anterior chamber.

6. ADVERSE REACTIONS. 6.1. Clinical Studies 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 associated with ophthalmic steroids including YUTIQ include cataract formation and subsequent cataract surgery, elevated intraocular pressure, which may be associated with optic nerve damage, visual acuity and field defects, secondary ocular infection from pathogens including herpes simplex, and perforation of the globe where there is thinning of the cornea or sclera. Studies 1 and 2 were multicenter, randomized, sham injection-controlled, masked trials in which patients with non-infectious uveitis affecting the posterior segment of the eye were treated once with either YUTIQ or sham injection, and then received standard care for the duration of the study. Study 3 was a multicenter, randomized, masked trial in which patients with non-infectious uveitis affecting the posterior segment of the eye were all treated once with YUTIQ, administered by one of two different applicators, and then received standard care for the duration of the study. Table 1 summarizes data available from studies 1, 2 and 3 through 12 months for study eyes treated with YUTIQ (n=226) or sham injection (n=94). The most common ocular (study eye) and non-ocular adverse reactions are shown in Table 1 and Table 2.

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Cataract[1]	63/113 (56%)	13/56 (23%)
Visual Acuity Reduced	33 (15%)	11 (12%)
Macular Edema	25 (11%)	33 (35%)
Uveitis	22 (10%)	33 (35%)
Conjunctival Hemorrhage	17 (8%)	5 (5%)
Eye Pain	17 (8%)	12 (13%)
Hypotony Of Eye	16 (7%)	1 (1%)
Anterior Chamber Inflammation	12 (5%)	6 (6%)
Dry Eye	10 (4%)	3 (3%)
Vitreous Opacities	9 (4%)	8 (9%)
Conjunctivitis	9 (4%)	5 (5%)
Posterior Capsule Opacification	8 (4%)	3 (3%)
Ocular Hyperemia	8 (4%)	7 (7%)
Vitreous Haze	7 (3%)	4 (4%)
Foreign Body Sensation In Eyes	7 (3%)	2 (2%)
Vitritis	6 (3%)	8 (9%)
Vitreous Floaters	6 (3%)	5 (5%)
Eye Pruritus	6 (3%)	5 (5%)
Conjunctival Hyperemia	5 (2%)	2 (2%)
Ocular Discomfort	5 (2%)	1 (1%)
Macular Fibrosis	5 (2%)	2 (2%)
Glaucoma	4 (2%)	1 (1%)
Photopsia	4 (2%)	2 (2%)

(continued)

Table 1: Ocular Adverse Reactions Reported in ≥ 1% of Subject Eyes and Non-Ocular Adverse Reactions Reported in ≥ 2% of Patients

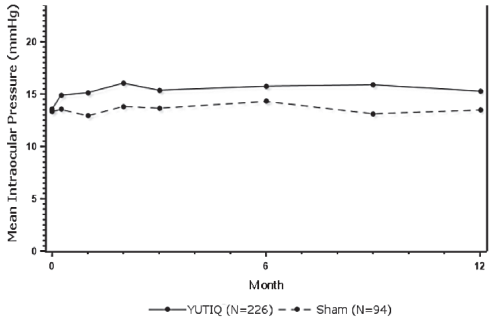
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
ADVERSE REACTIONS	**YUTIQ (N=214 Patients) n (%)**	**Sham Injection (N=94 Patients) n (%)**
Nasopharyngitis	10 (5%)	5 (5%)
Hypertension	6 (3%)	1 (1%)
Arthralgia	5 (2%)	1 (1%)

1. Includes cataract, cataract subcapsular and lenticular opacities in study eyes that were phakic at baseline. 113 of the 226 YUTIQ study eyes were phakic at baseline; 56 of 94 sham-controlled study eyes were phakic at baseline.

Table 2: Summary of Elevated IOP Related Adverse Reactions

ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham (N=94 Eyes) n (%)
IOP elevation ≥ 10 mmHg from Baseline	50 (22%)	11 (12%)
IOP elevation > 30 mmHg	28 (12%)	3 (3%)
Any IOP-lowering medication	98 (43%)	39 (41%)
Any surgical intervention for elevated IOP	5 (2%)	2 (2%)

Figure 1: Mean IOP During the Studies



8. USE IN SPECIFIC POPULATIONS. 8.1 Pregnancy. Risk Summary. Adequate and well-controlled studies with YUTIQ have not been conducted in pregnant women to inform drug associated risk. Animal reproduction studies have not been conducted with YUTIQ. It is not known whether YUTIQ can cause fetal harm when administered to a pregnant woman or can affect reproduction capacity. Corticosteroids have been shown to be teratogenic in laboratory animals when administered systemically at relatively low dosage levels. YUTIQ should be given to a pregnant woman only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a risk of birth defect, loss, or other adverse outcomes. In the United States general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2% to 4% and 15% to 20%, respectively. **8.2 Lactation.** Risk Summary. Systemically administered corticosteroids are present in human milk and can suppress growth, interfere with endogenous corticosteroid production. Clinical or nonclinical lactation studies have not been conducted with YUTIQ. It is not known whether intravitreal treatment with YUTIQ could result in sufficient systemic absorption to produce detectable quantities of fluocinolone acetonide in human milk, or affect breastfed infants or milk production. The developmental and health benefits of breastfeeding should be considered, along with the mother's clinical need for YUTIQ and any potential adverse effects on the breastfed child from YUTIQ. **8.4 Pediatric Use.** Safety and effectiveness of YUTIQ in pediatric patients have not been established. **8.5 Geriatric Use.** No overall differences in safety or effectiveness have been observed between elderly and younger patients.

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THE RETINA PIPELINE

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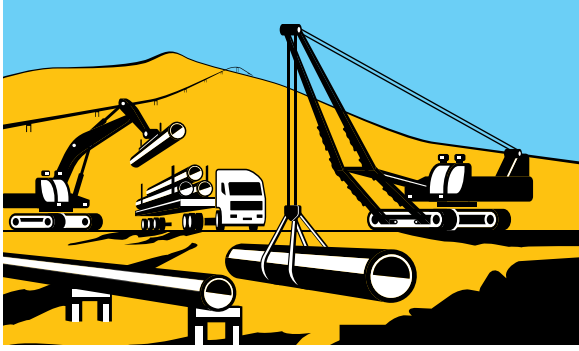

RISK OF DEATH AND VASCULAR EVENTS ELEVATED POST-RAO

Patients who present with a retinal artery occlusion (RAO) are recommended to have emergent stroke workup, although the true risk of death and subsequent vascular events post-RAO is unclear. Looking to bridge this gap, researchers recently found an increased risk of death, stroke, and myocardial infarction (MI) in patients with RAO at both short- and long-term intervals compared with a matched control population diagnosed with cataract.[1]

The retrospective study used aggregated electronic health records of 34,874 patients with at least 1 year of follow-up who had an RAO event at a mean 66 years of age. The rate of death after RAO diagnosis was higher than after cataract diagnosis at 2 weeks, 30 days, and 1, 5, and 10 years. The risks of stroke and MI after RAO were also higher at 2 weeks, 30 days, and 1, 5, and 10 years.[1]

Although the risk was lower than previously reported within 1 month of RAO diagnosis, these results support awareness of the association between death, MI, and stroke after RAO, emphasizing the need for multidisciplinary evaluation and long-term follow-up of these patients.[1]

1. Wai KM, Knapp A, Ludwig CA, et al. Risk of stroke, myocardial infarction, and death after retinal artery occlusion [published online ahead of print October 26, 2023]. *JAMA Ophthalmol.*

PUBLIC INSURANCE LINKED TO DEVELOPMENTAL ISSUES IN INFANTS

A recent study suggests an association between a patient's insurance type and neurodevelopmental impairment (NDI) in preterm infants screened for retinopathy of prematurity (ROP). Outcomes also supported the early neurodevelopmental safety of anti-VEGF treatment, which was not found to be associated with worse NDI.[1]

The retrospective study used US Census Bureau income data and electronic health records of 706 infants screened for ROP. Results showed that public health insurance was associated with a four-fold increased risk of moderate to severe NDI in cognitive and language domains (odds ratios: 3.65 and 3.96, respectively), as well as a three-fold increased risk in the motor domain (odds ratio: 2.60).[1]

Clinical factors that were associated with an increased risk of moderate to severe NDI included lower birth weight, diagnosis of intraventricular hemorrhage, male sex, and older age at the time of neurodevelopment assessment. In unadjusted analyses, infants with ROP who received either laser or anti-VEGF treatment had lower neurodevelopmental scores in multiple domains up to 3 years of age. Treatment type was not associated with worse neurodevelopmental outcomes in any domain in the multivariable model.[1]

1. Karmouta R, Strawbridge JC, Langston S, et al. Neurodevelopmental outcomes in infants screened for retinopathy of prematurity [published online ahead of print October 26, 2023]. *JAMA Ophthalmol.*

DIVERSITY LACKING IN SUBSPECIALTY FELLOWSHIP APPLICANTS

Researchers conducted a cohort study of ophthalmology subspecialty fellowship data from the 2021 San Francisco Match to examine the applicants' gender, racial, and ethnic diversity. According to their findings, female applicants were underrepresented in the retina subspecialty, while underrepresented in medicine (URiM) applicants were underrepresented across all subspecialties.[1]

A total of 537 fellowship candidates were included; among them, 224 applicants (42.6%) were female, and 60 applicants (12.9%) had URiM status. The study found that male and female applicants had similar match rates (70.5% and 69.2%, respectively; $P = .74$), and the highest percentage of female matches was identified in pediatric ophthalmology. In addition, URiM applicants had lower match rates compared with non-URiM applicants (55% vs 72.2%; $P = .007$). Of matched fellows in each subspecialty, URiM applicants comprised 13.9% in glaucoma, 10% in pediatric ophthalmology, 7.3% in cornea, and 6.6% in retina.[1]

This study demonstrates that diversity efforts are still needed in ophthalmology training programs to achieve an equitable racial and ethnic balance between the ophthalmic field and the general population.[1]

1. Ali M, Menard M, Zafar S, Williams Jr BK, Knight OJ, Woreta FA. Sex and racial and ethnic diversity among ophthalmology subspecialty fellowship applicants. *JAMA Ophthalmol.* 2023;141(10):948-954.

ALGORITHM PREDICTS PROGRESSION TO GEOGRAPHIC ATROPHY

A retrospective multicenter study demonstrated that a fully automated deep-learning algorithm was able to successfully predict progression from intermediate AMD (iAMD) to geographic atrophy (GA) based on the analysis of spectral-domain OCT (SD-OCT) scans.[1]

A total of 417 patients with iAMD were included in the study. The deep-learning algorithm was trained and cross-validated on one dataset of SD-OCT volumes and was further validated on two external SD-OCT datasets. Prediction of progression to GA within 1 year was evaluated using various metrics, including: area under the receiver-operator characteristic curves (AUROC), area under the precision-recall curve (AUPRC), sensitivity, and specificity. For dataset one (n = 316), the AUROC for prediction of progression from iAMD to GA was 0.94 (95% CI, 0.92-0.95; AUPRC, 0.90; sensitivity, 0.88; specificity, 0.90). In dataset two (n = 53), an independent validation dataset, the model also predicted progression to GA with an AUROC of 0.94 (CI, 0.91-0.96).[1]

These findings suggest that AI may be a helpful tool in combination with standard imaging and diagnostics to guide clinical decision-making in the treatment of patients with iAMD who are at risk of progressing to GA.[1]

1. Dow ER, Jeong HK, Katz EA, et al. A deep-learning algorithm to predict short-term progression to geographic atrophy on spectral-domain optical coherence tomography [published online ahead of print October 19, 2023]. *JAMA Ophthalmol.*

GLOW TRIAL DATA BREATHES LIFE INTO KODIAK PROGRAM

Kodiak Sciences announced the reinitiation of its tarcocimab program after the phase 3 GLOW trial of KSI-501 met all primary and secondary endpoints with high statistical significance. The trial investigated every-24-week dosing with 5 mg tarcocimab versus sham for patients with moderately severe and severe nonproliferative diabetic retinopathy without diabetic macular edema. At 1 year, 41.1% of patients treated with tarcocimab every 24 weeks experienced at least a two-step improvement in Diabetic Retinopathy Severity Scale score versus 1.4% of patients in the sham group. Visual acuity remained stable throughout the study, and the mean change in central subfield thickness was -15.1 µm in the treatment group compared with 7.8 µm in the sham arm.[1]

Treatment with tarcocimab also led to an 89% reduced risk of sight-threatening complications and a 95% reduced risk of the development of diabetic macular edema versus sham.[1]

The company halted the program in July after the phase 3 GLEAM and GLIMMER studies failed to meet their primary endpoints. With FDA guidance and the positive trial data, Kodiak is planning another pivotal trial with an enhanced commercial formulation of KSI-501. The trial will support a single biologics license application submission for macular edema following retinal vein occlusion, wet AMD, and nonproliferative diabetic retinopathy.[1] ■

1. Kodiak reboots tarcocimab tedromer development program following strong positive results in phase 3 diabetic retinopathy GLOW study and following dialogue with US regulatory authorities on a regulatory pathway for BLA submission [press release]. Kodiak Sciences. November 6, 2023. Accessed November 8, 2023. ir.kodiak.com/news-releases/news-release-details/kodiak-reboots-tarcocimab-tedromer-development-program-following

Eyewire+ Pharma Update

- **Ocular Therapeutix** announced that it has received an FDA agreement under a Special Protocol Assessment for the design of its phase 3 pivotal trial for Axpaxli (axitinib intravitreal implant), also known as OTX-TKI, for the treatment of wet AMD. The trial will enroll approximately 300 treatment-naïve patients who will receive either a single implant or aflibercept (Eylea, Regeneron), followed by rescue anti-VEGF based on prespecified criteria.
- At the 2023 Eyecelerator@AAO meeting, **Nanoscope Therapeutics** was awarded "Best of Show" for retina. Samuel Barone, MD, CEO, presented on the company's multicharacteristic opsin platform. Stephen H. Tsang, MD, PhD, later presented topline data from the phase 2 STARLIGHT trial of MCO-010 optogenetic therapy for vision loss in Stargardt disease during AAO Retina Subspecialty Day.
- **Endogena Therapeutics** received FDA approval of its investigational new drug application and is initiating a first-in-human study next year for its geographic atrophy (GA) drug candidate, EA 2351. The drug targets retinal pigment epithelial cells.
- **Samsung Bioepis** announced that the FDA has approved ranibizumab-nuna (Byooviz) as a biosimilar product interchangeable with ranibizumab (Lucentis, Genentech/Roche). The biosimilar was originally approved in September 2021 for the treatment of wet AMD, macular edema following retinal vein occlusion (RVO), and myopic choroidal neovascularization.
- **Genentech/Roche** received FDA approval for faricimab-svoa (Vabysmo) for the treatment of macular edema following RVO.
- **Annexon** announced that the European Medicines Agency granted Priority Medicine designation to ANX007 for the treatment of GA. Approval was based on successful phase 2 ARCHER trial data, which showed a statistically significant, durable, dose-dependent preservation of visual function in patients with GA.
- **Roche** announced the discontinuation of clinical development of vicasinabin (RG7774), an oral drug candidate under investigation for nonproliferative diabetic retinopathy that completed phase 2 trials.
- **Ocuphire Pharma** announced the completion of a positive end-of-phase 2 FDA meeting for oral APX3330 for the treatment of diabetic retinopathy. The company plans to move forward with phase 3 studies based on positive phase 2 ZETA-1 trial data.

Want more retina news from *Eyewire+*?

INDICATION

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

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

A moment worth protecting

Every moment is precious for your patients with geographic atrophy. Help protect their moments from the start with IZERVAY™.

Learn more at
IZERVAYecp.com

iZervay™
(avacincaptad pegol intravitreal solution) 2 mg

- Neovascular AMD
  - In clinical trials, use of IZERVAY was associated with increased rates of neovascular (wet) AMD or choroidal neovascularization (7% when administered monthly and 4% in the sham group) by Month 12. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.
- Increase in Intraocular Pressure
  - Transient increases in intraocular pressure (IOP) may occur after any intravitreal injection, including with IZERVAY. Perfusion of the optic nerve head should be monitored following the injection and managed appropriately.

ADVERSE REACTIONS

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

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

US-AP-2300207 09/23

IVERIC BIO
An Astellas Company

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 609-474-6755.

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

2 DOSAGE AND ADMINISTRATION
2.1 General Dosing Information
IZERVAY must be administered by a qualified physician.

2.2 Recommended Dosage
The recommended dose for IZERVAY is 2 mg (0.1 mL of 20 mg/mL solution) administered by intravitreal injection to each affected eye once monthly (approximately every 28 ± 7 days) for up to 12 months.

2.4 Injection Procedure
Only 0.1 mL (2 mg) should be administered to deliver a single dose. Any excess volume should be disposed.

Prior to the intravitreal injection, patients should be monitored for elevated intraocular pressure (IOP) using tonometry. If necessary, ocular hypotensive medication can be given to lower the IOP.

The intravitreal injection procedure must be carried out under controlled aseptic conditions, which includes the use of surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent). Adequate anesthesia and a broad-spectrum topical microbicide should be given prior to the injection.

Inject slowly until the rubber stopper reaches the end of the syringe to deliver the volume of 0.1 mL. Confirm delivery of the full dose by checking that the rubber stopper has reached the end of the syringe barrel.

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure (IOP). Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry.

Following intravitreal injection, patients should be instructed to report any symptoms suggestive of endophthalmitis (e.g., eye pain, redness of the eye, photophobia, blurring of vision) without delay.

Each vial and syringe should only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial and syringe should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter needle, and injection needle should be changed before IZERVAY is administered to the other eye. Repeat the same procedure steps as above.

Any unused medicinal product or waste material should be disposed of in accordance with local regulations.

3 DOSAGE FORMS AND STRENGTHS
Intravitreal solution: 20 mg/mL clear to slightly opalescent, colorless to slightly yellow solution in a single-dose vial.

4 CONTRAINDICATIONS
4.1 Ocular or Periocular Infections
IZERVAY is contraindicated in patients with ocular or periocular infections.

4.2 Active Intraocular Inflammation
IZERVAY is contraindicated in patients with active intraocular inflammation.

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

5.2 Neovascular AMD
In 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. Patients receiving IZERVAY should be monitored for signs of neovascular AMD.

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

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

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

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

The safety of avacincaptad pegol was evaluated in 733 patients with AMD in two sham-controlled studies (GATHER1 and GATHER2). Of these patients, 292 were treated with intravitreal IZERVAY 2 mg (0.1 mL of 20 mg/mL solution). Three hundred thirty-two (332) patients were assigned to sham.

Adverse reactions reported in ≥2% of patients who received treatment with IZERVAY pooled across GATHER1 and GATHER2, are listed below in Table 1.

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

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

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

8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
Risk Summary
There are no adequate and well-controlled studies of IZERVAY administration in pregnant women. The use of IZERVAY may be considered following an assessment of the risks and benefits.

Administration of avacincaptad pegol to pregnant rats and rabbits throughout the period of organogenesis resulted in no evidence of adverse effects to the fetus or pregnant female at intravenous (IV) doses 5.1 times and 3.2 times the human exposure (based on AUC) at the maximum recommended human dose (MRHD) of 2 mg once monthly, respectively.

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 intravenous (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 5.1 times the MRHD, based on Area Under the Curve (AUC).

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 3.2 times the human exposure at the MRHD, based on AUC.

8.2 Lactation
There is no information regarding the presence of avacincaptad pegol in human milk, the effects of the drug on the breastfed infant or on milk production.

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.

17 PATIENT COUNSELING INFORMATION
Advise patients that following IZERVAY administration, patients are at risk of developing neovascular AMD, endophthalmitis, elevated intraocular pressure and retinal detachments. If the eye becomes red, sensitive to light, painful, or if a patient develops a change in vision, instruct the patient to seek immediate care from an ophthalmologist.

Patients may experience temporary visual disturbances and blurring after an intravitreal injection with IZERVAY and the associated eye examinations. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

Manufactured by:
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FOUNDERS LECTURE AT ARDS 2023

Gregg T. Kokame, MD, MMM, shares his expertise on AMD subtypes.

BY DANIEL WANG, MD

The 2023 Aspen Retinal Detachment Society (ARDS) meeting in Snowmass, Colorado, included the annual Founders Lecture. This year, we honored Gregg T. Kokame, MD, MMM, for his extensive work with AMD subtypes, and polypoidal choroidal vasculopathy (PCV) in particular. Below you will find a robust summary of his lecture, which included several clinically relevant pearls.

Registration is open for ARDS 2024, set for March 2-6. Visit aspenretina.com *for more information and get ready to hit the slopes!*

- Timothy G. Murray, MD, MBA

We have made significant progress in the diagnosis and management of AMD, but it continues to be a complex condition with substantial ocular morbidity on a global scale. During the 2023 ARDS Founders Lecture, Gregg T. Kokame, MD, MMM, provided a review of the categorization and management of wet AMD (Figures 1 and 2). This update encompassed the condition's anatomic variations and how he customizes his treatment approach based on the specific subtype. Dr. Kokame underscored the significance of ethnic disparities in AMD and highlighted the subtype of PCV.

