

RETINA[®] SPECIALIST

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0.18 mg

YUTIQ(fluocinolone acetonide
intravitreal implant) 0.18 mg

Discover continuous calm in uveitis¹

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^{1,2}**
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

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.



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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

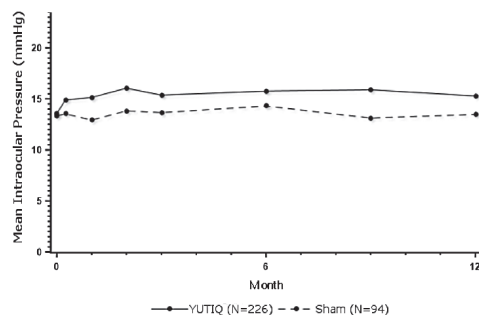
Ocular		
ADVERSE REACTIONS	YUTIQ (N=226 Eyes) n (%)	Sham Injection (N=94 Eyes) n (%)
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular		
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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EDITORIAL

By Charles C. Wykoff, MD, PhD



FDA engagement

The U.S. Food and Drug Administration has been quite active in the retina-verse lately.

First the successes. 2023 has yielded a record number of new approvals. The complement inhibitors pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and avacincaptad (Izervay, Iveric Bio/Astellas Pharma), were approved for treatment of geographic atrophy, while an 8-mg dose of aflibercept (Eylea HD, Regeneron Pharmaceuticals) was approved for neovascular age-related macular degeneration, diabetic macular edema and diabetic retinopathy.

Other recent successes hold promise for future approvals. NT-501 (Neurotech Pharmaceuticals), a surgical implant containing genetically modified retinal pigment epithelium cells that produce ciliary neurotrophic factor, significantly slowed the progression of photoreceptor loss in patients with macular telangiectasia type 2. Emily Chew, MD, presented results from two pivotal trials at the American Society of Retina Specialists meeting.¹

I consider retinal imaging another recent success, based on both an explosion of artificial intelligence-based image quantification tools and cumulative FDA feedback that photoreceptor loss can be an approvable endpoint for multiple diseases.

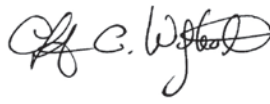
But not all is rosy. The FDA issued two prominent Complete Response Letters (CRL), citing problems in new drug applications. In June, a CRL for aflibercept 8 mg cited inspection findings at an outsourced filler—issues that were efficiently addressed. In August, the FDA sent a CRL for ONS-5010 (Outlook Therapeutics), ophthalmic formulation of bevacizumab, citing

chemistry, manufacturing and controls, as well as a lack of substantial evidence.

Other pipeline candidates have encountered unforeseen hurdles. KSI-301, or tarcocimab (Kodiak Sciences), an anti-VEGF biopolymer conjugate, didn't meet noninferiority compared to aflibercept in pivotal DME trials, and there was also an unexpected increase in cataracts. The future of this molecule is unclear.

FDA guidance on trial design in retina appears to be shifting. First, the practice of using sham injections, historically used in most pivotal trials in retina, may no longer be considered adequate masking, particularly for an endpoint with any possibility of subjectivity.

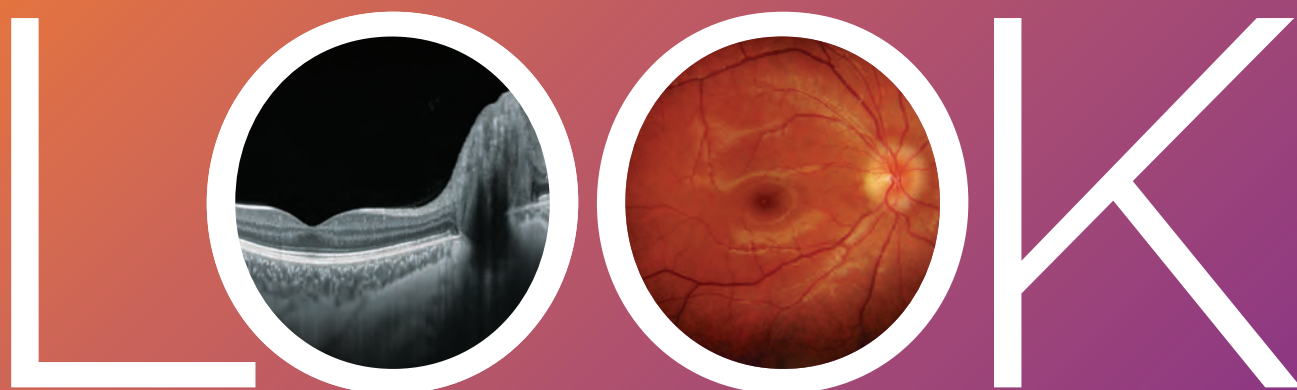
Second, despite multiple agents approved based on noninferiority, the agency is strongly recommending superiority trial designs; this could lead to less than optimal designs from a patient-outcomes perspective.