ETHNIC CONSIDERATIONS

Dr. Kokame emphasized the distinctions between Asian and non-Asian AMD patients, noting that AMD in Asian patients typically manifests with smaller lesions and a slower growth rate. This raises questions regarding the efficacy of certain therapies, particularly newer treatments such as Syfovre (pegcetacoplan, Apellis), in the Asian population. Dr. Kokame stressed the importance of clinically relevant classification systems, specifically mentioning the consensus nomenclature for categorizing wet AMD proposed by Richard F. Spaide, MD. This framework outlines the subtypes of choroidal neovascularization (CNV): type I, type II, type III, and PCV.[1]

THE SUBTYPES

For initial patient evaluations, Dr. Kokame employs a variety of imaging techniques, including fundus photography, fluorescein angiography, ICG angiography, OCT, and OCT angiography.[2] Subsequently, patients are typically monitored using OCT alone, he said.

Type III CNV includes an intraretinal neovascular component, termed *retinal angiomatous proliferation*, and is exceptionally sensitive to anti-VEGF treatment, leading Dr. Kokame to recommend as-needed treatment for patients with this subtype of AMD. He suggested that treatment can be extended aggressively and stopped in some, but not all, cases.[3,4]

Type II CNV, found above the retinal pigment epithelium (RPE) and under the retina, is often enveloped by a layer of RPE. This type is also highly responsive to anti-VEGF therapy, often enabling a quick treat-and-extend protocol and eventual discontinuation of treatment.[3,4]

Type I CNV, beneath the RPE and above Bruch membrane, is the most common CNV and has the most variable therapeutic response. Among the subtypes of wet AMD, type I CNV is the most prevalent but exhibits variable sensitivity to anti-VEGF treatments, sometimes proving resistant.[3-5]

Dr. Kokame discussed several case studies to illustrate the differences in treatment response among the various AMD subtypes.

PCV UNDER THE MICROSCOPE

PCV received significant attention in Dr. Kokame's presentation due to its clinical importance. PCV has a varied prevalence among different ethnic groups and is often underrecognized and misdiagnosed. Dr. Kokame asserted that identifying PCV is crucial due to its effect on treatment and its predictive role in anti-VEGF resistance.

ICG angiography remains the standard for diagnosing

ABOUT THE SPEAKER

Gregg T. Kokame, MD, MMM

- Chief of Ophthalmology and Clinical Professor, University of Hawaii John A. Burns School of Medicine, Honolulu
- Founding Partner and Senior Consultant, Retina Consultants of Hawaii, Honolulu
- Medical Director, Hawaii Macula and Retina Institute, Oahu, Hawaii

Figure 1. Program Directors Donald J. D'Amico, MD, (left) and Dr. Murray (right) present Dr. Kokame (center) with the 2023 Founders Lecture Award.

Images courtesy of Kevin Caldwell Photography

Figure 2. Dr. Kokame discussed the different subtypes of AMD, including polypoidal choroidal vasculopathy.

PCV, demonstrating typical aneurysmal polyps at the edges of the choroidal neovascular network, Dr. Kokame said.

PCV can manifest as either type I or type II CNV; the more common type I has a well-defined branching vascular network (both feeder and draining vessels), whereas type II has polyps but no defined branching vascular network.[3-5]

Notably, PCV exhibits a 50% prevalence of anti-VEGF resistance, with the closure of polyps serving as a predictor of clinical response. Given its relatively high prevalence, particularly among Asian patients, PCV demands careful consideration when evaluating patients with wet AMD.[3-5]

In Asian regions, aflibercept (Eylea, Regeneron) is often recommended for the treatment of PCV, although ranibizumab (Lucentis, Genentech/Roche) and bevacizumab (Avastin, Genentech/Roche) are often also employed. Dr. Kokame reviewed the EVEREST II study, which demonstrated that a combination of photodynamic therapy (PDT) and anti-VEGF therapy with ranibizumab yielded improved visual outcomes, increased odds of complete polypoidal lesion regression, and fewer treatments compared with anti-VEGF monotherapy.[6]

Dr. Kokame also discussed distinctions between anti-VEGF agents, including aflibercept, ranibizumab, brolucizumab (Beovu, Novartis), and faricimab (Vabysmo, Genentech/Roche). Aflibercept is typically favored in Asia for PCV, showing better visual gains in the PLANET study compared with data from the EVEREST II study. The HAWK study showed that brolucizumab administered every 8 or 12 weeks resulted in consistent visual acuity gains that were comparable with aflibercept dosed every 8 weeks.[7] Anatomic outcomes favored brolucizumab over aflibercept, with 76% of patients treated with brolucizumab receiving a dose every 12 weeks after the initial loading phase.[7] While faricimab holds promise for treatment, it requires further study in the context of PCV patients, according to Dr. Kokame.

Dr. Kokame then shared his current treatment algorithm for PCV, which involves monitoring patients with inactive PCV and treating patients with active PCV with leakage or bleeding based on location and severity. Laser or PDT treatment may be considered for extrafoveal PCV, while subfoveal PCV (depending on vision and the presence of dense subretinal hemorrhage) may be treated with anti-VEGF monotherapy or a combination of PDT and anti-VEGF. An FDA-approved laser for PDT (ML6710i, Modulight) is anticipated to expand access to this treatment option, he added.

KEY PEARLS

A thorough understanding of AMD subtypes is vital, Dr. Kokame concluded, as it can predict treatment responses and influence treatment decisions. PCV remains a crucial but often overlooked subtype of wet AMD, particularly in individuals of Asian descent. This knowledge helps inform tailored treatment approaches, optimizing the efficacy of planned interventions. ■

1. Spaide RF, Jaffe GJ, Sarraf D, et al. Consensus nomenclature for reporting neovascular age-related macular degeneration data: Consensus on Neovascular Age-Related Macular Degeneration Nomenclature Study Group. *Ophthalmology*. 2020;127(5):616-636.
2. Mettu PS, Allingham MJ, Nicholas PC, Cousins SW. Neovascular morphology by IC angiography and response to loading-dose anti-VEGF therapy in patients with neovascular AMD. *Invest Ophthalmol Vis Sci*. 2016;57(12).
3. Kokame GT, Liu K, Kokame KA, Kaneko KN, Omizo JN. Hawaii Causcasian PCV study. *Ophthalmologica*. 2020;243(3):178-186.
4. Kokame GT, deCarlo TE, Kaneko KN, Omizo JN, Lian R. Asian and Caucasian PCV study. *Ophthalmol Retina*. 2019;3(9):744-752.
5. Kokame GT, deCarlo TE, Kaneko KN, Omizo JN, Lian R. Anti-vascular endothelial growth factor resistance in exudative macular degeneration and polypoidal choroidal vasculopathy. *Ophthalmol Retina*. 2019;3(9):744-752.
6. Lim TH, Lai TYY, Takahashi K, et al; EVEREST II Study Group. Comparison of ranibizumab with or without verteporfin photodynamic therapy for polypoidal choroidal vasculopathy: the EVEREST II Randomized Clinical Trial. *JAMA Ophthalmol*. 2020;138(9):935-942.
7. Ogura Y, Jaffe GJ, Cheung CMG, et al. Efficacy and safety of brolucizumab versus aflibercept in eyes with polypoidal choroidal vasculopathy in Japanese participants of HAWK. *Br J Ophthalmol*. 2022;106(7):994-999.

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- Financial disclosure: None

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CLINICAL TRIALS IN THE SPOTLIGHT


This year's Clinical Trials at the Summit was packed with pipeline therapeutics.

BY HANNAH KHAN, MSII, AND AAMIR A. AZIZ, MSIII

The third annual Clinical Trials at the Summit (CTS) meeting, held in Park City, Utah, brought together retina specialists and industry partners to discuss advances in clinical research and showcase novel ideas. Leaders Arshad M. Khanani, MD, MA; Peter K. Kaiser, MD; and Jeffrey S. Heier, MD, worked diligently to ensure the latest retinal research was on display. The unique panel format, led by world-class faculty and leaders in the retina space, formulated a collaborative and innovative environment (Figures 1-3).

WET AMD

Sophie J. Bakri, MD, MBA, shared that no safety concerns were noted at the primary endpoint in the DAVIO phase 1 study of vorolanib (EYP-1901, EyePoint Pharmaceuticals), a tyrosine kinase inhibitor delivered via the company's Durasert sustained delivery platform. Patients demonstrated a reduction in treatment burden at 12 months, and 35% of patients were free of supplemental injections at 12 months.

Thomas A. Ciulla, MD, MBA, chief medical advisor-retina and chair of the scientific advisory board at Clearside Biomedical, discussed a favorable safety profile with CLS-AX, the company's tyrosine kinase inhibitor, delivered suprachoroidally. He noted that patients in the higher dose cohorts demonstrated a 77% to 85% reduction in treatment burden.

Robert L. Avery, MD, presented the real-world TRUCKEE study evaluating the safety, efficacy, and durability of faricimab (Vabysmo, Genentech/Roche) in patients with wet AMD. He said that patients demonstrated significant visual and anatomical improvements following one and three injections of faricimab. The real-world results have shown the importance and benefit of dual inhibition, he added.

DELIVERY AND DEVICES

Dr. Khanani presented the 5-year results from the Portal study with the port delivery system (PDS) with ranibizumab (Susvimo, Genentech/Roche), stating that no new cases of endophthalmitis were documented, and the device was generally well-tolerated at 100 mg/mL with stable BCVA and central subfield thickness.

Shamika Gune, MD, MS, group medical director at Genentech, also presented on the PDS, sharing that no additional macular atrophy was noted with continued ranibizumab delivery when compared with monthly intravitreal injections of ranibizumab.

Image courtesy of Tawnie Baranick of T-ART photos

Figure 1. The 2023 "Summit of Excellence" Lifetime Achievement Award was presented to Robert Y. Kim, MD, chief medical officer at 4D Molecular Therapeutics. Pictured here (left to right) are Peter K. Kaiser, MD; Jeffrey S. Heier, MD; Dr. Kim; and Arshad M. Khanani, MD, MA.

Carlos Quezada-Ruiz, MD, discussed updates on the safety of the PDS, with an expected return in 2024.

Quan Dong Nguyen, MD, MSc, presented the suprachoroidal triamcinolone real-world study for uveitic macular edema, noting that patients gained 2 to 3 lines of vision with reduced retinal thickness.

Courtney M. Crawford, MD, discussed the new commercial processes for ABBV-RGX-314, Regenxbio's subretinal gene therapy for wet AMD and diabetic retinopathy (DR), noting that data show similar efficacy to the previous formulation.

DIABETIC EYE DISEASE

Michael A. Singer, MD, PhD, presented data from the PALADIN study and discussed the safety and consistency of the 0.19 mg fluocinolone acetonide intravitreal implant (Alimera Sciences) for diabetic macular edema. He also touched on the NEW DAY study comparing the implant with aflibercept (Eylea, Regeneron). Dr. Singer discussed treatment resistance and noted that faricimab should be introduced as an option prior to considering steroids.

David R. Lally, MD, presented on Ocuphire's ZETA-1 phase 2 trial of an oral DR therapy, which did not meet its primary endpoint. Still, no patients treated with APX3330

Image courtesy of Tawnie Baranick of T-ART photos

Figure 2. The 2023 CTS "Lifetime Achievement – Summit of Excellence Award" was presented to Daniel F. Martin, MD. Pictured here (left to right) are Jeffrey S. Heier, MD; Arshad M. Khanani, MD, MA; Pam Martin; Dr. Martin; and Peter K. Kaiser, MD.

had a binocular ≥ 3-step Diabetic Retinopathy Severity Score worsening from baseline compared with 16% of those treated with placebo (P = .04) after 24 weeks. The end-of-phase 2 meeting with the FDA is planned for Q4 2023.

GENE THERAPY

The conference boasted several updates on various gene therapy candidates, including 4D-150 (4D Molecular Therapeutics), presented by Veeral Sheth, MD, MBA. Intravitreal 4D-150 was found to be well-tolerated in the phase 1/2 PRISM study with the maintenance of visual acuity and anatomy in previously treated wet AMD patients with significant reduction in treatment burden.

Nadia K. Waheed, MD, MPH, chief medical officer for Beacon Therapeutics, discussed the company's gene therapy for X-linked retinitis pigmentosa, AGTC-501, with 3-month data from the SKYLINE study showing improvements in visual sensitivity.

NOVEL MECHANISMS OF ACTION

Ramanath Bhandari, MD, founder and interim chief executive officer for Revopsis, presented on RO-101, the company's surrogate antibody that targets ang-2 and VEGF-A. Initial data show that the therapeutic demonstrated superior binding affinity to ang-2 when compared with faricimab. Dr. Bhandari noted that RO-101 is undergoing safety/toxicology testing with first-in-human trials expected in 2024.

Eduardo Uchiyama, MD, presented the phase 1 DOVETAIL study of RG6179 (Genentech/Roche), a recombinant monoclonal antibody designed to inhibit IL-6 signaling. The

Image courtesy of Arshad M. Khanani, MD, MA

Figure 3. Fun at CTS 2023 with world-class faculty and leaders! Pictured here (left to right) are David S. Boyer, MD; Ramin Tadayoni, MD, PhD; Arshad M. Khanani, MD, MA; Jeffrey S. Heier, MD; Peter K. Kaiser, MD; Diana V. Do, MD; and SriniVas R. Sadda, MD.

therapy is generally well-tolerated, he said, showing improvements in vision and retinal thickness for up to 20 weeks.

Peter A. Campochiaro, MD, presented on an AAV vector-based gene therapy, EXG102-031 (Exegenesis Bio), stating that subretinal suppression of VEGF-A demonstrated decreased neovascularization and exudation.

FIRST TIME RESULTS

Dr. Khanani presented on OTX-TKI (Ocular Therapeutix), a bioresorbable implant with axitinib under investigation for the treatment of wet AMD, DR, and other retinal diseases. Initial data show that the therapy provided visual acuity and anatomical stability at 12 months.

Dr. Khanani also presented favorable data from the phase 3 DIAMOND study of OCS-01 (Oculis)—a topical formulation of dexamethasone—confirming the benefit of treatment for patients with diabetic macular edema. He noted that 25% of treated patients gained 3 lines by week 6 and 27.4% by week 12. In addition, patients saw a 63.6 µm reduction in central subfield thickness by week 6.

UNTIL NEXT TIME

We are looking forward to the innovation, collaboration, engagement, sponsorship, and support for CTS 2024! ■

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WHERE IT ALL BEGAN

Daniel Su, MD, was born in Taiwan, and his family moved to New Zealand when he was young; they moved again during his high school years, this time to California.

He studied electrical engineering at the Univeristy of California Los Angeles and was preparing for a career in medical device engineering. However, he was insipired to pursue medicine while working on a project involving the da Vinci surgical robot (Intuitive Surgical).

HIS PATH TO RETINA

Dr. Su first became interested in ophthalmology while working as an undergraduate in a lab that studied rhodopsin. Although he kept an open mind and explored other subspecialities during residency, he gravitated toward retina specialists and senior residents who wanted to pursue retina. Dr. Su found this group of physicians to be down to earth, compassionate, and fun to be around. Ultimately, the breadth of pathology, intricate and challenging surgeries, and innovative environment led him to pursue a career in retina.

SUPPORT ALONG THE WAY

Dr. Su has been fortunate to have great mentors at every step of his training. In residency, Uday Devgan, MD; Pradeep Prasad, MD, MBA; and David Sarraf, MD, fostered his growth as an ophthalmologist and supported his goals of pursuing a career in retina.

During fellowship at Wills Eye Hopsital, Dr. Su had the opportunity to learn from many amazing mentors, including Arunan Sivalingam, MD; Michael A. Klufas, MD; Omesh P. Gupta, MD, MBA; Jason Hsu, MD; Allen C. Ho, MD; and Carl D. Regillo, MD.

After training, Dr. Su found mentors and colleagues within his own practice. Thomas G. Chu, MD; Firas M. Rahhal, MD; and David S. Boyer, MD, are a constant source of advice for everything retina and beyond.

Daniel Su, MD, is a partner at the Retina-Vitreous Associates Medical Group in Los Angeles and an adjunct clinical assistant professor at the Keck School of Medicine at the University of Southern California. He is a consultant for Ocuphire and a consultant and speaker for Regeneron. He can be reached at **dsu@laretina.com**.

Dr. Su's Advice: The relationships you develop with your mentors and peers during training do not end after residency and fellowship. Continue to invest in those relationships and seek advice whenever you need help. It's not only the relationships we build with our patients, but also the ones we have with our peers and mentors that make the field of retina so rewarding.

AN EXPERIENCE TO REMEMBER

Dr. Su's most memorable encounters to date have involved patients who were referred to him to rule out possible retinal pathologies, but none were found. Instead, Dr. Su had to rely on his comprehensive ophthalmology training to recognize visual field abnormalities that led to the diagnosis of stroke or brain tumor.

These "karate kid" moments make him appreciate his training from residency, even if at the time it might not have seemed relevant to an aspiring retina specialist. ■

HOW TO RECOGNIZE BARDET-BIEDL SYNDROME

Early diagnosis and genetic testing are necessary to initiate proper multidisciplinary intervention.

BY MARIANA ABI KARAM, MD, AND JACLYN L. KOVACH, MD

Bardet-Biedl syndrome (BBS) is a rare, autosomal recessive, inherited systemic disease categorized as a nonmotile ciliopathy. Mutations in 26 genes have been identified to cause BBS, with *BBS1* being the most frequent (23%), followed by *BBS10* (15%) and *BBS2* (10%).[1,2] Rods and cones contain the primary cilia-like structures affected by such mutations; thus, this disease process hinders protein transport and leads to their intracellular accumulation, photoreceptor death, and vision loss.[2] Here, we describe the findings of three siblings diagnosed with BBS.

CASE REPORT

A 20-year-old woman presented to our clinic with nyctalopia and a gradual decrease in vision. At presentation, her BCVA was 20/50 OD and 20/80 OS. She had high myopia and astigmatism. Past medical history included obesity since childhood, operated polydactyly, polycystic ovary syndrome, and a learning disability. Her twin brother and a younger brother each had polydactyly, obesity, and learning disabilities as well. She also had a paternal aunt with a history of polydactyly and death from ovarian cancer at age 27, and her maternal grandfather and aunt had severe diabetes mellitus.

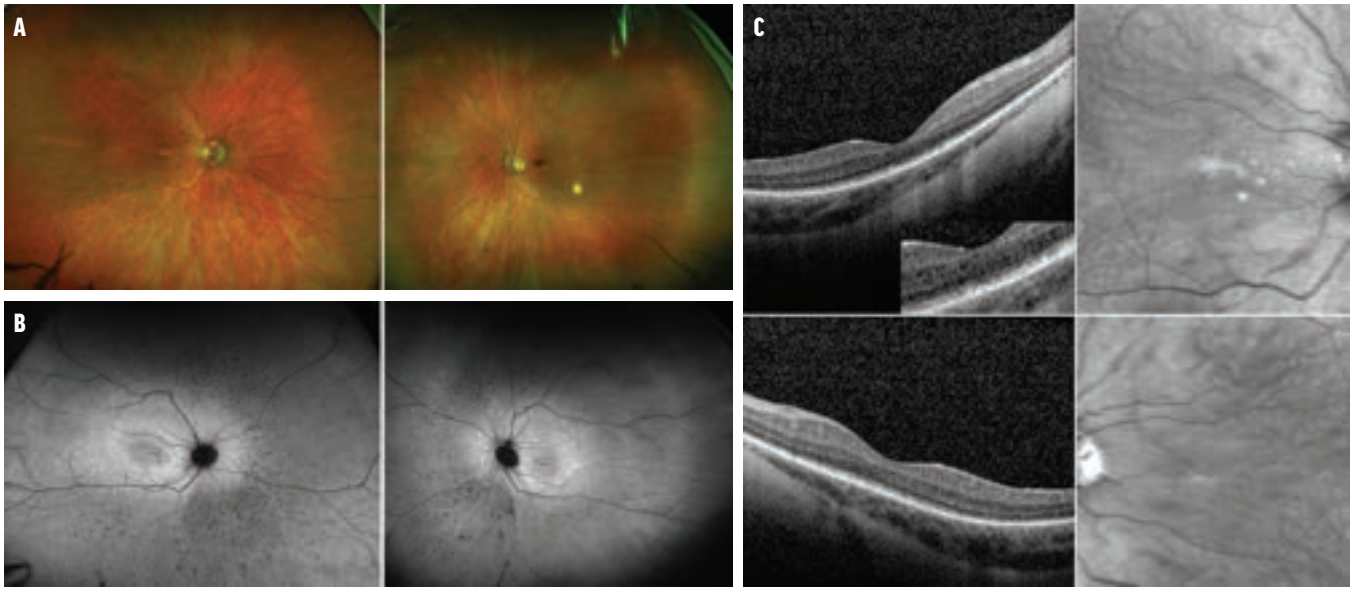

Figure 1. Fundus photography of a 20-year-old woman shows pigmentary changes in the macula and periphery of the right and left eyes (A). FAF shows diffuse retinal pigmentary changes in the right and left eyes (B). SD-OCT demonstrates ellipsoid zone disruption in the right and left eyes (C).

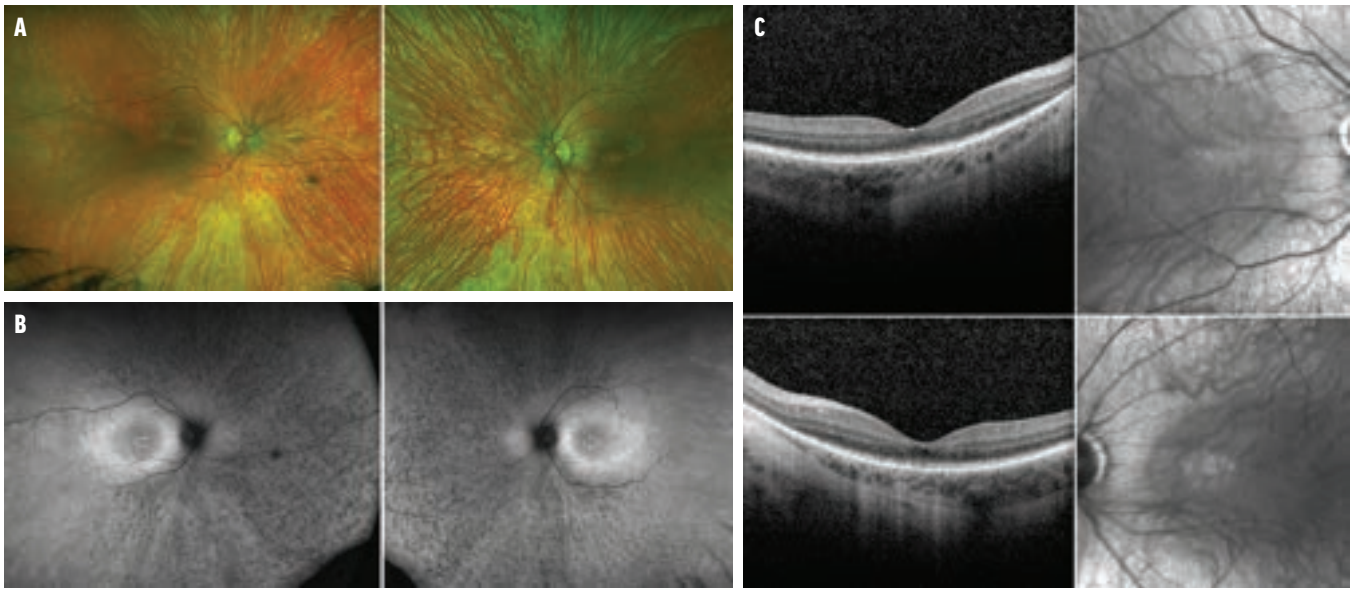

Figure 2. Fundus photography of the right and left eyes of the twin brother shows macular and peripheral pigmentary changes (A). FAF of the right and left eyes shows diffuse retinal pigmentary changes (B). SD-OCT of right and left eyes demonstrates ellipsoid zone disruption (C).

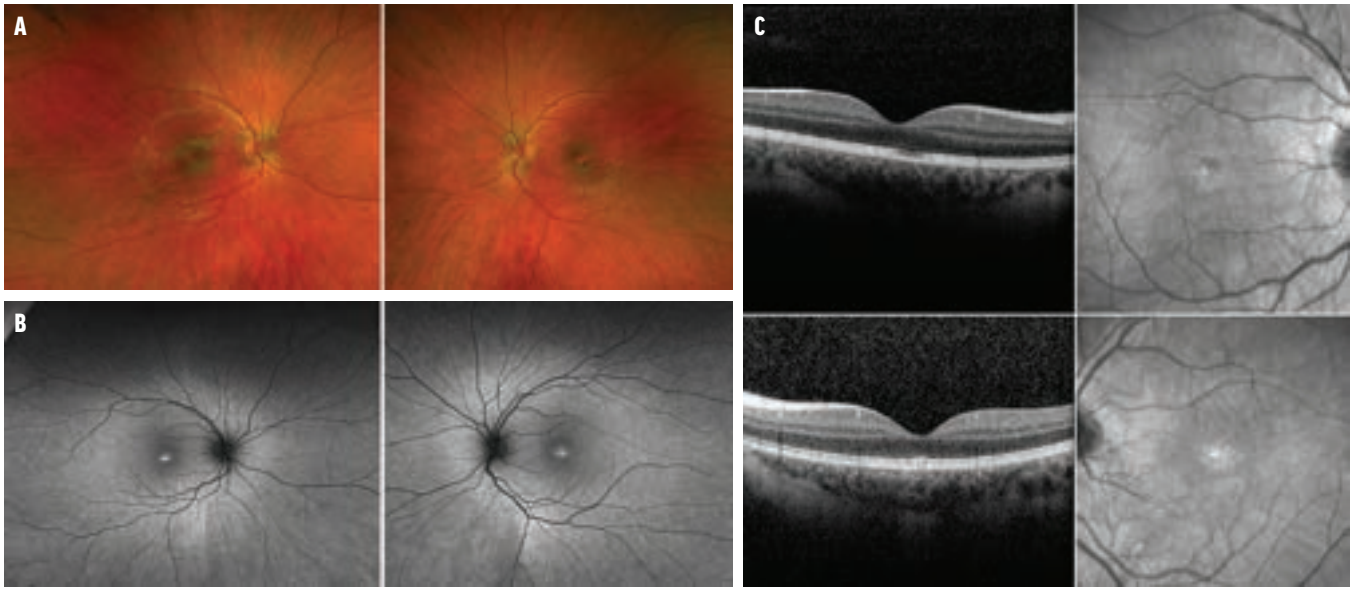

Figure 3. Fundus photography of the right and left eyes of the 17-year-old brother shows more subtle pigmentary changes compared with his older siblings (A). FAF of the right and left eyes shows a subtle pigmentary retinopathy and a hyperautofluorescent macular lesion (B). SD-OCT demonstrates subretinal deposits in the fovea of each eye (C).

Slit-lamp examination was normal. Color fundus imaging and fundus autofluorescence (FAF) revealed central macular and peripheral pigmentary changes in each eye (Figure 1A and B). Spectral-domain OCT (SD-OCT) demonstrated outer retinal disruption (Figure 1C).

The patient's twin brother had a history of operated polydactyly, obesity, more severe cognitive impairment, high myopia, and astigmatism. His BCVA was 20/30 OU, tested with Allen pictures blocked. Color fundus imaging and FAF revealed pigmentary changes in the macula, along with more extensive peripheral pigmentary changes compared with his sister (Figure 2A and B). SD-OCT demonstrated marked outer retinal disruption (Figure 2C).

The twins' 17-year-old brother had a history of operated polydactyly, obesity, and mild cognitive impairment, along with moderate myopia and astigmatism. His BCVA was 20/40 OD and 20/30 OS. Color fundus imaging and FAF revealed a milder pigmentary retinopathy compared with his siblings and a hyperautofluorescent lesion in the macula of each eye (Figure 3A and B). SD-OCT imaging demonstrated subretinal deposits in the fovea corresponding with the hyperautofluorescent lesions,

which are likely a precursor to future photoreceptor disruption and degeneration (Figure 3C).

Genetic Testing

The three siblings underwent genetic testing, which revealed a homozygous pathogenic *BBS1* gene with a c.1169T>G (p.Met390Arg) variant in each sibling. This sequence change replaces methionine with arginine at codon 390 of the *BBS1* gene. The genotype matches the phenotype.

Genetic testing established a diagnosis of BBS for all three siblings. Given their obesity, risk of diabetes, and cognitive impairment, they were referred to their pediatrician for a renal, cardiac, neurological, and genitourinary evaluation.

DISCUSSION

The prevalence of BBS is estimated to be between 1 in 140,000 and 1 in 160,000 newborns in North America and Europe, with 44 new cases reported annually in the United States.[3] Its most exhibited features are retinal rod-cone dystrophy with variable presentations (94% of cases), obesity and related complications, cognitive delays, and genitourinary and renal dysfunction.[1] Retinal dystrophy can range from subtle macular pigmentary changes to bull's eye maculopathy, along with peripheral pigmentary changes with atrophy and bone spicules.[1,3]

Patients usually present in the first decade of life with symptoms of nyctalopia, gradual loss of peripheral vision, color discrimination deficits, and decreased visual acuity. Affected individuals can experience significant vision loss in the third decade of life. Strabismus, astigmatism, and cataracts may also be found.[1]

Other systemic features include brachydactyly; syndactyly; deficits in hearing and smell; facial, cranial, and dental dysmorphia; and gastrointestinal, skin, and renal diseases. Neurologic findings, such as seizures, ataxia, and developmental delays (speech and behavior), are also present. BBS shows a range of expressivity that can vary between families and individuals within the same family.[1]

Diagnosing BBS

The differential diagnosis of BBS is comprised of various syndromic pigmentary retinopathies, including ciliopathies (ie, Joubert syndrome, characterized by brain abnormalities, and Senior Loken syndrome, characterized by progressive kidney disease), Refsum syndrome, familial isolated vitamin E deficiency, and Alström syndrome, among others.[1,4,5] It is the second most common autosomal recessive syndromic ciliopathy, after Usher syndrome, which is also known to cause sensorineural hearing loss.[1,5]

High suspicion of BBS is inferred from personal and family history and clinical findings; however, genetic testing and counseling are required to confirm the diagnosis.[1,4,6] Given its widespread systemic involvement, obtaining an accurate diagnosis is paramount in the management of childhood obesity, diabetes mellitus, kidney dysfunction, and heart defects that can become life-threatening.[1]

Treatment Approaches

Management of BBS is primarily aimed at reducing symptoms and focuses on addressing the individual's specific needs. Multidisciplinary care involving various specialists may be necessary, including low vision services.[1] In 2020, the FDA approved setmelanotide injections (Imcivree, Rhythm Pharmaceuticals) for progressive weight gain management in patients with BBS older than 6 years of age. The results of a 66-week trial that enrolled 44 individuals with BBS and obesity showed that treatment with setmelanotide led to an average decrease in body mass index of 7.9%.[7,8]

Many genetic syndromes have systemic complications that can be progressive and debilitating if left untreated. Identifying BBS early allows for prompt initiation of appropriate medical interventions and therapies.

STRIVE FOR BETTER OUTCOMES

Early syndrome recognition and genetic testing are important steps in the diagnosis and management of genetic disorders such as BBS and can lead to better outcomes and improved quality of life. Testing also enables timely referrals to specialists, informs family planning, and allows earlier access to treatments and participation in clinical trials. ■

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TREATING RETINAL VASOPROLIFERATIVE TUMOR


A technique using cryotherapy may be the most effective approach.

BY NASSIM A. ABREU-ARBAJE, MD, AND MIGUEL CRUZ-PIMENTEL, MD

Retinal vasoproliferative tumors (RVPTs) were first described by histopathologists Henkind and Morgan in 1966.[1] Microscopic visualization of tumors that have undergone endoresection shows a mixture of glial and vascular proliferation. Glial cells appear in a fusiform pattern, and the vascular components exhibit dilated vessels with mural hyalinization and some thrombosis. These tumors can sometimes promote retinal pigment epithelium (RPE) proliferation around the blood vessels or in areas previously exposed to hemorrhages.[2,3] The term *RVPT* was proposed by Shields et al in 1995 in a report of 103 cases of peripheral acquired retinal vascular tumors.[4]

PRESENTATION AND DIAGNOSIS

These tumors can be primary, idiopathic, or secondary and are generally associated with retinitis pigmentosa, retinopathy of prematurity, Coats disease, toxoplasmosis, or trauma, among other conditions.[4] Idiopathic tumors tend to be more frequent, comprising 80% of reported cases.[5,6] RVPTs affect both men and women and can appear at any age, but women older than 50 years of age seem to make up the majority.[6]

An RVPT generally presents as a solitary mass either red or orange in color. Hard exudates, subretinal fluid, vitreous hemorrhage, cystoid macular edema (CME), epiretinal membrane, and RPE hypertrophy are clinical findings that may also be present. There have been reports of bilateral disease and cases of multiple tumors. In approximately 60% to 90% of cases, the tumor is localized in the inferior quadrants, and 45% to 75% of tumors are located temporally.[4]

Feeder vessels may also be present, a feature that may lead clinicians to confuse an RVPT with a retinal capillary hemangioma, the major differential diagnosis. Other differentials include:

- choroidal melanotic melanoma, which is distinguished by its typical echographic findings and choroidal localization;
- peripheral hemorrhagic and exudative choroidopathy, which is usually present in much older patients; and
- lesions such as uveal tuberculoma or granulomas due to sarcoidosis, which can be present in the periphery, as with RVPTs, but tend to be accompanied by vitreous cells and have a pale appearance.[4,7]

Patients tend to seek medical attention after experiencing decreased vision, but many of these tumors are diagnosed on routine fundus examination without the presence of any symptoms. In addition to visual decline, floaters, photopsia, and metamorphopsia may occur.[8]

TREATMENT

To date, there is no consensus on the ideal treatment for RVPTs, although, according to Shields et al, 51% of cases require some form of treatment.[4] The proposed treatment criteria are the presence of subretinal fluid and/or hard exudates near the macula, CME, and the presence of epiretinal membrane.[4] Different treatment options have been proposed, including the following:

Cryotherapy is the most used therapy; RVPTs tend to be peripheral, and cryotherapy can be applied in a transconjunctival fashion with indirect ophthalmoscopy. The preferred technique is the *triple freeze-thaw*, in which the surgeon aims to freeze the tumor up to the apex and then allow it to thaw, repeating this process three times (Video).[4] Of note, applying cryotherapy can cause immediate postoperative augmentation of the subretinal fluid and persistence or appearance of CME because of the inflammation this procedure produces. Retinal detachment has also been documented due to the contraction of the lesion and subsequent retinal tear formation.[9,10]

Laser photocoagulation is not as widely used because the laser is not able to penetrate thick tumors. As such, Shields et al has suggested this option be reserved for small tumors.[4] Of note, Garcia-Arumi et al reported increased tumor recurrence in patients who were initially treated with laser photocoagulation alone.[10]

Some reports on **photodynamic therapy** have suggested good results using this management strategy; however, limitations may be encountered when trying to treat tumors located preequatorially or close to the ora serrata.

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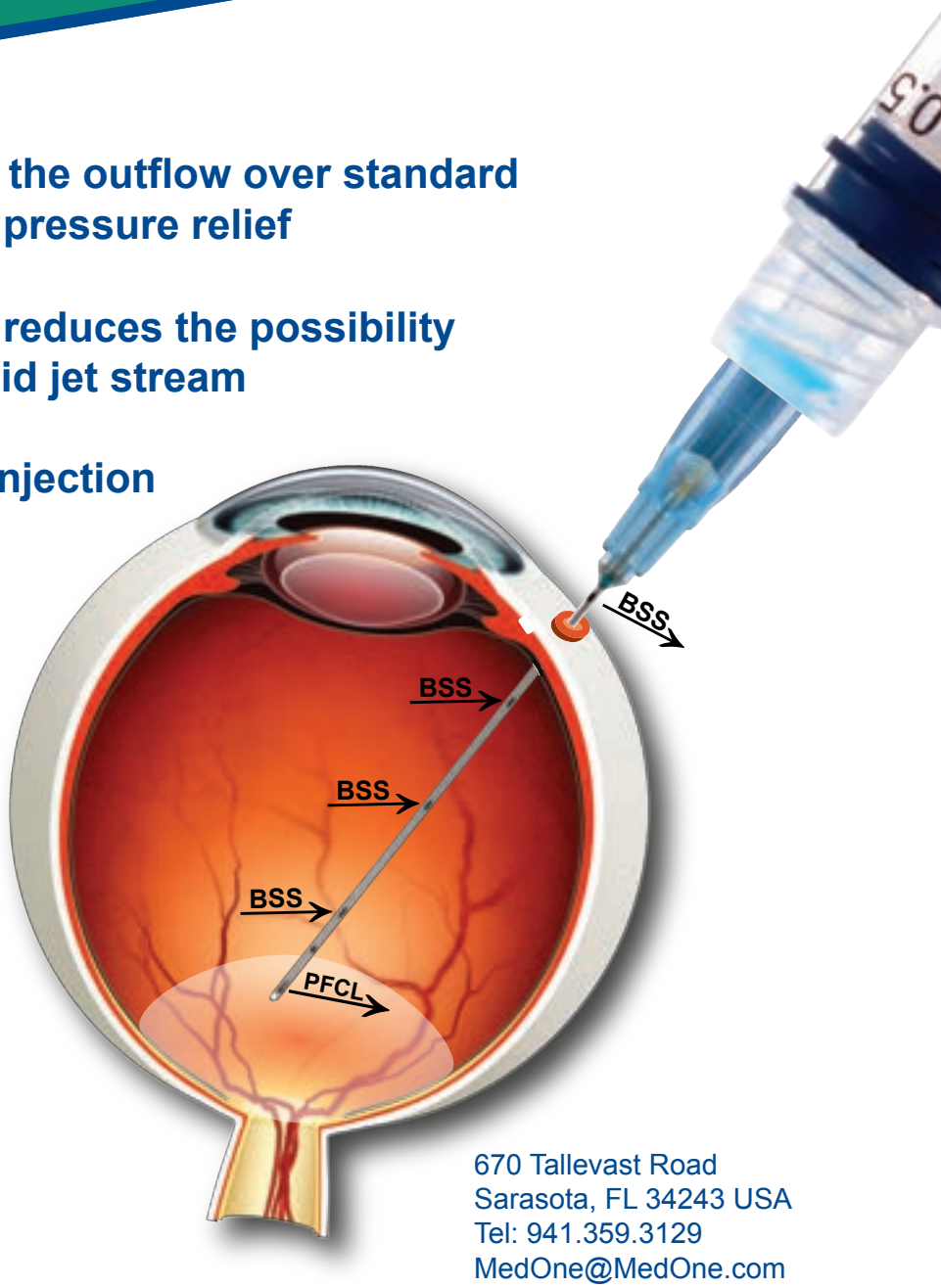

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AMD PIPELINE UPDATES: A DIFFERENT WAY OF THINKING ABOUT THE COMPLEMENT CASCADE

A new layout of the complement cascade highlights the major changes to this year's two-sided poster.

BY PETER K. KAISER, MD

We may look back on 2023 as a breakthrough year. After decades of research and a handful of almost-there drug candidates, the US Food and Drug Administration determined that two different treatments for geographic atrophy (GA) were safe and effective. Rather than holding our patients' hands as they marched toward inevitable vision loss, we retina specialists may be able to avert devastating vision loss in a significant number of patients.

But researchers aren't satisfied with only two options. Dozens of other pipeline candidates remain under investigation for the treatment of GA, many of them complement inhibitors like the approved treatments, pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad pegol (Izervay, Iveric Bio). We lack the depth of experience to know whether complement inhibition will ultimately prove to be the best long-term approach to GA therapy. But for now, we have a breakthrough—and we'll take it.

With all the focus on dry AMD and GA, it's easy to forget that seismic shifts have come (or are coming) in wet AMD therapy. The era of biosimilars has arrived, and we should expect more biosimilar candidates under investigation to clear regulatory hurdles in the coming years. Real-world evidence of the safety and efficacy of dual inhibition therapy with faricimab (Vabysmo, Genentech/Roche) has shown that this approach works. To that end, we dedicated significant space in this year's pipeline update to educating readers on multitarget therapies that were recently approved or are under investigation. The next age of wet AMD therapy may very well rely on simultaneous inhibition of several targets, and the data researchers publish in the coming years will inform the viability of this approach. ■

Remember that the drugs listed in this poster are not exhaustive. If there is a drug that you think we should include in next year's poster, email us at cdeming@bmctoday.com.

PETER K. KAISER, MD

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- Chaney Family Endowed Chair in Ophthalmology Research; Professor of Ophthalmology, Cleveland Clinic Lerner College of Medicine; staff surgeon in the vitreoretinal department at the Cole Eye Institute, Cleveland Clinic; founding director of the Digital Optical Coherence Tomography Reading Center at the Cole Eye Institute, all in Cleveland, Ohio
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TO DATE, THERE IS NO CONSENSUS ON THE IDEAL TREATMENT FOR RPVT [...] THE PROPOSED TREATMENT CRITERIA ARE THE PRESENCE OF SUBRETINAL FLUID AND/OR HARD EXUDATES NEAR THE MACULA, CME, AND THE PRESENCE OF EPIRETINAL MEMBRANE.