While the retina landscape has evolved tremendously since the FDA approved pegaptanib in 2004, our goals remain the same: preserve and restore as much vision as possible, as safely as possible, for each patient. The FDA has proven to be a critical partner in this journey, and it's playing a more important role than ever in shaping the future of retina. 

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1. Chew E. Phase 3 randomized studies of efficacy and safety of revakinagene tararectel producing ciliary neurotrophic factor (CNTF) in macular telangiectasia type 2. Paper presented at the American Society of Retina Specialists 41st annual scientific meeting; Seattle, WA; July 30, 2023.

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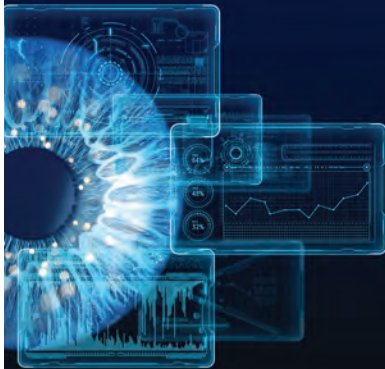
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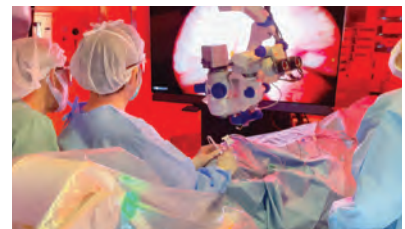
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Transgene shows restorative properties

in nAMD

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FIVE EVENTS MAKE FOR A BUSY SUMMER IN RETINA

1. Aflibercept 8 mg seeks its place in the retina specialist's tool chest

With the FDA approval of aflibercept 8 mg (Eylea HD, Regeneron Pharmaceuticals) for three indications in retina—neovascular age-related macular degeneration, diabetic macular edema and diabetic retinopathy—retina specialists have a new option for longer-term treatment intervals. The label recommendation for nAMD is eight to 16 weeks after three monthly loading doses, and, for DME, eight to 12 weeks after the loading doses.

While Eylea HD has the potential to address issues patients have coming into the office every month or every other month for intravitreal injections, Michael Javaheri, MD, with Retina Specialists of Beverly Hills in Southern California, tells *Retina Specialist Magazine* he would encourage any patient undergoing anti-VEGF treatment to discuss the option with their doctor.

“While many patients may be satisfied with their current treatment, they may prefer the reduced frequency of injections that Eylea HD offers, with



the peace of mind that comes with the well-established efficacy and safety of Eylea,” he says.

“These first weeks of using the treatment have been seamless for myself and my patients, and I’m looking forward to seeing the meaningful improvements in vision that Eylea HD can bring to the millions of people living with serious retinal diseases,” Dr. Javaheri adds.

Dr. Javaheri is a paid speaker and consultant to Regeneron and Genentech/Roche.

2. FDA approves avacincaptad pegol, another option for geographic atrophy

Avacincaptad pegol 2 mg is a complement C5 inhibitor (ACP, Izervay, Iveric Bio/Astellas Pharma) the Food and Drug Administration approved for monthly treatment of GA. The approval was based on results from the Phase III GATHER1 and GATHER2 pivotal Phase III trials. Upon its approval, Astellas said the drug would be available in two to four weeks.