For example, reaching lesions that are very anterior can be difficult if there is poor pupil dilation, opaque medium, or if the physician does not have the required lens.[11]

Brachytherapy is mainly indicated for large lesions (ie, > 2.5 mm thick). Successful treatment has been reported with the use of iodine-125 and ruthenium-106 with remission rates of 97% and 88%, respectively.[12,13] Care is advised due to the possible risk of side effects from radiation, such as dry eye, radiation-induced optic neuropathy, radiation retinopathy, cataract, and neovascular glaucoma.[12]

Surgical resection is a rare therapeutic approach and is historically reserved for cases that did not respond to treatment with cryotherapy. Patients who are phakic and are treated with endoresection may develop cataract.[14,15]

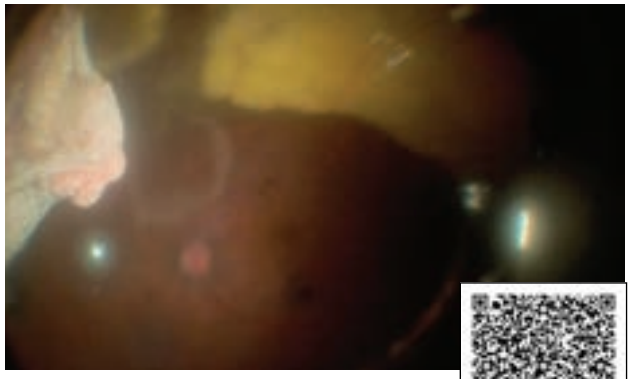
The main indication for **intravitreal injection** is to address the subsequent CME that can occur with treatment. Reports have been published on the use of anti-VEGF therapy and steroids.[9,16]

FINAL THOUGHTS

Fortunately, RVPTs are rare entities, although the visual prognosis is variable. The diagnosis is often made because of decreased vision or during routine fundus examination when no symptoms are present. This latter circumstance poses greater potential for decreased function long-term because of a lack of clear guidance on follow-up and treatment criteria.

Effective treatment has been noted mainly with the use of cryotherapy, but larger lesions may require a more invasive approach with greater risk of severe adverse events. It is important to note that the complete remission of the tumor does not guarantee a good visual outcome. ■

WATCH IT NOW



Video. Triple Freeze-Thaw Technique With Cryotherapy

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Diabetic Eye Disease: The Therapeutic Landscape

A look at the treatment pipeline for diabetic retinopathy and diabetic macular edema.

BY TERESA E. FOWLER, MD; OLLYA V. FROMAL, MD; AND NIERAJ JAIN, MD



Of roughly 37 million Americans with diabetes, an estimated 9.6 million (26.4%) have diabetic retinopathy (DR) with 1.8 million (5%) of those cases considered vision-threatening.[1,2] Compared with data published in 2004, these numbers have more than doubled.[3] Despite recent advances in the field of anti-VEGF therapy, many patients continue to suffer from treatment-resistant macular edema (Figure).

Recent DR clinical trials have sought to improve outcomes, prolong treatment duration, and mitigate the iatrogenic risks associated with treatment. Many phase 2 and 3 studies are underway for novel antibodies, small molecules, gene therapies, topicals, and oral options, as well as novel delivery mechanisms (Table). Here, we review the landscape of clinical trials for DR/diabetic macular edema (DME) management, highlighting select studies that may improve our ability to manage these conditions.

INTRAVITREAL

RC28-E (RemeGen), a fusion protein targeting FGF2 and VEGF, has been shown to reduce vascular leakage and apoptosis in preclinical models.[4] A phase 3 trial (NCT05885503) recruiting 316 patients with DME is comparing 2 mg RC28-E with aflibercept (Eylea, Regeneron), with each arm receiving the assigned agent every 4 weeks for five injections, then every 8 weeks through week 48. The primary outcome is change in BCVA.

UBX1325 (foselutoclax, Unity Biotechnology) reduces retinal vascular inflammation via inhibition of Bcl-xl, an apoptosis-regulating protein. The phase 2 BEHOLD study (NCT04857996) showed that, for 65 patients with DME resistant to anti-VEGF therapy, a single UBX1325 injection led to sustained BCVA improvement from baseline (+6.2 ETDRS letters) compared with sham at 48 weeks.[5]

The phase 2b ASPIRE study (NCT06011798) will include 40 patients with NPDR and persistent center-involving DME (CI-DME) despite three or more anti-VEGF injections in the prior 6 months. All patients will receive three monthly loading doses of aflibercept, then treatment (10 µg UBX1325 every 8 weeks) or control (aflibercept every 8 weeks). The primary outcome is mean change in BCVA at 24 weeks; secondary measures include central subfield thickness (CST) changes, ETDRS gains, and safety.

OPT-302 (Opthea) is an anti-VEGF therapy that blocks VEGF-C and VEGF-D and is designed to be used in combination with current anti-VEGF agents. In a phase 2 trial (NCT03397264) of patients with persistent DME, 52.8% of participants treated with OPT-302 in combination with aflibercept achieved a visual gain of ≥ 5 ETDRS letters at 12 weeks compared with baseline. The company has yet to announce further plans in the DME space.

THR-149 (Oxurion), a bicyclic peptide that selectively inhibits human plasma kallikrein, was under investigation for the treatment of DME. In November, the company announced that part B of the phase 2 KALAHARI trial

AT A GLANCE

- Clinical studies for diabetic retinopathy and diabetic macular edema continue to investigate new delivery systems and explore novel targets.
- Several phase 2 and 3 studies are investigating novel antibodies, small molecules, gene therapies, topicals, and oral medications for diabetic eye disease.
- At least eight oral therapies are under investigation to treat diabetic eye disease, potentially changing the treatment landscape considerably.

(NCT04527107) did not meet the primary endpoint of improved vision at month 3 compared with aflibercept.[6]

AG-73305 (Allgenesis Biotherapeutics), a bispecific Fc-fusion protein, is in a phase 2a trial (NCT05301751) evaluating the drug's safety and efficacy for the treatment of DME. Preliminary data for six patients treated with the 0.5 mg and 1 mg doses (n = 3 each) suggest that the drug is well-tolerated, and early improvements in BCVA at week 1 were maintained for 3 months.[7]

Vorolanib (EYP-1901, EyePoint Pharmaceuticals), a tyrosine kinase inhibitor, is a potential 9-month treatment option for moderately severe to severe NPDR. The ongoing phase 2 PAVIA trial (NCT05383209) enrolled 77 patients randomly assigned to 2 mg or 3 mg vorolanib or sham, and interim data show a positive safety profile at 3 months. The 12-month trial will evaluate the improvement of ≥ 2 Diabetic Retinopathy Severity Score (DRSS) steps at week 36.[8]

RO7200220 (Hoffmann-La Roche) is an interleukin-6 inhibitor in phase 2 (NCT05151731) for the treatment of DME. Patients will randomly receive 0.25 mg of the study drug every 8 weeks, 1.0 mg every 4 or 8 weeks, or ranibizumab (Lucentis, Genentech/Roche) every 4 weeks. The trial is evaluating safety and efficacy up to week 72. The company is also investigating RO7200220 in combination with ranibizumab (NCT05151744).

Tarcocimab (KSI-301, Kodiak Sciences), an intravitreal anti-VEGF biologic that uses an antibody biopolymer conjugate platform, is dosed every 24 weeks. The phase 3 GLOW study (NCT05066230) met its primary endpoint with 41.1% of treated patients demonstrating at least a 2-step DRSS improvement versus 1.4% of patients in the sham group. Based on the positive findings, the company is reinitiating the program, having paused it after the phase 3 GLEAM and GLIMMER trials failed to meet their primary endpoints.[9]

GENE THERAPY

ABBV-RGX-314 (Regenxbio), a transgene encoding an anti-VEGF antibody fragment packaged in an AAV8 vector for one-time suprachoroidal injection, showed promising results in the ALTITUDE trial (NCT04567550) for NPDR and mild PDR without CI-DME. At 1 year, 70.8% of patients treated with $5x10^{11}$ GC/eye of ABBV-RGX-314 experienced DRSS improvement compared with 25% of controls, and no patients worsened by 2 steps or more compared with 37.5% of the control group. Of the 50 patients treated with ABBV-RGX-314, three eyes (6%) experienced intraocular inflammation that resolved with topical steroids.[10]

4D-150 (4D Molecular Therapeutics) is an intravitreally injected gene therapy that expresses aflibercept and a microRNA targeted to VEGF-C. The phase 2 trial (NCT05930561) aims to enroll 72 patients with CI-DME and BCVA of 25 to 83 ETDRS letters, divided into dose-confirmation and dose-expansion groups using fixed-regimen aflibercept as a control

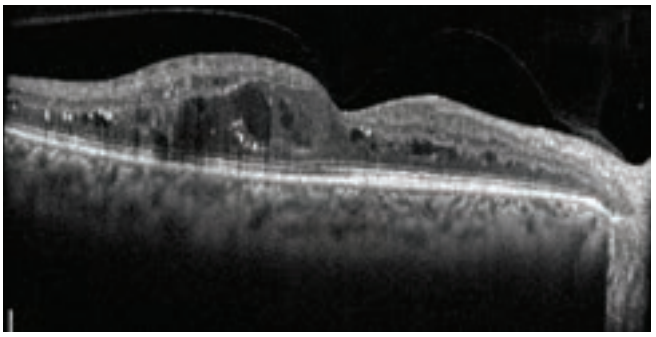

Figure. OCT of the macula of a patient with persistent intraretinal fluid despite serial anti-VEGF treatment.

over 52 weeks.[11] The primary outcome is the number of rescue injections, with secondary measures including change in BCVA, CST, DRSS, and adverse events through 104 weeks.

CORTICOSTEROIDS

OXU-001 (Oxular) is a suprachoroidal injection of dexamethasone microspheres delivered via the company's Oxulumis microcatheter. The 52-week phase 2 OXEYE study (NCT05697809) for DME compares adverse events, BCVA, CST, and interval to recurrence between intravitreal dexamethasone (Ozurdex, Allergan/AbbVie) and suprachoroidal OXU-001. Preclinical studies show that therapeutic levels of OXU-001 were maintained in the retina for 12 months post-injection. The safety and tolerability of the Oxulumis microcatheter is also being tested in a separate 24-week study (NCT05512962) using triamcinolone acetonide.

IBE-814 IVT (Ripple Therapeutics) is an intravitreal dexamethasone implant in the phase 2 RIPPLE-1 trial (NCT04576689) for the treatment of DME and retinal vein occlusion. The 6-month data showed mean chances in CST of -68 µm and -94 µm in the low- and high-dose cohorts, respectively. Patients in the high-dose cohort experienced a mean BCVA gain of +8.7 letters (one patient required rescue), and patients in the low-dose cohort experienced a mean BCVA loss of -1.9 letters (eight required rescue).[12]

ORAL AND SUBCUTANEOUS

Studies show that **fenofibrate**, an oral medication used to manage dyslipidemia, reduced the frequency of laser treatment for DR and slowed DR progression.[13,14] The DRCR Retina Network Protocol AF (NCT04661358) is comparing DR progression over 4 years in patients with mild to moderate NPDR without CI-DME taking daily oral fenofibrate versus placebo.[15]

Tonabersat, an oral connexin43 inhibitor developed for use as an anticonvulsant and migraine preventative, is in a phase 2 trial (NCT05727891) for the treatment of DME. Connexin43, a gap junction hemichannel expressed in retinal cells, is upregulated in states of retinal damage.[16,17] In the trial, 128 patients with CI-DME and BCVA ≥ 20/25 will

Now Approved for Wet AMD

LASTING CONTROL, FEWER INJECTIONS[1-3]

As demonstrated by vision outcomes in PULSAR at Week 48—fewer injections vs EYLEA 2 mg

EYLEA® HD
(aflibercept) Injection 8 mg

PULSAR study design and primary endpoint: Multicenter, randomized, double-masked 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 to receive EYLEA HD Q12W (n=335),* EYLEA HD Q16W (n=338),* or EYLEA 2 mg Q8W (n=336),* following 3 initial monthly doses for each treatment group. In the EYLEA HD groups, patients could be treated as frequently as every 8 weeks based on protocol-defined visual and anatomic criteria starting at Week 16. The primary endpoint was the mean change in BCVA (ETDRS letters) from baseline at Week 48 for the EYLEA HD Q12W and Q16W groups vs EYLEA 2 mg Q8W, with a noninferiority margin of 4 letters.[1,2]

- 6.7 letters for EYLEA HD Q12W (n=299),† 6.2 letters for EYLEA HD Q16W (n=289),† and 7.6 letters for EYLEA 2 mg Q8W (n=285)†
- LS mean differences were noninferior to EYLEA 2 mg: -1.0 letters (95% CI, -2.9 to 0.9) for EYLEA HD Q12W and -1.1 letters (95% CI, -3.0 to 0.7) for EYLEA HD Q16W
- Fewer mean number of injections: 6.1 for EYLEA HD Q12W and 5.2 for EYLEA HD Q16W vs 6.9 for EYLEA 2 mg Q8W‡

*FAS at baseline. †FAS; observed values (censoring data post ICE) at Week 48.
‡Patients who completed Week 48: EYLEA HD Q12W (n=316), EYLEA HD Q16W (n=312), EYLEA 2 mg Q8W (n=309).

IMPORTANT SAFETY INFORMATION FOR EYLEA HD AND EYLEA

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

- Intravitreal injections, including those with aflibercept, have been associated with endophthalmitis and retinal detachments. 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 or retinal detachment without delay and should be managed appropriately. Intraocular inflammation has been reported with the use of EYLEA HD and EYLEA.
- Acute increases in intraocular pressure have been seen within 60 minutes of intravitreal injection, including with EYLEA HD and EYLEA. Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with VEGF inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately.
- There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA HD and EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause).
  - EYLEA HD: The incidence of reported thromboembolic events in the wet AMD study (PULSAR) from baseline through week 48 was 0.4% (3 out of 673) in the combined group of patients treated with EYLEA HD compared with 1.5% (5 out of 336) in patients treated with EYLEA 2 mg. The incidence in the DME study (PHOTON) from baseline to week 48 was 3.1% (15 out of 491) in the combined group of patients treated with EYLEA HD compared with 3.6% (6 out of 167) in patients treated with EYLEA 2 mg.

REGENERON®

777 Old Saw Mill River Road, Tarrytown, NY 10591

EYLEA HD Is the FIRST and ONLY Anti-VEGF Treatment Approved in Wet AMD for Immediate Dosing at Q8W and Up to Q16W Intervals Following 3 Initial Monthly Doses[1]

EXTENDED DOSING

More than 80% of EYLEA HD patients maintained ≥Q12W dosing through Week 48[2,*,†]

VISION

Noninferior vision gains achieved at Week 48 with fewer injections vs EYLEA 2 mg[1,2,*,‡]

ANATOMY

Demonstrated anatomic outcomes data[2,3]

SAFETY

Safety of EYLEA HD was consistent with the established profile of EYLEA 2 mg[1,4]

*EYLEA HD and EYLEA 2 mg patients received 3 initial monthly injections.
†Pooled EYLEA HD groups; patients who completed Week 48 in PULSAR (n=628).
‡Vision gains were measured by mean change in BCVA (ETDRS letters) from baseline. FAS; observed values (censoring data post ICE) at Week 48: EYLEA HD Q12W (n=299), EYLEA HD Q16W (n=289), EYLEA 2 mg Q8W (n=285).

EXPLORE THE CLINICAL DATA AT EYLEAHDhcp.us

IMPORTANT SAFETY INFORMATION FOR EYLEA HD AND EYLEA
WARNINGS AND PRECAUTIONS (continued)

- EYLEA: The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

ADVERSE REACTIONS

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

INDICATIONS

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

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

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

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

References: 1. EYLEA HD full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2023. **2.** Brown DM; on behalf of the PULSAR study investigators. Aflibercept 8 mg in patients with nAMD: 48-week results from the phase 3 PULSAR trial. Data presented at: Angiogenesis 2023; February 11, 2023. **3.** Data on file. Regeneron Pharmaceuticals, Inc. **4.** EYLEA full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. February 2023.

08/2023
EHD.23.02.0013

EYLEA® HD (aflibercept) Injection 8 mg, for intravitreal use AND EYLEA® (aflibercept) Injection 2 mg, for intravitreal use
BRIEF SUMMARY OF PRESCRIBING INFORMATION

4. CONTRAINDICATIONS

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

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments Intravitreal injections including those with aflibercept have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. 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 or retinal detachment without delay and should be managed appropriately [*see Dosage and Administration (2.6 EYLEA HD, 2.4 EYLEA) in the full Prescribing Information and Patient Counseling Information (17)*].

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

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

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

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

- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.3 for EYLEA HD, 5.4 for EYLEA)*]

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

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

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

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

EYLEA: The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW 1 and VIEW 2) for 24 months (with active control in year 1) [*see Clinical Studies (14.1) in the full Prescribing Information*]. Safety data observed in the EYLEA group in a 52-week, double-masked, phase 2 study were consistent with these results.

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

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

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

[a]Represents grouping of related terms in PULSAR

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

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

8 USE IN SPECIFIC POPULATIONS

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

Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA HD or EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept [*see Clinical Pharmacology (12.1) in the full Prescribing Information*], treatment with EYLEA HD or EYLEA may pose a risk to human embryofetal development. EYLEA HD and EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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

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

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

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

8.4 Pediatric Use The safety and effectiveness of EYLEA HD in pediatric patients have not been established. The safety and effectiveness of EYLEA have been demonstrated in two clinical studies of pre-term infants with Retinopathy of Prematurity. These two studies randomized pre-term infants between initial treatment with EYLEA or laser. Efficacy of each treatment is supported by the demonstration of a clinical course which was better than would have been expected without treatment [*see Dosage and Administration (2.9), Adverse Reactions (6.1), Clinical Pharmacology (12.3) and Clinical Studies (14.6) in the full Prescribing Information for EYLEA*].

8.5 Geriatric Use In PULSAR, approximately 90% (604/673) of the patients in the HDq12 and HDq16 groups were 65 years of age or older and approximately 51% (343/673) were 75 years of age or older. In PHOTON, approximately 44% (214/491) of the patients in the HDq12 and HDq16 groups were 65 years of age or older and approximately 10% (50/491) were 75 years of age or older. In the clinical studies for EYLEA 2 mg, approximately 76% (2049/2701) of patients randomized to treatment with EYLEA were ≥65 years of age and approximately 46% (1250/2701) were ≥75 years of age. No significant differences in efficacy or safety were seen with increasing age in these studies.

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

17 PATIENT COUNSELING INFORMATION In the days following EYLEA HD or EYLEA administration, patients are at risk of developing endophthalmitis or retinal detachment. If the eye becomes red, sensitive to light, painful, or develops a change in vision, advise patients and/or caregivers to seek immediate care from an ophthalmologist [*see Warning and Precautions (5.1)*]. Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA HD or EYLEA and the associated eye examinations [*see Adverse Reactions (6)*]. Advise patients not to drive or use machinery until visual function has recovered sufficiently.

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TABLE. CURRENT DIABETIC EYE DISEASE CLINICAL TRIALS

Drug (Company)	Condition	Mechanism	Delivery	NCT#	Status	Last Update
Phase 3						
OCS-01 (Oculis)	DME	Steroid, dexamethasone	Topical drop	NCT05066997	Active, not recruiting	January 2023
Fenofibrate	NPDR	Activates PPARα	Oral	NCT04661358	Recruiting	June 2023
Tarcocimab (KSI-301, Kodiak Sciences)	NPDR	VEGF inhibitor with antibody biopolymer conjugate platform	Intravitreal injection	NCT05066230	Active, not recruiting	September 2022
RC28-E (RemeGen)	DME, NPDR	Fusion protein targeting FGF2 and VEGF	Intravitreal injection	NCT05885503	Recruiting	September 2023
Phase 2						
UBX1325/Foselutoclax (Unity Biotechnology)	DME	Bcl-xl inhibitor	Intravitreal injection	NCT06011798	Not yet recruiting	August 2023
	DME			NCT04857996	Completed	April 2023
AG-73305 (Allgenesis)	DME	Fusion protein targeting VEGF and integrin	Intravitreal injection	NCT05301751	Recruiting	July 2023
EYP-1901 (EyePoint Pharmaceuticals)	NPDR	Tyrosine kinase inhibitor	Intravitreal implant	NCT05383209	Recruiting	February 2023
RO7200220 (Hoffman-La Roche)	DME	Interleukin-6 inhibitor	Intravitreal injection	NCT05151731	Recruiting	September 2023
RO7200220 (Hoffman-La Roche) + Ranibizumab	DME	Interleukin-6 inhibitor + anti-VEGF-A	Intravitreal injection	NCT05151744	Active, not recruiting	August 2023
4D-150 (4D Molecular Therapeutics)	DME	Gene therapy, VEGF-C miRNA + encoded aflibercept	Intravitreal injection	NCT05930561	Recruiting	August 2023
Per-011 (Perfuse Therapeutics)	NPDR	Targets endothelin pathway	Intravitreal implant	NCT06003751	Recruiting	August 2023
ABBV-RGX-314 (Regenxbio)	NPDR, mild PDR	Gene therapy, anti-VEGF antibody fragment	Suprachoroidal	NCT04567550	Recruiting	May 2023
OXU-001 (Oxular)	DME	Steroid microspheres, microcatheterization device	Suprachoroidal	NCT05697809	Recruiting	July 2023
D-4517.2 (Ashvattha)	DME	VEGF inhibitor in activated microglia and RPE	Subcutaneous	NCT05387837	Recruiting	February 2023
Tonabersat (InflammX Therapeutics)	DME	Connexin43 inhibitor	Oral	NCT05727891	Recruiting	August 2023
RZ402 (Rezolute)	DME	Plasma kallikrein inhibitor	Oral	NCT05712720	Recruiting	March 2023
OPL-0401 (Valo Health)	NPDR, mild PDR	ROCK1 and 2 inhibitor	Oral	NCT05393284	Recruiting	April 2023
Cu06-1004 (Curacle Co)	DME	VEGF and angiopoietin-2 inhibitor	Oral	NCT05573100	Active, not recruiting	July 2023
APX3330 (Ocuphire)	NPDR, mild PDR	Ref-1 inhibitor	Oral	NCT04692688	Completed	February 2023
Runcaciguat (Bayer)	NPDR	Soluble guanylate cyclase activator	Oral	NCT04722991	Active, not recruiting	September 2023
OTT166 (OcuTerra)	NPDR, mild PDR	Integrin inhibitor	Topical drops	NCT05409235	Active, not recruiting	September 2023
IBE-814 IVT (Ripple Therapeutics)	DME	Steroid, dexamethasone	Intravitreal implant	NCT04576689	Active, not recruiting	March 2023
Phase 1						
Carbidopa/Levodopa (Merck)	NPDR	Dopamine signaling enhancer	Oral	NCT05132660	Recruiting	June 2023
SOM-401 (Inflammasome Therapeutics)	DME	Nucleoside reverse transcriptase inhibitor	Intravitreal injection	NCT05699759	Recruiting	March 2023
OTX-TKI (Ocular Therapeutix)	NPDR	Tyroxine kinase inhibitor	Intravitreal implant	NCT05695417	Recruiting	June 2023

Abbreviations: DME, diabetic macular edema; NPDR, nonproliferative diabetic retinopathy; PDR, proliferative diabetic retinopathy; RPE, retinal pigment epithelium

receive oral 80 mg tonabersat or placebo for 6 months.[17] The primary outcome, mean change in CST, will be measured monthly through completion of the oral regimen and for 6 months of follow-up.[17]

D-4517.2 (Ashvattha Therapeutics) is a nanoparticle that inhibits VEGF receptors 1 and 2 tyrosine kinases in the retinal pigment epithelium, microglia, and macrophages. In a rat model of choroidal neovascularization, one dose reduced vascular leakage and choroidal neovascularization area comparable with aflibercept.[18] The phase 2 study (NCT05387837) compares three doses of subcutaneous D-4517.2 in patients with recurrent CI-DME. The trial is monitoring for adverse

events, changes in CST and BCVA, and effect duration.

APX3330 (Ocuphire) is a twice-daily oral formulation that targets the Ref-1 protein. The phase 2 ZETA-1 trial (NCT04692688) for patients with DR did not meet its primary endpoint of ≥ 2-step improvement in DRSS from baseline.[19] However, the trial did achieve statistical significance on the secondary endpoint of preventing clinically meaningful progression of DR (≥ 3-step DRSS worsening) at 24 weeks. The company is further analyzing the ZETA-1 data to gain potential phase 3 trial design insights.[19]

Runcaciguat (Bayer), a soluble guanylate cyclase activator, is an investigational oral therapy for the treatment of NPDR.[20] The phase 2 NEON-NPDR trial (NCT04722991) is evaluating the safety and efficacy of runcaciguat compared with placebo in 104 patients, with a primary endpoint of a DRSS improvement of ≥ 2 steps at 24 weeks.

RZ402 (Rezolute), a selective plasma kallikrein inhibitor, is being investigated for the treatment of CI-DME with once-daily oral dosing. The phase 2 trial (NCT05712720) will evaluate three doses of RZ402 compared with placebo in a total of 100 patients. The primary endpoints are number and severity of adverse events and change in CST from baseline.

OPL-0401 (Valo Health), an oral agent that inhibits Rho kinase signaling, is in a phase 2 trial (NCT05393284) for the treatment of NPDR and mild PDR. Approximately 90 patients will randomly receive either the study drug or placebo twice daily for 24 weeks. The primary endpoint is the proportion of patients with a ≥ 2-step DRSS improvement from baseline at 24 weeks.

CU06-1004 (Curacle) is a once-daily oral therapy that reduces vascular hyperpermeability induced by VEGF and angiopoietin-2. In a phase 2a study (NCT05573100), approximately 60 patients with DME were randomly assigned to one of three dosing regimens, with primary outcomes of change in CST at 12 weeks and determination of the optimal dose.

TOPICAL

OCS-01 (15 mg/mL dexamethasone, Oculis) eye drops met the primary and secondary endpoints in stage 1 of the phase 3 DIAMOND trial (NCT05066997). In the study, 148 patients with DME were randomly assigned to treatment with OCS-01 or vehicle, each six times daily for 6 weeks, followed by three times daily for 6 weeks. The primary endpoint was improvement in BCVA; at week 12, patients treated with OCS-01 achieved +7.7 ETDRS letters versus +3.7 ETDRS letters for those treated with vehicle. The treatment group achieved a higher percentage of patients with ≥ 15-letter BCVA improvement (27.4%) compared with vehicle (7.5%) at week 12.[21]

OTT166 (Ocuterra) topical drops target integrin, a cell adhesion molecule dysregulated in DR. Drop safety and biological activity were demonstrated in two phase 1b trials,[22] and in August, the phase 2 DR:EAM trial (NCT05409235) of 210 treatment-naive participants with NPDR/mild PDR completed enrollment.

THE FUTURE OF DIABETIC EYE DISEASE CARE

Numerous therapies for the treatment of DR/DME are in the pipeline. Several intravitreal agents and gene therapies have demonstrated favorable results, while topical and oral treatments may benefit patients who are intolerant of intravitreal injections. We remain optimistic that additional treatments are on the horizon for diabetic ocular disease. ■

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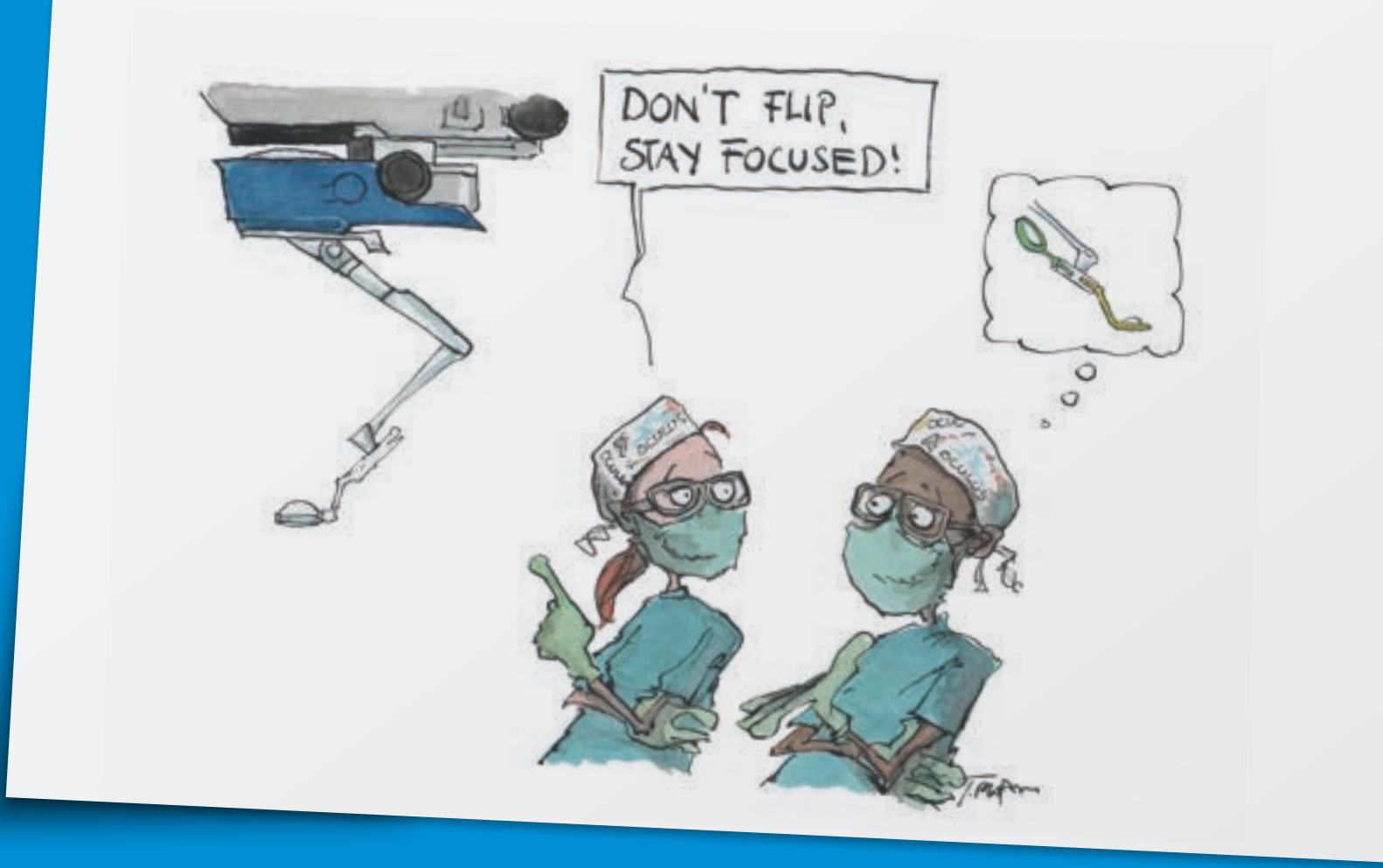

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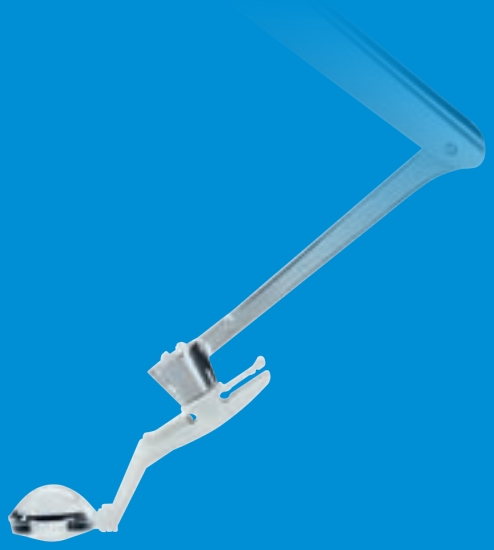

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The Future of Wet AMD Therapeutics

The pipeline is bursting with drug candidates that may one day provide more effective, durable, and cost-effective options.

BY ERIC JUNG, MD, AND ALEKSANDRA RACHITSKAYA, MD


It's been an exciting year for AMD with new therapeutic options in the clinic. The traditional set of anti-VEGF options has expanded to include biosimilars, high-dose variations, and dual-action combination therapies. With all this innovation, we may soon have a doubling of available choices to treat wet AMD.

Nonetheless, the path to market can be challenging, and several promising candidates have been discontinued or paused in the last year. Kodiak discontinued and then reinitiated its tarcocimab program with the release of positive phase 3 GLOW data.[1] The FDA did not approve Outlook Therapeutic's ONS-5010/Lytenava, and the company is pursuing an additional phase 3 trial (NCT05112861) set to complete in March 2024.[2] The port delivery system with ranibizumab (Susvimo, Genentech/Roche) was voluntarily recalled due to issues with septum dislodgement, and the company hopes to introduce an updated version soon.[3]

Research continues for other therapeutics, and trials are underway that strive to offer more effective, durable, and cost-effective options for patients—some are exploring gene therapy, tyrosine kinase inhibition, and alternative methods of drug delivery beyond intravitreal injection (Table 1).

GENE THERAPY

Gene therapy is an exciting alternative to ongoing intravitreal injections. By using viral vectors to deliver anti-VEGF transgenes, these therapies may offer a one-and-done treatment regimen to provide sustained anti-VEGF protein expression after initial administration.

ABBV-RGX-314 (Regenxbio) is being tested as a subretinal injection during vitrectomy in two phase 3 trials, ASCENT (NCT05407636) and ATMOSPHERE (NCT04704921). The studies are comparing the drug candidate with intravitreal aflibercept (Eylea, Regeneron) and ranibizumab (Lucentis, Genentech/Roche), respectively. This gene therapy produces sustained expression of ranibizumab-like proteins.

ABBV-RGX-314 is also under investigation with a one-time in-clinic suprachoroidal delivery method in the phase 2 AAVIATE trial (NCT04514653). The 6-month interim safety results showed that the suprachoroidal delivery was well-tolerated in 85 patients. Mild intraocular inflammation was reported with an increase in incidence with the third dose level (cohort 4, $1x10^{12}$ GC/eye); all inflammation resolved with topical corticosteroids. There was an 85% reduction in the annualized injection rate, with 67% of patients (all previously treated with anti-VEGF therapy) remaining injection-free in the highest dose group.[4] ABBV-RGX-314 at the third dose level was also evaluated with a short course of prophylactic ocular steroids, which meaningfully reduced the occurrence of mild to moderate intraocular inflammation.[5]

Ixoberogene soroparvovec (Ixo-vec [formerly ADVM-022], Adverum Biotechnologies) is in the phase 2

AT A GLANCE

- Gene therapy may offer a one-time treatment regimen to provide sustained anti-VEGF protein expression after initial administration.
- Tyrosine kinase inhibitors bind to intracellular domains of tyrosine kinase receptors and target the downstream receptor signaling of VEGF receptors, platelet-derived growth factor signaling, and more.
- Several therapies incorporate dual targets, such as inhibition of VEGF-C and VEGF-D, VEGF and fibroblast growth factor, VEGF and Ang-2, VEGF and C3b/C4b, and VEGF with Tie2 promotion.

TABLE 1. WET AMD TREATMENT PIPELINE					
Drug (Company)	**Mechanism**	**NCT #**	**Estimated Completion**	**Recruitment Status**	**Last Update**
Phase 3					
ABBV-RGX-314 (Regenxbio)	Subretinal adeno-associated viral (AAV) vector with a gene encoding for a monoclonal antibody fragment	NCT04704921 NCT05407636	May 2025 December 2025	Recruiting	May 2023 August 2023
BAT5906 (Bio-thera)	Recombinant anti-VEGF intravitreal injection	NCT05439629	June 2025	Recruiting	February 2023
IBI302 (Innovent Biologics)	Intravitreal injection of a bispecific fusion protein	NCT05972473 NCT05403749	February 2027 June 2024	Not yet recruiting	August 2023 June 2022
OPT-302 (Opthea)	Biologic inhibitor of VEGF-C and VEGF-D	NCT04757610 NCT04757636	December 2024	Recruiting	September 2022
RC28-E (RemeGen)	VEGF/FGF dual decoy receptor fusion protein	NCT05727397	December 2025	Recruiting	August 2023
OTX-TKI (Axpaxli, Ocular Therapeutix)	Intravitreal tyrosine kinase inhibitor gel implant	Not posted (phase 3) NCT04989699 (phase 1)	February 2023	Not yet recruiting Active, not recruiting	September 2022
Tarcocimab (KSI-301, Kodiak Sciences)	Intravitreal injection of an antibody biopolymer conjugate	NCT04964089	Complete	Complete	May 2023
Phase 2					
4D-150 (4D Molecular Therapeutics)	Intravitreal AAV anti-VEGF transgene expressing aflibercept and VEGF-C inhibitory RNAi	NCT05197270	November 2025	Recruiting	August 2023
ABBV-RGX-314 (Regenexbio)	Suprachoroidal AAV with a gene encoding for a monoclonal antibody fragment	NCT04514653	January 2024	Recruiting	May 2023
AKST4290 (Alkahest)	Oral CCR3 inhibitor	NCT04331730	Complete	Complete	October 2022
AXT107 (Asclepix Therapeutics)	Suprachoroidal anti-VEGF and Tie2 activation	NCT05859776	April 2025	Not yet recruiting	May 2023
CLS-AX (Clearside Biomedical)	Suprachoroidal tyrosine kinase inhibitor	NCT04626128	Complete	Complete	September 2023
D-4517.2 (Ashvattha Therapeutics)	Subcutaneous VEGF-R tyrosine kinase inhibitor	NCT05387837	June 2023	Recruiting	February 2023
EYP-1901 (EyePoint Pharmaceuticals)	Tyrosine kinase inhibitor intravitreal implant	NCT05381948	April 2024	Active, not recruiting	July 2023
Ixoberogene soroparvovec (Ixo-vec, Adverum Biotechnologies)	Intravitreal AAV carrying an aflibercept coding sequence	NCT05536973	February 2024	Recruiting	May 2023
PAN-90806 (PanOptica)	Topical tyrosine kinase inhibitor	NCT03479372	Complete	Complete	July 2019
RBM-007 (Ribomic)	Anti-fibroblast growth factor 2 aptamer intravitreal injection	NCT04640272	Complete	Complete	June 2023
UBX1325 (Unity Biotechnology)	Intravitreal injection of a Bcl-xl inhibitor	NCT05275205	Complete	Complete	October 2023

TABLE 1. WET AMD TREATMENT PIPELINE (CONTINUED)					
Drug (Company)	Mechanism	NCT #	Estimated Completion	Recruitment Status	Last Update
Phase 1					
AM712 (AffaMed)	Recombinant anti-VEGF humanized monoclonal antibody and Ang-2 antagonist peptide fusion protein	NCT05345769	June 2024	Recruiting	July 2023
AIV007 (AiViva Biopharma)	Periocular gel suspension broad-spectrum tyrosine kinase inhibitor	NCT05698329	April 2025	Recruiting	March 2023
Other Unique Trials					
Adjuvant doxycycline	Oral doxycycline, MMP-9 inhibition	NCT04504123	December 2023	Recruiting	March 2023
Episcleral brachytherapy (Salutaris Medical Devices)	Retrobulbar single brachytherapy treatment (fraction of 24 Gy Strontium90)	NCT02988895	May 2025	Active, not recruiting	August 2023
OCT angiography-directed photodynamic therapy triple therapy	Ranibizumab (Lucentis, Genentech/Roche), photodynamic therapy with verteporfin (Visudyne, Bausch + Lomb), and triamcinolone acetonide	NCT04075136	December 2024	Recruiting	May 2023

LUNA trial (NCT05536973) evaluating an intravitreal injection of one of two doses in conjunction with prophylactic steroids in patients with wet AMD. The 3-year data from the phase 1 OPTIC trial (NCT03748784) show that this aflibercept-encoding AAV.7m8 vector produced therapeutically active ranges of aflibercept protein; there was an 84% reduction in annualized anti-VEGF injections, with 53% of the participants at the 2E11 dose free of injections at 3 years.[6]

4D-150 (4D Molecular Therapeutics) is a dual anti-VEGF transgene that expresses aflibercept and VEGF-C inhibitory RNAi; the investigational therapy is dosed as a one-time intravitreal injection. The phase 1/2 trial (NCT05197270) consists of four cohorts: dose escalation (up to four dose levels), dose expansion (exploring two doses), steroid optimization, and population extension.

TYROSINE KINASE INHIBITORS

These small molecules bind to intracellular domains of tyrosine kinase receptors and target the downstream receptor signaling of VEGF receptors, platelet-derived growth factor signaling, and more.

Axitinib (CLS-AX, Clearside Biomedical) is in a phase 1/2a trial (NCT04626128) investigating one-time suprachoroidal delivery of the drug candidate. All four dose-escalating cohorts showed no serious safety signals, and cohorts three and four experienced a 73% reduction in treatment burden at 3 months.[7] The phase 2b ODYSSEY trial completed recruitment (NCT05891548).

EYP-1901 (EyePoint Pharmaceuticals) is an intravitreal sustained-release implant that is under investigation in the phase 2 DAVIO trial for patients with wet AMD (NCT05381948). Initial safety data suggest the therapy is well tolerated with no drug-related severe ocular adverse events. The company is expecting topline data in December.[8]

PAN-90806 (PanOptica) phase 1/2 clinical trial (NCT03479372) topline results showed safety and a biological response with this once-daily topical eye drop for the treatment of AMD. More than half of the treated patients completed the 12-week study without requiring rescue with an anti-VEGF injection, with 88% experiencing clinical improvement or disease stability.[9]

D-4517.2 (Ashvattha Therapeutics) is a monthly subcutaneous therapy in a phase 2 trial (NCT05387837) investigating the safety, tolerability, and pharmacokinetics of four different doses. In a mouse model, treatment with D-4517.2 led to an approximate two-fold decrease in choroidal neovascular lesion area compared with controls.[10]

OTX-TKI (Axpaxli, Ocular Therapeutix) is an investigational bioresorbable implant with axitinib. The company is initiating a phase 3 trial after the 12-month phase 1 (NCT04989699) data showed an 89% reduction in treatment burden for patients treated with the implant compared with those treated with aflibercept.[11] In the pivotal superiority trial, 300 patients will receive either a single OTX-TKI implant or one injection of aflibercept followed by as-needed anti-VEGF treatment.