A post-hoc analysis from the GATHER trials showed a relationship between GA growth and worsening vision loss, Carl Danzig, MD, reported at the Association for Research in Vision and Ophthalmology 2023 meeting.¹ The combined analysis correlated greater vision loss with increased GA growth. Dr. Danzig is director of vitreoretinal services at Rand Eye Institute,

Deerfield Beach, Florida.

“This is the first time a relationship between disease progression and worsening visual acuity has been observed in GA, connecting anatomy and function,” Dr. Danzig said at ARVO. “These data suggest that in the ACP-treated group, the reduction in growth of GA resulted in an overall lower rate of vision loss.”

The combined GATHER1 and GATHER2 post-hoc analysis data signaled a 56-percent risk reduction in the rate of persistent vision loss in GA patients receiving ACP compared to sham over the first 12 months of treatment. The trials defined persistent vision loss as a loss of ≥ 15 letters in best-corrected visual acuity from baseline measured at any two consecutive visits up to month 12.



Both GATHER trials showed a statistically significant rate of change in GA area over 12 months, Dr. Danzig reported at the American Society of Retina Specialists 2023 meeting.²

Dr. Danzig is a consultant to and a principal investigator for Iveric Bio.

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2. Danzig C. Intravitreal avacincaptad pegol in geographic atrophy: post-hoc analysis of vision loss from the GATHER clinical program. Paper presented at American Society of Retina Specialists 41st annual scientific meeting; Seattle, WA; July 30, 2023.

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3. What's next for ONS-5010?

The Food and Drug Administration established a Prescription Drug User Fee Act action date of August 29 for Outlook Therapeutics' biologic license application for ONS-5010/Lytenava, its investigative ophthalmic formulation of bevacizumab. However, when that date came around, Outlook received a Complete Response Letter (CRL) informing the company that the FDA cited three reasons for holding up its application:

- Outstanding chemistry, manufacturing and control (CMC) issues.

- Open observations from the preapproval manufacturing inspections.
- A lack of what the agency described as "substantial evidence" supporting action.

At a corporate update in early September, Outlook said it was planning to request a meeting with the FDA to discuss the CRL.

The FDA had already acknowledged results from the NORSE TWO pivotal trial, which demonstrated noninferiority to pharmacy-compounded bevacizumab (Avasatin, Genentech/Roche).

4. Pegcetacoplan injection kits pulled after vasculitis reports

After reports of vision-threatening retinal vasculitis in patients who had an injection of pegcetacoplan (Syfovre), manufacturer Apellis Pharmaceuticals said it would investigate the cases. Within weeks, Apellis issued a statement that said it had identified "internal structural variations" in the 19-gauge-x-1.5-inch filter needle included in some injection kits, but added that "a causal relationship has not been established between the structural variations" in the 19-g needle and the retinal vasculitis cases.

Nonetheless, Apellis informed retina specialists to stop using the 19-g filter needles and use only injection kits with the 18-g filter needle. The company added that it's now distributing injection kits with only the 18-g needle.

"This recommendation is out of an abundance of caution as patient safety is our top priority," Caroline Bauman, MD, chief medical officer



Apellis, said in a press release.

Thirty-six-month results from the GALE extension study failed to find any reports of occlusive or nonocclusive retinitis or vasculitis, said Nathan Steinle, MD, a vitreoretinal specialist with California Retina Associates in San Luis Obispo, who presented results at the American Society of Retina Specialists meeting.¹

GALE included 782 patients from the pivotal OAKS and DERBY trials.

The rate of infectious endophthalmitis across the trials was 1:3,700 injections, Dr. Steinle said, but no

cases were reported in the first six months of GALE. The rate of intraocular inflammation in the trials was 0.26 percent. He estimated the rate of retinal vasculitis, based on estimates of 60,000 total injections, is “on the order of 1:10,000, or 0.1 percent.”

Dr. Steinle noted that the injection technique for pegcetacoplan differs significantly from that for intravitreal anti-VEGF agents. Pegcetacoplan is a 100- μ L dose vs. 50 μ L for anti-VEGF agents, so the injection itself takes longer.