DUAL TARGET THERAPY

OPT-302 (Opthea), is a Fc-fusion protein designed to inhibit VEGF-C and VEGF-D. The phase 3 trials (NCT04757610, NCT04757636) are investigating combination therapy with OPT-302 and either aflibercept or

TABLE 2. BIOSIMILARS IN PHASE 3 TRIALS					
Drug (Company)	**Template Biologic**	**NCT #**	**Estimated Completion**	**Recruitment Status**	**Last Update**
ABP-938 (Amgen)	Aflibercept	NCT04270747	Complete	Complete	May 2023
CKD-701 (Chong Kun Dang)	Ranibizumab	NCT04857177	Complete	Complete	April 2021
FYB203 (Formycon AG)	Aflibercept	NCT04522167	Complete	Complete	June 2023
ONS-5010 (Lytenava, Outlook Therapeutics)	Bevacizumab	NCT03834753	Complete	Complete	February 2022
SB15 (Samsung Bioepis)	Aflibercept	NCT04450329	Complete	Complete	April 2022
SOK583A19 (Sandoz)	Aflibercept	NCT04864834	Complete	Complete	July 2023
Xlucane (Xbrane Biopharma)	Ranibizumab	NCT03805100	Complete	Complete	March 2022
SCD-411 (Sam Chun Dang Pharmaceutical)	Aflibercept	NCT04480463	Complete	Complete	October 2023
LUBT010 (Lupin)	Ranibizumab	NCT04690556	October 2022	Unknown	March 2021
OT-702 (LY9004, Ocumension Therapeutics)	Aflibercept	NCT04572698	December 2023	Not yet recruiting	October 2020
TAB014 (TOT Biopharm)	Bevacizumab	NCT05461339	March 2024	Recruiting	March 2023
GNR-067 (Generium)	Ranibizumab	NCT04667039	September 2024	Recruiting	September 2023
HLX04-O (Shanghai Henlius)	Bevacizumab	NCT04740671	November 2024	Recruiting	August 2023
AVT06 (Alvotech)	Aflibercept	NCT05155293	December 2024	Recruiting	June 2023

ranibizumab, with a primary endpoint of change in BCVA at week 52. In phase 2, the mean visual acuity gain in the 2.0 mg OPT-302 group was significantly superior to sham.[12]

RC28-E (RemeGen) is a dual decoy receptor fusion protein targeting VEGF and fibroblast growth factor undergoing phase 3 testing (NCT05727397). The trial is investigating intravitreal injection of the study drug every 12 weeks after a loading dose of three monthly injections compared with aflibercept every 8 weeks after a loading dose of three monthly injections.

Efdamrofusp alfa (IBI302, Innovent Biologics) is a recombinant human anti-VEGF and anticomplement (C3b and C4b) bispecific fusion protein. The company announced the first patient dosed in the phase 3 STAR trial (NCT05972473) evaluating intravitreal injections of 8 mg efdamrofusp alfa compared with aflibercept.[13] The phase 2 trial (NCT05403749) is ongoing.

AXT107 (Asclepix Therapeutics) is a suprachoroidal injection of a suspension that self-assembles into a gel inside the eye and blocks VEGF and promotes Tie2 signaling. The phase 1/2 trial (NCT05859776) is investigating low, mid, and high doses of the study drug in 15 patients to assess safety up to 40 weeks.

AM712 (AffaMed) is a candidate fusion protein targeting VEGF and Ang-2, similar to faricimab-svoa (Vabysmo, Genentech/Roche). The phase 1 clinical trial (NCT05345769), set for completion in June 2024, is evaluating ascending doses of the study drug, followed by its safety, tolerability, pharmacokinetics, and efficacy.

ALTERNATIVE APPROACHES

UBX1325 (Unity Biotechnology) is a small molecule Bcl-xl inhibitor that increases apoptosis of diseased senescent cells in the retinal pigment epithelium, suppressing inflammation and neovascularization. At 48 weeks in the completed phase 2 ENVISION trial (NCT05275205), 40% of patients treated with the study drug did not require anti-VEGF treatment, and 64% achieved an anti-VEGF treatment-free interval of more than 24 weeks. However, the company indicated that it will be focusing on the diabetic macular edema program for UBX1325.[14]

RBM-007 (Ribomic) is an anti-fibroblast growth factor 2 aptamer that inhibits angiogenesis and scar formation. The company completed the phase 2 trial (NCT04895293), which suggested a clinical benefit in treatment-naïve patients.

Tarcocimab (KSI-301, Kodiak Sciences), an intravitreal antibody biopolymer conjugate, met its primary endpoint in the phase 3 DAYLIGHT study (NCT04964089) of noninferior visual acuity gains with monthly KSI-301 compared with aflibercept every 8 weeks. The company plans to pursue another phase 3 trial to support a single biologics licensing agreement submission for wet AMD, nonproliferative diabetic retinopathy, and retinal vein occlusion.[1]

Other unique approaches to wet AMD therapy include an oral CCR3 inhibitor (NCT04331730, AKST4290, Alkahest); episcleral brachytherapy (NCT02988895, Salutaris Medical Devices); OCT angiography-directed photodynamic therapy triple therapy with ranibizumab, photodynamic therapy with

(Continued on page 57)

Treating GA: Today and Tomorrow

With two therapies out of the pipeline, the era of geographic atrophy treatment is here—with a host of other drugs under investigation.

BY MARGARET M. RUNNER, MD, AND JOHNATHAN D. WARMINSKI, MD


New treatments for geographic atrophy (GA) took center stage in the retina community this past year. With the approval of pegcetacoplan (Syfovre, Apellis Pharmaceuticals) in February, followed by avacincaptad pegol (Izervay, Iveric Bio/Astellas Pharma) in August, coining 2023 *The Year of GA* seems appropriate.[1] As the year comes to a close, let's review some of the promising new therapies for GA still in the pipeline, including antioxidants, gene and cell therapies, immunomodulators, a retinal prothesis, and visual cycle inhibitors (Table).

ANTIOXIDANTS

Elamipretide (Stealth Biotherapeutics) acts as a mitochondrial enhancer by binding to damaged cardiolipins to help restore oxidation within the mitochondria. The phase 2 ReCLAIM-2 trial (NCT03891875) found that patients who received subcutaneous delivery of elamipretide had a 43% reduction in ellipsoid zone total attenuation at 48 weeks (P = .003) compared with patients treated with placebo, which was associated with improvement in low-luminance visual acuity. Although the trial did not meet the primary endpoints of GA lesion progression and mean change in low-luminance visual acuity, the secondary endpoint results were promising enough for Stealth to support continued development of elamipretide in phase 3 trials.[2]

CT1812 (Cognition Therapeutics) is a selective σ-2 antagonist designed to regulate the damage-response processes that are impaired in GA. The phase 2 study (NCT05893537) is assessing the efficacy, safety, and tolerability of a single oral dose of 200 mg CT1812 compared with placebo. The primary endpoint is the change in GA lesion area from baseline over 104 weeks.[3]

GENE AND CELL THERAPIES

ASP7317 (Astellas Pharma), a subretinal therapy derived from human embryonic stem cells, is designed for the treatment of GA in patients who have already lost some central vision. The phase 1b trial (NCT03178149) is enrolling approximately 18 patients and is evaluating three different doses of ASP7317 in conjunction with immunosuppressive therapy. The primary outcomes include safety and tolerability at 52 weeks, with secondary endpoints of change in GA lesion area and BCVA at week 52.

JNJ-1887 (formerly HMR59, Janssen) is a one-time intravitreal injection under investigation for the treatment of both GA and wet AMD. The pooled phase 1 trial data showed that the therapy was well tolerated with no dose-limiting toxicities or serious or systemic adverse events.[4] The phase 2 trial (NCT05811351) is evaluating a high and low dose in combination with prophylactic steroids compared with a sham arm.

AT A GLANCE

- Several gene and cell therapies are under investigation for the treatment of geographic atrophy (GA), including JNJ-1887 (Janssen), RG6501 (OpRegen, Lineage Cell Therapeutics), and ASP7317 (Astellas Pharma).
- Immunomodulation is the most prevalent mechanism for treating GA, with at least five clinical trials underway.
- Novel approaches to GA therapy include a retinal prothesis, antioxidants, and visual cycle inhibitors.

TABLE. INVESTIGATIONAL THERAPIES FOR GEOGRAPHIC ATROPHY

Drug (Company)	Mechanism	Delivery Method	NCT #	Status	Estimated Completion	Last Update
Phase 3						
ALK-001 (Gildeuretinol, Alkeus Pharmaceuticals)	Visual cycle modulator	Oral	NCT03845582	Complete	Complete	February 2022
Tinlarebant (LBS-008, Belite Bio)	Visual cycle modulator	Oral	NCT05949593	Recruiting	August 2027	November 2023
Phase 2						
ANX007 (Annexon Biosciences)	Immunomodulator	Intravitreal	NCT04656561	Complete	Complete	July 2022
AVD-104 (Aviceda Therapeutics)	Immunomodulator	Intravitreal	NCT05839041	Recruiting	July 2025	October 2023
CT1812 (Cognition Therapeutics)	Antioxidant	Oral	NCT05893537	Recruiting	July 2027	October 2023
Danicopan (ALXN2040, Alexion Pharmaceuticals/AstraZeneca)	Immunomodulator	Oral	NCT05019521	Active, not recruiting	July 2024	July 2023
Elamipretide (Stealth Biotherapeutics)	Antioxidant	Subcutaneous	NCT03891875	Complete	Complete	October 2023
IONIS-FB-LRx (Ionis Pharmaceuticals /Roche)	Immunomodulator	Subcutaneous	NCT03815825	Active, not recruiting	April 2024	August 2023
JNJ-1887 (Janssen)	Gene therapy	Intravitreal	NCT05811351	Recruiting	July 2025	November 2023
RG6501 (OpRegen, Lineage Cell Therapeutics)	Cell therapy	Subretinal	NCT05626114	Recruiting	April 2029	October 2023
Phase 1						
ASP7317 (Astellas Pharma)	Cell therapy	Subretinal	NCT03178149	Recruiting	August 2024	June 2023
ONL1204 (ONL Therapeutics)	Immunomodulator	Intravitreal	NCT04744662	Active, not recruiting	March 2024	July 2023
Device Development						
Prima (Pixium Vision)	Retinal prosthesis	Subretinal	NCT04676854	Active, not recruiting	February 2024	February 2023

RG6501 (OpRegen, Lineage Cell Therapeutics) is an allogeneic retinal pigment epithelial cell therapy that has shown promise in a phase 1 trial. The subretinally delivered therapy led to retinal structural improvement in five patients and an average BCVA gain of 12.8 letters at 1 year compared with baseline.[5] The phase 2 trial (NCT05626114) is evaluating the proportion of patients (n = 60) successfully treated with the subretinal delivery method, as well as the incidence and severity of adverse events 3 months postoperatively.

IMMUNOMODULATORS

ANX007 (Annexon Biosciences) is a neuroprotective inhibitor of C1q. The phase 2 ARCHER trial (NCT04656561, n = 270) failed to meet the primary endpoint of statistically significant reduction in GA lesion growth at 12 months. However, there was a greater reduction in lesion growth between months 6 and 12 compared with months 1 to 6, suggesting a possible delayed effect with C1q inhibition and an improved effect with longer duration of therapy.[6]

ANX007 also showed a dose-dependent protection from vision loss and did not increase the rate of choroidal neovascularization conversion. At 12 months, the risk reduction of a ≥ 15 letter vision loss was 72% for monthly and 48% for every-other-month ANX007 injections. Plans are underway for phase 3 trials, and ANX007 received Priority Medicine designation by the European Medicines Agency for the treatment of GA.[6]

AVD-104 (Aviceda Therapeutics) is a sialic acid-coated nanoparticle designed to bind to specific sialic acid-binding immunoglobulin-type lectin receptors and repolarize overactivated macrophages into their resolution phenotype.[7,8] AVD-104 also binds and upregulates complement factor H. Interim data from the phase 2 part 1 safety trial (NCT05839041) found a single intravitreal injection of AVD-104 was well tolerated with no drug-related or serious adverse events. Early efficacy data of the first patients (15/30) to reach the 3-month endpoint found 80% had visual acuity gain from baseline. Part 2 of the trial is actively enrolling (n = 290, 75% with extrafoveal GA lesions) to compare four treatment groups with a primary endpoint of rate of GA lesion change.[7]

Danicopan (ALXN2040, Alexion Pharmaceuticals/AstraZeneca) is a small-molecule inhibitor of complement factor D that is under investigation as an oral therapy. The phase 2 trial (NCT05019521, n = 332) is evaluating four treatment arms: 100 mg or 200 mg twice daily, 400 mg once daily, and matching placebo. The trial includes a 6-week screening period, a 104-week treatment period, and a 30-day follow-up period. Danicopan is also being investigated as a treatment for paroxysmal nocturnal hemoglobinuria.[9]

IONIS-FB-LRx (Ionis Pharmaceuticals/Roche) is an antisense oligonucleotide inhibitor of hepatic production of complement factor B, which is associated with hyperactivity of the alternative pathway seen in GA. Phase 1 studies found a significant dose-dependent reduction in plasma levels of complement factor B with subcutaneous injections of IONIS-FB-LRx compared with placebo. The phase 2 GOLDEN trial (NCT03815825, n = 330) is ongoing with data expected in early 2024.[10]

ONL1204 (ONL Therapeutics) is a Fas inhibitor aimed at reducing Fas-mediated retinal cell apoptosis and inflammatory cytokines. The phase 1b part 1 (n = 6) safety assessment (NCT04744662) of a single intravitreal injection of the study drug found early efficacy with an average reduction in GA lesion growth of 42% at 6 months compared with the untreated fellow eye.[11] Further results from phase 1b part 2 (n = 16) assessing the safety and tolerability of two injections (every 3 months) are expected in early 2024. ONL1204 is also being tested in rhegmatogenous retinal detachment, central retinal artery occlusion, and glaucoma.

VISUAL CYCLE INHIBITORS

ALK-001 (Gildeuretinol, Alkeus Pharmaceuticals) is a deuterium-enriched vitamin A initially developed for Stargardt disease and GA. Orally administered ALK-001 replaces the body's own vitamin A and, theoretically, slows the buildup of toxic vitamin A dimer formation. The phase 3 SAGA trial (NCT03845582, n = 200) is complete with data pending. The company recently announced positive data for the TEASE-1 trial for patients with Stargardt disease.[12]

Tinlarebant (LBS-008, Belite Bio), an oral antagonist of retinol-binding protein used to reduce the accumulation of vitamin A-based toxins, is in clinical trials for GA and Stargardt disease. The phase 1 trial (n = 71) confirmed that the drug is safe and tolerable, and that once-daily oral administration achieved potentially therapeutic levels.[13] The phase 3 PHOENIX trial (NCT05949593) is enrolling approximately 430 patients and is evaluating the rate of change in GA lesion size with once-daily oral 5 mg tinlarebant.

BIONIC VISION IN THE PIPELINE

Pixium Vision recently announced 48-month data for its Prima System, a subretinal implant stimulated by augmented-reality glasses.[1]

For more on this system and other vision-restoring approaches, see *Macular Degeneration: Time to Focus on Vision* in the May/June issue.

1. Pixium Vision announces 48-month trial results in severe atrophic AMD [press release]. Eyewire+. November 14, 2023. Accessed November 15, 2023. bit.ly/3R2fNPL

RETINAL PROSTHESIS

The **Prima System (Pixium Vision)** is a retinal prothesis that stimulates a subretinal microchip for improving visual acuity in severe center-involving GA (see, *Bionic Vision in the Pipeline*). The European pivotal study (n = 5) showed that the implant was safe and well tolerated with early efficacy data demonstrating a mean visual gain of 32 ETDRS letters from baseline when patients used the system's zoom feature. Results from the PRIMAvera trial (n = 38, NCT04676854) are expected by spring 2024.[14]

2023 RECAP

This year has been full of ups and downs in the GA research space, and we are learning much about clinical trial design, the regulatory pathway, tracking lesion growth, and drug delivery methods. Even failed trials have added significantly to our understanding of the GA therapeutic landscape. Next year is already shaping up to be another one for the record books, and we are excited to see the next steps in the era of GA therapy. ■

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Robotics in the Retina OR

Vitreoretinal surgery is entering a new phase with the advent of robots for observation and manipulation.

BY SHINTARO NAKAO, MD, PHD; KOTARO TADANO, PHD; AND KOH-HEI SONODA, MD, PHD



The recent growth of robotics in the surgical field has been remarkable. For example, the da Vinci surgical system (Intuitive Surgical) was a significant advancement in the field of urology, and it is now used in many fields, including gastrointestinal surgery, gynecology, respiratory surgery, and cardiac surgery.[1] Some estimate that the global robotic surgery market will grow approximately four-fold by 2030.[2]

However, the accuracy of the da Vinci system is reported to be 1 mm, which is insufficient for vitreoretinal surgery,[3] and a robotic system dedicated to vitreoretinal surgery remains elusive. Researchers have been working on robotics in the field of ophthalmology since the late 1990s.[4] Because vitreoretinal surgery is performed in the very limited space of the vitreous cavity, delicate and precise procedures are required. The human hand is also limited in terms of the agility, tremor cancellation, and precision required for vitreoretinal surgery. Thus, highly accurate robotic surgery could be suitable for vitreoretinal surgery.

ROBOTICS RUNDOWN

Current robotic surgery systems in ophthalmology can be broadly classified as operation systems, operation assistance systems, or observation systems.[5]

Operational robots are the most common. Ueta et al investigated the positioning accuracy of a robotic prototype for vitrectomy and reported that the system achieved a positioning accuracy of about 30 µm, which is approximately 1/10 to 1/5 of manually conducted accuracy.[6] In animal models, the researchers succeeded in creating a posterior vitreous detachment and retinal vessel micro-cannulation.

Edwards et al conducted a first-in-human study of remotely controlled robot-assisted retinal surgery using the PRECEYES surgical system (Carl Zeiss Meditec).[7] They found that membrane peeling took longer with a robotic system than with manual surgery, but they were also able to perform subretinal injection of recombinant tissue plasminogen activator for subfoveal hemorrhage secondary to wet AMD.[7,8]

A number of other telemanipulated robotic systems have been developed that show promise in providing intraocular dexterity when positioning microstents and grippers and maneuvering forceps during membrane peeling (with a precision better than 5 µm).[9]

Several operation assistance systems are under development, including handheld robotic surgical tools for controlling tremor, force sensing, and intraocular dexterity.[9,10] Researchers are also working on a passive support robot for ophthalmic surgery, which is a commercially available system that was customized for ophthalmic surgery.[11] The robot stabilizes the elbow and arm, making it possible to perform more stable procedures in continuous curvilinear capsulorhexis and suturing.[11]

ROBOTS IN THE OR

Although advances in endoscope technology enable detailed observation of tissues under the iris that cannot be observed with conventional systems, an endoscope is not a widely used tool in vitrectomy.[12] This is due, in part, to the fact that the surgeon must operate it, as the operative field

AT A GLANCE

- Current robotic systems in ophthalmology are broadly classified as operation systems, operation assistance systems, or observation systems.
- Several operation assistance systems are under development, including a robot for controlling tremor and a passive surgery support robot for ophthalmic surgery.
- The authors developed an observation robot to hold an endoscope, which is approved as a medical device in Japan.

Image courtesy of Riverfield

Figure. The surgeon operates the endoscope-holding robot using a foot switch while viewing the endoscope screen.

of ophthalmic surgery is too small for an assistant to hold it.

Based on this unmet need, our team developed an observation robot (OQrimo, Riverfield) to hold an endoscope, which was approved as a medical device in Japan in April (Figure).[13] An operator moves the robotically controlled endoscope with the foot switch, and the robot is designed with a safety function to withdraw from the eye when a certain amount of external pressure is applied.

The robot may be useful during surgical scenarios that warrant a bimanual technique, such as the treatment of fibrous membranes in proliferative retinopathies, particularly anterior hyaloidal fibrovascular proliferation.

The system is also designed to hold a light pipe, which may be helpful for illuminating the peripheral retina during cases of retinal detachment repair. The navigation system shows the observation area of the endoscope, making it easy to use.

Further clinical utility is under investigation, including automatic recognition of retinal lesions and instrument tracking.[14] Furthermore, our team is developing an endoscope with a 10 mm or 15 mm insertion section (current models have a 30 mm insertion section) to reduce the risk of the endoscope coming into contact with the retina.

There are some limitations to this system. First, because many vitrectomies do not require observation or treatment of the peripheral retina, there are only a limited number of cases that require the use of an endoscope. Second, this robot does not have insurance coverage, which places a financial burden on the medical practice. Third, it may be difficult to add new equipment to a crowded OR. Finally, it comes with a learning curve and would require a licensing system similar to other surgical tools.

THE FUTURE

Although this robotic system is helpful, many needs still exist within vitreoretinal surgery; surgeons continue to struggle with recurrent macular holes, proliferative diabetic retinopathy, and proliferative vitreoretinopathy, to name a few. The advent of intraoperative OCT and 3D heads-up surgery has enabled more precise surgical intervention, with the hopes of improving surgical outcomes. In the same way, robotic surgery may enable new vitreoretinal techniques to further improve outcomes and preserve patients' vision. ■

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PVR Pipeline Roundup

At ASRS 2023, experts discussed two medical therapies under investigation.

BY ALEX BRODIN, ASSOCIATE EDITOR

Proliferative vitreoretinopathy (PVR) is a well-known vision-threatening complication of rhegmatogenous retinal detachment (RRD) and a common cause of RRD repair failure. The incidence of PVR in all cases of RD is estimated to be between 5% and 10%,[1] and it is implicated in 50% to 75% of cases of redetachment after surgery.[2] These data underscore a serious unmet clinical need to appropriately treat this condition; however, research is still ongoing as far as the best way to prevent and manage PVR. To further heighten this sense of urgency, visual outcomes with PVR can be quite poor, even with anatomic success.[3] Standard PVR treatment typically involves performing additional surgery. Although multiple adjunctive therapies have been used to try to prevent or treat PVR, there is still no FDA-approved medication for the management of this condition.

This year at the American Society of Retina Specialists (ASRS) annual meeting, speakers shared clinical trial updates on two therapeutics used in combination with surgical intervention that are attempting to address this unmet need. This article highlights the findings and takeaways shared at the meeting.

METHOTREXATE

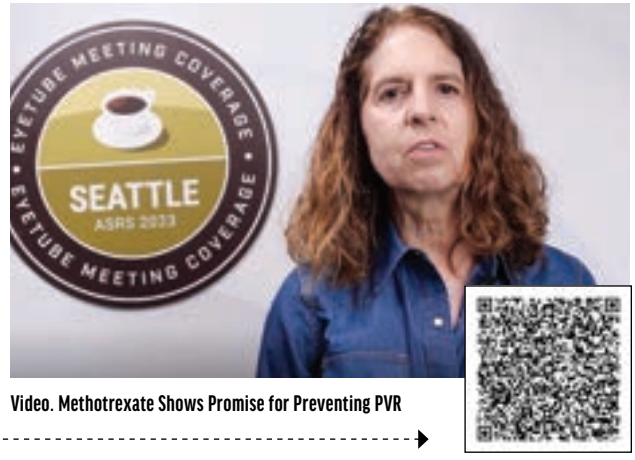
Christina J. Flaxel, MD, presented results from the randomized, multicenter phase 3 GUARD trial (NCT04136366) evaluating the safety and efficacy of an intravitreal injection of 0.8% methotrexate (ADX-2191, Aldeyra Therapeutics) for the treatment of PVR (Video).

Methotrexate has already been proven effective at treating a variety of conditions, including ocular inflammatory diseases. The specific formulation of the drug used in this study (0.8%) is distinct from compounded methotrexate with a 2-year shelf life, among other properties.

Study Design

Patients eligible for inclusion in this trial had recurrent RD due to PVR with greater than 3 clock hours of starfolds (81%) or open-globe injury (19%). The initial study design randomized patients into either an intervention group (routine surgery plus methotrexate injection; n = 68) or a control group (routine surgery alone; n = 38). However, some researchers were hesitant to withhold the drug from those in the control group, and the design was modified so that all patients in the trial received treatment with methotrexate.

WATCH IT NOW



Video. Methotrexate Shows Promise for Preventing PVR

AT A GLANCE

- Proliferative vitreoretinopathy is implicated in 50% to 75% of cases of redetachment after retinal detachment repair surgery.
- In the GUARD trial, 24% of patients treated with methotrexate experienced recurring retinal detachment requiring reoperation within 6 months compared with 39% in the historical control group.
- In the FIXER trial of infliximab, final BCVA was significantly better in the treatment group by approximately 2 ETDRS letters.

PVR IS A FRUSTRATING AND ELUSIVE CONDITION THAT DOES NOT YET HAVE A SUITABLE SOLUTION BEYOND REOPERATION.

A total of 13 injections were given over a 4-month period; the first injection was given in the OR, the next eight were given weekly, and the last four were given every other week. The primary endpoint was recurrent RD requiring reoperation within 6 months compared with a designated historical control group (n = 292).

Results and Key Takeaways

The primary endpoint of this study was achieved; of the patients in the intervention group, 24% experienced recurring RD requiring reoperation within 6 months compared with 39% in the historical control group (*P* = .024).

The most common adverse event was punctate keratitis (16%; n = 16). Of the patients affected, none had severe reactions; nine cases were mild, and two were moderate.

INFLIXIMAB

Ayman Elnahry, MD, PhD, shared updates on the FIXER phase 2 randomized, controlled clinical trial of infliximab for the treatment of PVR (NCT04891991). Infliximab is a chimeric monoclonal antibody that inhibits tumor necrosis factor-α, an inflammatory cytokine and mediator of ocular inflammation that plays an important role in the development of PVR.

Infliximab has previously been studied in the treatment of other systemic and ocular conditions with good results. For example, researchers have evaluated it as a treatment for patients with wet AMD who did not respond to ranibizumab (Lucentis, Genentech/Roche), and it has been shown to help reduce intraocular inflammation in cases of noninfectious uveitis.[4] Specific to the treatment of PVR, a study by Savur et al used an experimental dispase-induced PVR animal model to determine that injection with infliximab effectively inhibited the development of PVR by reducing cytokine levels compared with sham.[5]

The FIXER phase 2 trial is the first-in-human study designed to evaluate a tumor necrosis factor-α inhibitor for the treatment of PVR due to RRD.

Study Design

The goal of this trial was to evaluate the safety and efficacy of infliximab when administered intravitreally upon completion of vitrectomy for RRD repair. Inclusion criteria were patients at least 18 years of age with primary RRD and PVR of grade C or higher, according to the Updated Retina Society Classification.[6] Those with a globe injury, recurrent RRD, other retinal disease, pregnancy or breastfeeding status, or history of tuberculosis were excluded.

Patients were randomly assigned to vitrectomy with complete membrane peeling and silicone oil tamponade either with (n = 33) or without (n = 35) infliximab injection; surgeons were masked to the treatment allocation until completion of surgery. Silicone oil was removed 3 months postoperatively. At 3 months, patients who experienced recurrent RD repeated the same protocol as the initial randomization.

The primary endpoint was anatomic success, defined as complete retinal reattachment without tamponade at 6 months after silicone oil removal. Secondary endpoints included final visual acuity; single-operation success rate; rate of recurrent RD; and macular thickness, function, and vascular density.

Results and Key Takeaways

Of the 68 patients enrolled, 60 were included in the final analysis (30 in each group); the remaining eight were lost to follow-up. Statistical analysis revealed that 30 eyes in the infliximab group experienced final anatomic success versus 29 eyes that underwent surgery alone. The single-operation success rate was higher in the treatment group (86.7%) compared with controls (76.7%), although this result was not statistically significant (*P* = .317).

Final BCVA was found to be significantly better in the treatment group by approximately 2 ETDRS letters (*P* = .044), and no differences were noted in IOP or macular findings. The researchers suggest that the 2-letter improvement in BCVA could be due to the lower rate of recurrent RD in the infliximab group.

GETTING CLOSER

PVR remains a frustrating and elusive condition that does not yet have a suitable solution beyond reoperation. However, the findings presented at ASRS 2023 offer hope that an adjunctive medical therapy will soon be available to more effectively treat—and, better yet, prevent—this serious complication. ■

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RISING STARS IN RETINA

Get to know outstanding retina fellows from the class of 2023.

Alexis Warren, MD

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

My father is a retina specialist, and when I had the opportunity to see him at work, I was insantly mesmerized—at the age of 10. Although I didn't quite grasp the concept of ophthalmology at the time, his fervor and enthusiam for the retina were magnetic.

As I grew, I started to better understand the intracies of his job, and I was inspired to make it my own reality.

One of the greatest gifts my father gave to me was the idea that I could have a career that I loved enough that it didn't feel like work. His passion for retina has always been so palpable that it was natural for it to feel like home for me.

_RT:_ Who do you look to as mentors in the field?

At the Illinois Eye and Ear Infirmary, I have access to some of the best retina mentors. Jennifer I. Lim, MD, and William F. Mieler, MD, have helped to shape the retina physician I am.

In addition, Keith Carter, MD, past AAO president and the deparment chair at the University of Iowa, helped to ignite my own passion for mentoring. With his support throughout my residency, I became involved in programs that foster relationships with underrepresented trainees interested in ophthalmology. I still turn to him for guidance and consider him a life-long mentor and friend.

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

Within the first 3 months of fellowship, I had three on-call overnight vitrectomies with RV Paul Chan, MD, MSc, MBA. I was nervous and tired, but his calm demeanor put me at ease, and all the patients did well. It's times like those that I know I picked the right job because I wouldn't have traded that experience for anything.

_RT:_ What are you hoping to accomplish once you are in practice?

In addition to a strong clinical/surgical practice, I would like to maintain my presence in various subspecialty programs. I find it rewarding to pay it forward by recruiting and encouraging the next generation of retina specialists. I hope that my legacy will be about advocacy—not just for medical trainees, but also patients and ophthalmology community physicans. And it may be a long shot, but it might be nice to be AAO president one day.

FIRST CAREER MILESTONE

Dr. Warren is now an assistant professor and vice chair of Diversity, Equity, and Inclusion in the Department of Ophthalmology and Visual Sciences, in the Medicine and Biological Sciences Division at the University of Chicago.

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

Many are turned off by the hectic schedule and unpredictable pathologies. Some of that is true, but the beauty of retina is that there is more than one way to do things. We have many tools that allow us to practice however we want. What's most important is picking a specialty where you will feel fulfilled, excited, and challenged. Life is what you make of it, and we all want to see you do retina your way. ■

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3D PRINTING IN VITREORETINAL SURGERY

This new technology may one day become a major player in ophthalmology.

BY YURI V. CHABAN, MD(C), MENG; SIDDHARTHA MUKHERJEE, BSC(C); SAMANTHA M.A. ORR, MD; AND NETAN CHOUDHRY, MD, FRCS

First developed in the 1980s for product manufacturing, 3D printing has evolved rapidly. Ophthalmology is now applying 3D printers to produce patient-tailored orbital prostheses, preoperative anatomical models, prescription spectacles, and intraocular devices.[1-5] This technology is of particular interest to vitreoretinal surgery due to the possibility of quick, inexpensive production of surgical instruments that can be customized to a surgeon's preferences and needs.

SURGICAL INSTRUMENTATION

The success of the 3D-printed medical device market, recently valued at $2.55 billion globally, can be attributed to its unique advantages over traditional manufacturing processes (see *Printing Principles*).[6,7] For example, 3D printing significantly reduces prototyping time and cost compared with traditional production lines and can create complex geometric designs not possible with the latter. Such a low-cost production method enables the possibility of disposable instruments. 3D printing also promotes accessibility with affordable entry-level machines and, soon, access to a growing body of open-source designs.[8]

These principles have already been leveraged to produce instruments in general, orthopedic, oral, and maxillofacial surgical settings.[9] Substituting basic surgical instruments with their 3D-printed counterparts has become a feasible option, and printed kits for dental surgery are already available for purchase.[10,11]

The ability to modify conventional instruments quickly and cost-effectively according to the patient, procedure, and/or surgeon's needs truly illustrates the power of this technology. For example, patient-tailored endoscope caps with an enhanced field of view can be printed to target a specific esophagogastric lesion for therapy.[12] Furthermore, laparoscopic devices have been designed according to a surgeon's hand size and personal preferences for enhanced intraoperative ergonomics and comfort.[13] 3D printing also enables the production of novel instruments, such as a minimally invasive surgical system proposed for kidney tumor removal, which is automatically generated based on specific patient (eg, tumor size and distance from abdominal wall), task (eg, laparoscopy or endoscopy), and surgeon (eg, preferred force transmission or number of manipulator arms) parameters.[14]

Despite the success of 3D-printed instrumentation in other fields, its potential in ophthalmic and vitreoretinal surgery is only just starting to be explored (Table). Initial research shows that the biocompatibility of most 3D-printed materials is well-primed to handle sensitive ocular tissues; researchers have already designed a storage device that preserves a donor cornea for transplantation.[15] In fact, the first intraocular model of the Canabrava ring (AJL Ophthalmic), a pupil expansion device, was designed by 3D printing and is now mass-manufactured using thermoplastic polymethyl methacrylate.[5] A 3D-printed adaptor for endoillumination during vitreoretinal surgery is an excellent example of a cost-effective solution to limited access.[16]

Within academic institutions, the relatively inexpensive and quick production timeline of this technology may offer unparalleled benefits in innovation and ergonomics when prototyping new instruments, such as customizable vitreoretinal forceps.[17]

These concepts are currently being applied to assess the feasibility of 3D-printed trocars for transconjunctival vitrectomy systems, with the opportunity for personalization according to both patient and surgeon needs.[18,19]

TABLE. PUBLISHED REPORTS OF 3D PRINTING IN VITREORETINAL SURGERY			
Study	**Product**	**Printing Method**	**Material***
Choi et al (2018)[20]	Preoperative planning model	Stereolithography	Polymer
Liao et al (2022)[16]	Endoillumination adaptor	Material extrusion	Polymer
Lussenburg et al (2022)[19]	Trocar	Stereolithography	Polymer
Navajas and Hove (2017)[18]	Trocar	Material jetting	Polymer
Zou et al (2021)[21]	Preoperative planning model	Stereolithography	Polymer
**The composition of a given polymer material is often proprietary information.*			

SURGICAL PLANNING

3D printed models also may be helpful during surgical planning. For example, 3D-printed globe models from CT and MRI data of more than 100 uveal melanomas allowed a recent study's treatment team to better appreciate key structures (eg, IOLs, unusual tumor shapes) and optimize stereotactic radiosurgery.[3] Finer pathology has also been 3D-modelled using OCT, such as a patient's epiretinal membrane with adhesion and traction points, which helped identify where to start peeling during vitrectomy.[20]

This principle was further applied to 12 patients with myopic foveoschisis, whereby 3D printing was used to build globe models and macular buckles with an indentation height corresponding to the height of retinoschisis.[21] Titanium stent macular buckles were shaped according to these models. Post-vitrectomy, all cases of macular schisis had resolved without postoperative complications.[21]

While work is already underway to address the printing costs of this technique and the additional operation required to mark extraocular muscles for modelling, its high safety and success rates showcase the strong potential that 3D printing has as a preoperative planning tool.

PRODUCTION IN THE CLINIC

Because medical-grade 3D printing technology is available at affordable prices, a small investment by a surgical center can secure enough printers to run in parallel and meet its production needs. The surgeon would be able to collaborate with an engineer ahead of each patient's procedure to share ideas and/or modify existing tools, enabling the creation of single-use, procedure-specific, surgeon-matched instruments. These instruments are rendered and presterilized in-house, further reducing processing cost and time.

The performance of any novel design and/or procedure can be assessed preoperatively by printing patient-specific surgical models, which may also serve as useful aids in practicing and teaching. As these printers can also produce medical devices of interest to other departments, production and personnel costs can be shared to make this technology accessible within a range of institutional budgets.

PRINTING PRINCIPLES

The American Society for Testing and Materials group recognizes seven categories of 3D printing technologies according to how the layers are created and the raw materials used.[1] The characteristics of 3D printers are essential in machine selection. Despite the range of technologies, all operate on a layer-by-layer printing principle according to the following generic steps:

Step No. 1: Digital Model Generation. A digital model is generated, often with a computer-aided design package, to describe the product's geometry for printing.

Step No. 2: Printable File Conversion. The digital model is converted into a format that is compatible with the selected 3D printer, assessed for errors, processed by a slicing software into layer-by-layer instructions, and transferred to the 3D printer.

Step No. 3: Construction. Construction of the physical product begins—an automated process that can take several hours to days depending on the material and technology used, as well as the model's size and design complexity.

Step No. 4: Removal. Once finished, the product is removed from the 3D printer by simply detaching it from the printing platform or through a more complicated method (eg, chemical or heat treatments).

Step No. 5: Post-Processing. A physical product may require additional processing before use. If internal supports were required for stability during the construction process, these must be removed prior to completion. In addition, some materials may require heat treatment, ultraviolet curing, or surface finishing for strength, safety, and aesthetics.

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CHALLENGES AND FUTURE DIRECTIONS

The lag in uptake of 3D-printed ophthalmic instruments is due, in part, to the processing limitations of current technologies. Accuracy is essential when producing ophthalmic surgical instrumentation, often millimeters in size, and, thus, vat polymerization techniques have found their way into the spotlight. However, prototype vitreoretinal trocars produced from an industry-standard stereolithography printer were too fragile and suffered from channel deformities.[19] Printing with a thicker, ribbed helical design overcame these issues but required significantly more insertion force, posing a greater risk of intraoperative ocular trauma.

The opportunity to personalize ophthalmic instrumentation to patient and surgeon needs, such as customizing cannula length and valve design according to scleral thickness and procedure fluidics, respectively, is promising with advancements in 3D printing technologies, offering enhanced accuracy, resolution, and potential to combine different materials.[22,23]

Cost-effectiveness and medical regulation are important considerations with 3D printing for ophthalmic surgical instrumentation. While entry-level printers can be purchased for less than $5,000, advanced models are significantly more expensive.[9] Further, the expertise of a software designer is often required for intricate geometries, with added labor costs. Of course, the benefits of 3D printing in reducing material, assembly, tools, and costs typically significantly outweigh those of traditional manufacturing, particularly in the setting of low-volume production of customizable targets.

One disadvantage is the uncertainty regarding how to sterilize 3D-printed products, which depends on the material.[24] Thermoplastic polymers, for example, may be best sterilized using surface-based methods (eg, hydrogen peroxide gas) to avoid deformation by heat, but special care must be taken for areas of complex design that can trap leftover resin.

Ultimately, a detailed review of the target workflow and application is essential in successfully adopting this technology into intraocular surgery, particularly as printer manufacturers begin to optimize their materials and settings. ■

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THE BENEFITS OF VITRECTOMY FOR UVEAL MELANOMA

The use of vitrectomy techniques is the only way to maximize the best possible vision for patients with uveal melanoma.

BY TARA A. McCANNEL, MD, PHD

The treatment of uveal melanoma—with brachytherapy, radiotherapy, local resection, and enucleation—is focused first and foremost on controlling the tumor and preventing distant metastasis.[1] While these therapeutic approaches do not require vitreoretinal surgical training, they are not intended to preserve the patient's vision. Tumor patients can survive despite treatment complications, such as radiation retinopathy, untreated retinal detachment (RD), or vitreous hemorrhage—all of which can be addressed with pars plana vitrectomy (PPV). In fact, if visual outcome is important, vitreoretinal surgery is required to help patients see better.

At the University of California, Los Angeles (UCLA) Ocular Oncology Center, we combine vitreoretinal surgical techniques and brachytherapy in the treatment of melanoma to help improve patients' visual outcomes. For example, research shows that a silicone oil fill during PPV can:

- shield the healthy retina from iodine-125 radiation by 50% to 60%[2];
- reduce retinopathy compared with plaque therapy alone at 2 years[3]; and
- significantly improve vision in large choroidal melanomas compared with plaque therapy alone at 2 years.[4]

We have switched to using Palladium-103, which our research demonstrates is even better shielded by silicone oil, with a reduced exposure rate of between 75% and 80%[5] compared with iodine-125 alone.

HOW IT WORKS

During brachytherapy, a plaque is placed over the tumor on the sclera, exposing healthy tissue to radiation. Placing a vitreous-attenuating substance in the vitreous cavity can help to reduce some of the radiation. In a one-to-one matched case-controlled study of 20 cases of uveal melanoma treated with a 23-mm-diameter iodine-125 plaque and PPV with silicone oil 1,000 cSt placement, we found significantly better visual acuity at 2 years than with plaque therapy alone.[4] Of the 40 eyes included in the study, 39 (98%) achieved local tumor control, and metastasis occurred in 15% of study eyes and 45% of controls (P = .082).

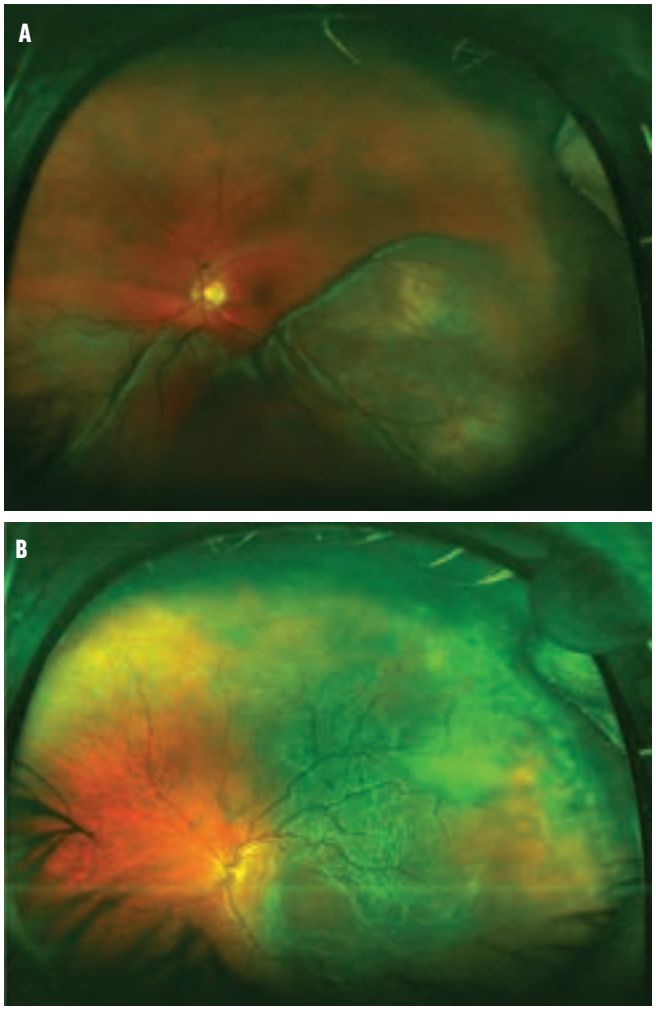

Figure 1. This patient has a large melanoma tumor with a serous RD (A). The patient underwent PPV with silicone oil and had good results 1 month after surgery (B).

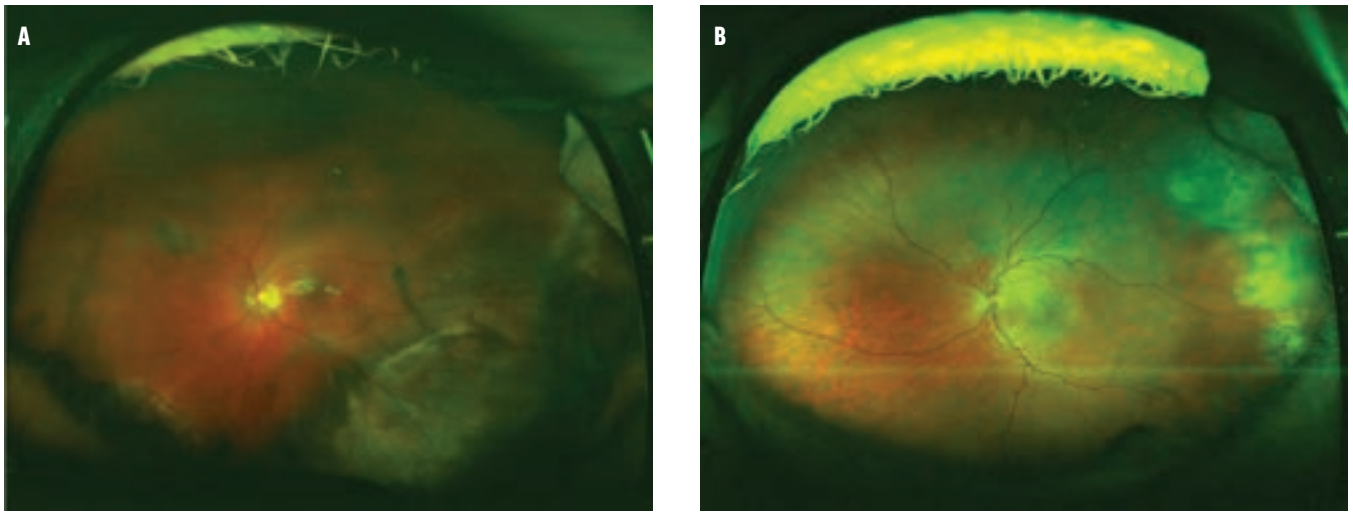

Figure 2. A patient with melanoma presented with an RD (A) that was treated with pneumatic retinopexy (B).

As for the visual outcomes, the final VA was 0.83 logMAR for study patients and 2.06 logMAR for controls (P = .0064). Of those with positive visual outcomes, 65% of study eyes and 25% of controls achieved VA ≥ 20/200 (P = .025). As for those with a poor final VA, 35% of study eyes and 80% of controls achieved a VA of < 20/200 (P = .0053); 5% of study eyes and 35% of controls had a final VA of light perception or no light perception (P = .044).[4]

OTHER PPV INDICATIONS

Vitrectomy is also an important treatment consideration beyond silicone oil shielding. Serous and rhegmatogenous RDs and vitreous hemorrhage can persist for months before patients are referred to a retina surgeon, even though we have the technical skills necessary to help these patients see better immediately (Figures 1 and 2). For example, a patient presented to UCLA with a 2.6 mm melanoma and a retinal tear with detachment. After pneumatic retinopexy, the patient underwent plaque therapy with PPV and silicone oil. Eight years later, the tumor remained well-treated, the retina was attached, and VA was 20/40.

THE PATH TO VISION PRESERVATION

Vitrectomy is the only path we have, for now, to achieve superior visual outcomes in patients with uveal melanoma. Research shows that shielding with silicone oil improves vision, and PPV for RDs, vitreous hemorrhage, and other treatment complications can restore vision. The good news is that we already have the tools to allow patients to see their best. We must encourage ocular oncologists of the future to become skilled vitreoretinal surgeons in tumor eyes and make vision for patients a priority. ■

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KEY TAKEAWAYS

- Vitrectomy with silicone oil 1,000 cSt fill can shield the healthy retina from iodine-125 radiation by 50% to 60%, or by at least 75% to 80% when Palladium-103 is used instead.
- When vitrectomy with silicone oil was used for 20 cases of large uveal melanoma treated with a 23-mm-diameter iodine-125 plaque, vision was found to be significantly better in the group treated with vitrectomy and silicone oil (P = .0064) compared with plaque alone at 2 years. More specifically, 65% of the silicone oil patients versus 25% of the plaque-alone patients achieved VA of 20/200 or better.
- Vitrectomy is an important technique in tumor eyes to treat serous retinal detachment, rhegmatogenous retinal detachment, persistent vitreous hemorrhage, macular pucker, macular holes, and more.

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RETINAL BIOMARKERS OF SYSTEMIC DISEASE: PART TWO

These findings can help to steer you in the right direction when imaging the retina.

BY SAMANTHA M.A. ORR, MD; AUSTIN PEREIRA, MD, MENG; SIMRAT SODHI, MSC; NIVEDITHA PATTATHIL, MD; AND NETAN CHOUDHRY, MD, FRCSC

Ocular biomarkers include molecular, histological, radiographical, and physiological characteristics indicative of a disease state or intervention response.[1] In ophthalmology, the term *biomarker* often refers to OCT or OCT angiography (OCTA) findings in the context of retinal pathologies such as AMD, as addressed in part one of this two-part series.[2] Retinal biomarkers on OCT, clinical examination, and fundus photography can also have major implications in systemic disease.[1]

Because many systemic conditions affect the eye, we can use fundus photography and advanced ophthalmic imaging to gain insight into the status, risk, and response of systemic disease.[1] In the era of personalized medicine and improved prognostication, AI has been employed to develop novel biomarkers using retinal imaging.[3] Through deep-learning algorithms, these programs can detect relevant features through saliency mapping.[1,4] Here, we review updated retinal biomarkers with critical implications for systemic disease diagnosis, prognosis, treatment, and monitoring.

CARDIAC RISK

Cardiovascular disease (CVD) risk has traditionally been estimated using risk calculators such as the Framingham risk score and the systematic coronary risk evaluation (SCORE), which consider several criteria, including age, blood pressure, and cholesterol level.[5-7] Many of these risk factors, along with CVD itself, are associated with retinal arteriolar narrowing, hemorrhage, and cotton-wool spots.[5,8] Poplin et al predicted the risk of major adverse cardiac events using retinal images alone and reported similar accuracy to SCORE.[5]

Coronary artery calcium (CAC) score is a preclinical marker of atherosclerosis measured with cardiac CT. Rim et al developed a deep-learning algorithm model that analyzed fundus photography to predict the probability of CAC presence. The model generated a comparable score to that obtained with CT and better predicted the presence of CAC in three test sets compared with any individual cardiovascular risk factor investigated, the highest of which was age, followed by glucose level.[7]

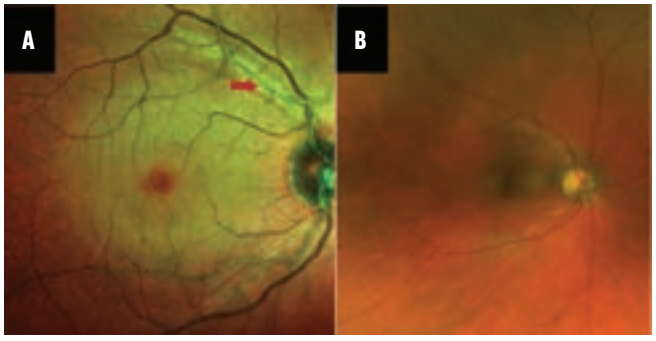

Figure 1. Pseudocolor images of hypertensive retinopathy (A, B) show vascular changes, including arteriolar narrowing, arteriovenous crossing, and arteriosclerosis with a silver wiring appearance of the vessels (red arrow).

HYPERTENSION

Hypertensive retinopathy presents with arteriolar narrowing, arteriovenous crossing, exudates, hemorrhages, and, at its most severe, papilledema (Figure 1).[8,9] Recently, subtle retinal changes were used to prognosticate

An Overview of Biomarkers in Retinal Disease
To read part one of this series, visit retinatoday.com or scan the QR code:

hypertensive end-organ damage, such as risk of CVD and stroke.[3] Using deep-learning algorithms, hypertension can be detected using retinal fundus photos alone.[10,11]

Changes in the vasculature of distinct retinal layers can be found on OCTA.[8,9] For example, the foveal avascular zone is enlarged in patients with hypertension compared with patients without hypertension. There may also be decreased vessel density in the superficial and deep capillary plexuses, although reports are inconsistent.[8,9] Finally, flow deficits in the choriocapillaris have been described in patients with uncontrolled hypertension.[8]

The new field of adaptive optics imaging allows documentation of microscopic retinal changes, including the inner and outer diameter of arterioles.[8] In patients with hypertension, there appears to be a smaller inner diameter with a thicker vessel wall, resulting in a larger wall-to-lumen ratio. This measure does not depend on absolute measurements, which can be helpful for comparison between patients and when monitoring progression.[8]

SLEEP APNEA

Obstructive sleep apnea (OSA) is characterized by chronic intermittent hypoxia, which can lead to retinal hypoxia.[12] Research shows an association between OSA and retinal vein occlusion and central serous chorioretinopathy.[13,14] Anatomical and vascular changes have also been detected on ophthalmic imaging in patients with OSA, even in the absence of pathology (Figure 2). Characterizing these retinal changes has proven difficult given varied measures of OSA severity, differences in baseline characteristics, and difficulties in determining disease duration.[12,15,16]

Morphological vascular changes have been reported, including increased vascular tortuosity and arteriolar changes similar to mild hypertensive retinopathy (Figure 3).[12,17] One case study of a patient with OSA included swept-source OCT and vascular perfusion mapping that confirmed vascular tortuosity in both the retinal arteries and the superficial capillary plexus veins of both eyes without leakage.[17]

Changes in choroidal thickness have been controversial, although a meta-analysis revealed that significantly thinner choroidal thicknesses were found in patients with moderate and severe OSA compared with patients in the control group.[13] This is thought to be related to autonomic dysfunction and inflammation.[13]

There have been inconsistent reports of changes in the ganglion cell-inner plexiform layer (GCIPL) thickness in OSA, with some patients experiencing thickening and others experiencing thinning, highlighting the need for larger studies with similar baseline patient characteristics.[15] Although results differ between studies, most show decreased vascular density in the deep capillary layer on OCTA.[12,16] Using an AI neural network, risk of OSA has been associated with low retinal vascular density and fractal dimensions.[18]

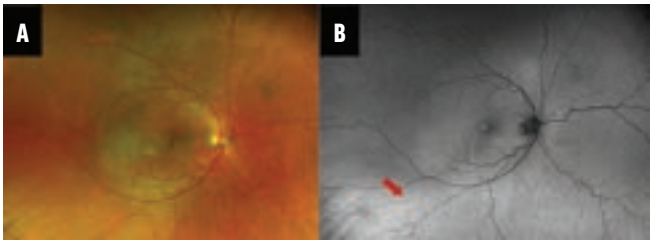

Figure 2. Pseudocolor imaging of OSA shows vascular changes, including diffusely increased venular and arteriolar tortuosity and arteriolar changes (A). Fundus autofluorescence imaging shows a diffuse area of hyperreflectivity inferiorly (B, red arrow).

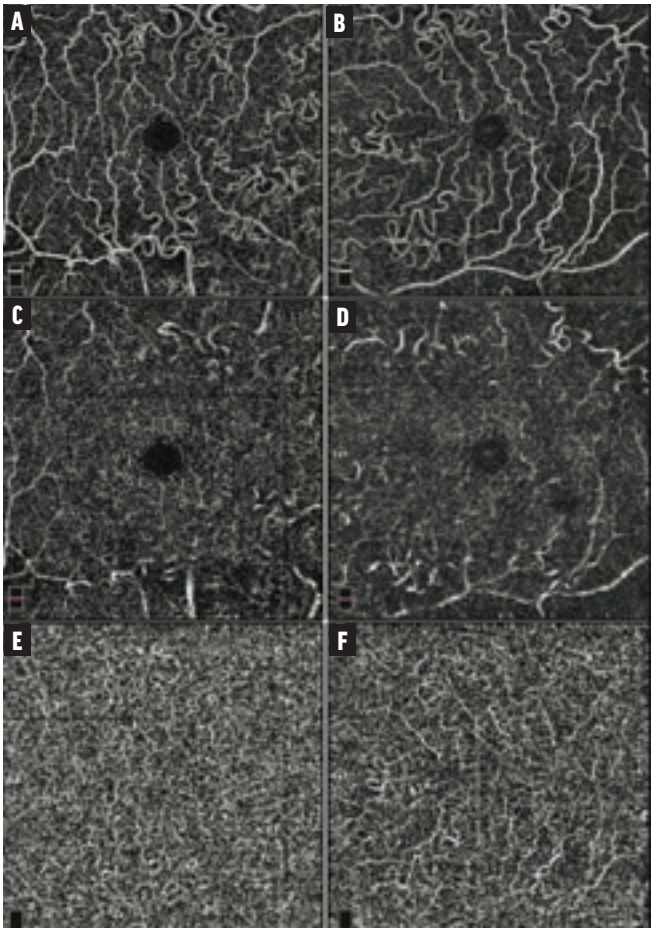

Figure 3. The en face OCTA of both eyes of an OSA patient shows vascular tortuosity in the superficial capillary plexus (A, B), deep capillary plexus (C, D), and choriocapillaris (E, F).

COGNITIVE FUNCTION

Researchers have continued to search for clinically valuable retinal biomarkers to detect and predict the risk of Alzheimer disease (AD).[19-21] One study determined that ultra-widefield color photography and autofluorescence imaging actually have limited value in predicting an AD diagnosis, although the images included in the study likely were not able to capture an ultra-widefield view, as they were cropped to remove eyelid artifacts.[22,23]

OCT and OCTA measures are more valuable, particularly GCIPL thickness.[22] On saliency mapping, superficial perfusion

density and foveal avascular zone size were relevant to an AD diagnosis.[22] Wang et al looked at OCTA scans of patients with AD with mild cognitive impairment and found that superficial vascular density was significantly lower in patients with AD compared with controls.[20] Yan et al described significantly decreased vascular density in patients with AD compared with controls, and this measure correlated with cognitive scores, such as the mini mental status exam.[21]

MULTIPLE SCLEROSIS

Although the typical ophthalmic manifestation of multiple sclerosis (MS) is optic neuritis, subtle retinal changes seen on OCT can mirror neuro-axonal degeneration occurring in the brain.[23] Through retrograde degeneration, the retinal nerve fiber layer composed of unmyelinated axons can thin and degenerate over time.[23] The origin of these axons is the ganglion cell layer, which reflects in vivo conditions of the cells and is more susceptible to decreased perfusion.[23]

Even without optic neuritis, peripapillary retinal nerve fiber layer and GCIPL thickness appear to correlate with MS activity and progression.[24] GCIPL thinning correlates with clinical progression and increased relapses.[23] Radiologic progression with new lesions on MRI and increased rate of lesion development also correlate with accelerated GCIPL thinning. Furthermore, microcystic macular edema on OCT in patients with MS is associated with poorer visual and global disability scores.[25] Given the established correlation between disease activity and progression with OCT measures, clinical trials of MS therapeutics have used OCT measures as a treatment efficacy outcome.[23]

TAKEAWAYS

The applicability of ophthalmic imaging in the prediction, detection, and prognosis of systemic disease is growing. Retinal biomarkers, such as measures of microvasculature, are now a research focus to determine what more can be learned from the eye. A wealth of ophthalmic data is collected daily in clinics around the world, and AI algorithms provide an exciting opportunity to gain novel, clinically valuable information to positively affect patient care. ■

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(Continued from page 39)
verteporfin (Visudyne, Bausch + Lomb), and triamcinolone acetonide (NCT04075136); and adjuvant doxycycline/MMP-9 inhibition (NCT04504123).

BIOSIMILARS

Many companies are rushing to introduce anti-VEGF biosimilars, and more than 10 drug candidates are in phase 3 clinical trials with biosimilars of bevacizumab (Avastin, Genentech/Roche), aflibercept, and ranibizumab (Table 2).

THE LANDSCAPE

Exciting therapies are on the horizon for wet AMD. We may soon be using gene therapy, tyrosine kinase inhibitors, or a variety of other approaches in the clinic; the future of wet AMD treatment, and the practice of retina, may look quite different in just a few years. ■

Editor's Note: Data are cited as of November 13, 2023.

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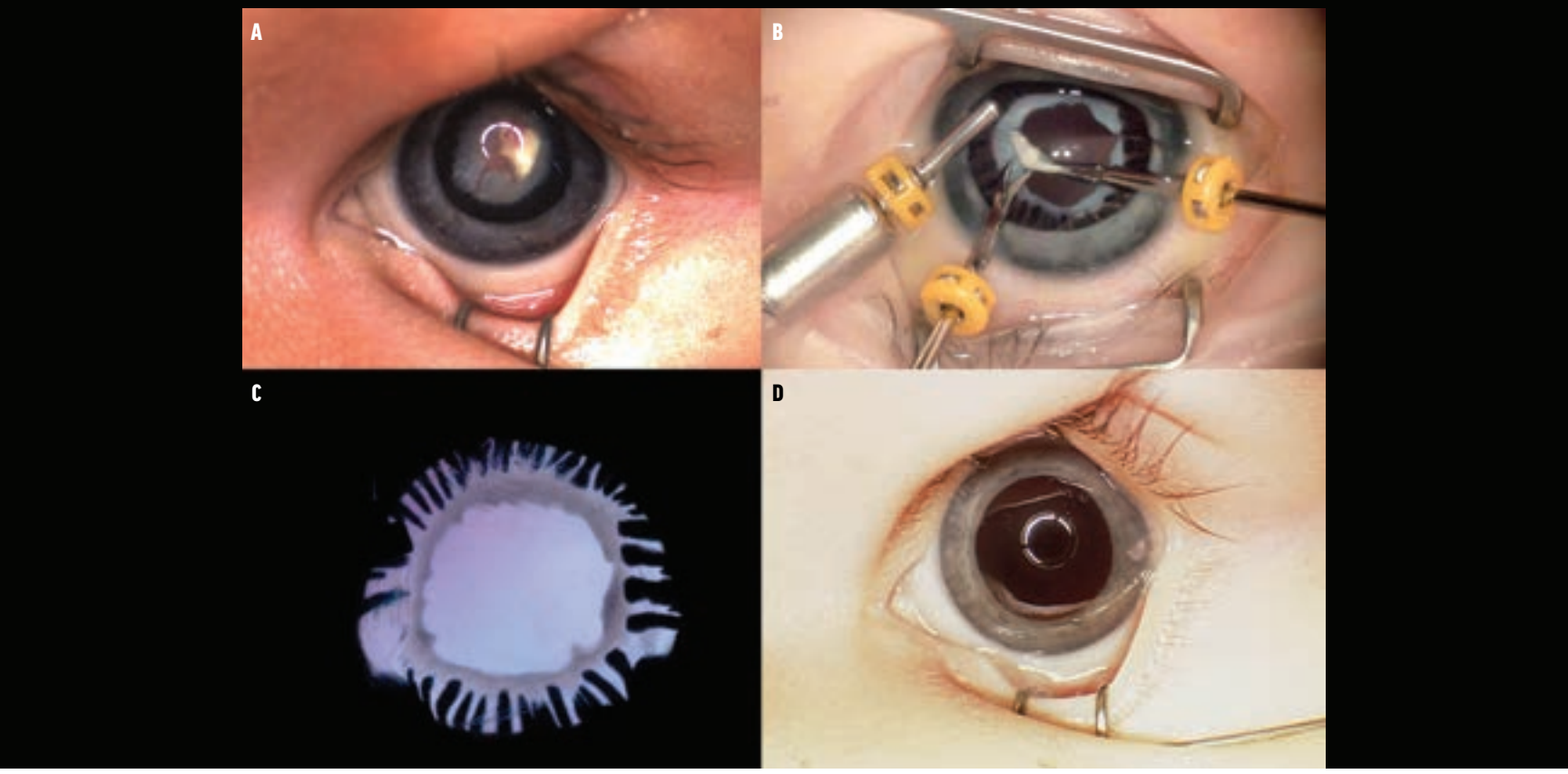

SURGICAL OPTIONS FOR PFV PLAQUE DISSECTION

A severe case of anterior persistent fetal vasculature was managed with limbus-based vitrectomy.

BY YOSHIHIRO YONEKAWA, MD

An infant boy was referred for unilateral leukocoria. Examination revealed a dense plaque on the posterior lens with elongated ciliary processes, consistent with severe anterior persistent fetal vasculature (Figure A). B-scan ultrasonography did not show any posterior lesions.

TREATMENT

A limbus-based vitrectomy was performed. An anomalous crystalline lens was aspirated, and scissors and forceps were used to dissect the plaque (Figure B). Intraoperative retroillumination beautifully showed the fibrous ring that was tethering the anterior segment (Figure C). This ring was also segmented and removed. The visual axis was nicely cleared (Figure D). ■

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