Apellis said that more than 78,000 vials of pegcetacoplan have

been distributed since approval, with eight confirmed cases and two suspected cases of retinal vasculitis.

Apellis said that its own medical and safety committee reviews all postmarketing adverse events reported to the company. Any suspected cases are sent onto an external panel of retina specialists for further investigation.

Steinle is a consultant and principal investigator for Apellis and also disclosed relationships with Genentech/Roche, Novartis and Regeneron Pharmaceuticals.

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5. Implantations of PDS with ranibizumab are poised to resume by year-end

The refillable port delivery system (PDS, Susvimo, Genentech/Roche) with ranibizumab, voluntarily recalled last year after reports of septum dislodgement from the Phase III clinical trial, is set to come back onto the market.

Carlos Quezada Ruiz, consultant and group medical director, clinical science, Genentech/Roche, said at OIS Retina that the company has been reviewing the product and that the preliminary results have been “very promising and we’re predicting we’re going to be restarting implantations by the end of the year.”

Meanwhile, a subgroup analysis of the Portal extension trial of PDS found that 95 percent of recipients didn’t need supplemental anti-VEGF injections between the scheduled six-month refills, David Massop, MD, a retina specialist with Wolfe Eye Clinic in Des Moines, Iowa, reported at ASRS.¹ The average best-corrected visual acuity was 70.6 letters at base-

line and 68.8 letters at 50 months, both of which are the equivalent of 20/40 vision.

Researchers found that a high percentage of age-related macular degeneration patients who had long-term experience with the implant didn’t need supplemental treatments

between refills over three years and had maintained visual acuity through five years.

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IN BRIEF

The GLEAM and GLIMMER Phase III trials evaluating **tarcocimab tedromer**, also known as **KSI-301 (Outlook Therapeutics)**, in diabetic macular edema failed to meet their primary endpoint of noninferiority to aflibercept. As a result, the company announced it would discontinue further development of the drug.

Adverum Biotechnologies has completed patient enrollment in the Phase II LUNA trial evaluating **ixoberogene soroparvovec (ixovec)** for the treatment of neovascular age-related macular degeneration.

Atsena Therapeutics reports dosing the first patient in the Phase I/II LIGHTHOUSE study evaluating subretinal injection of **ATSN-201** for the treatment of X-linked retinoschisis.

DORC has received notification that the Food and Drug Administration has granted its application for orphan drug designation for its dual combination of **Trypan Blue** and **Brilliant Blue G** ophthalmic solution.

EyePoint Pharmaceuticals reported positive interim masked safety data for **EYP-1901** from the ongoing Phase II PAVIA trial evaluating the therapy as a potential nine-month treatment for moderately severe to severe nonproliferative diabetic retinopathy and the DAVIO 2 trial as a potential six-month sustained-delivery maintenance treatment for nAMD. All treatment arms in PAVIA have reached at least three months post-dosing follow-up. 

The dark side of pentosan

The vision consequences of a long-discontinued treatment for interstitial cystitis.

By **Anand Gopal, MD,**
Jordan Deaner, MD,
and **Jason Hsu, MD**



Anand Gopal, MD



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A 61-year-old woman presented to our practice for a second opinion for gradually progressive decreasing vision in her right eye diagnosed previously as macular degeneration. She described increasing difficulty adjusting from outdoor to indoor lighting in both eyes over the preceding years.

Her ocular history was notable for dry eye syndrome. She had photorefractive keratectomy for myopia years prior. Her medical history included hyperlipidemia, migraines and interstitial cystitis (IC), but she wasn't on current treatment. She denied tobacco use. Family history was notable for a maternal grandmother with dry age-related macular degeneration. She was taking rosuvastatin and cyclobenzaprine.

Examination findings

Visual acuities were 20/200 OD and 20/20 OS. Intraocular pressures were normal in both eyes. Anterior segment evaluation demonstrated mild bilateral nuclear sclerotic cataracts. No anterior chamber or anterior vitreous inflammation were evident.

A fundus examination of the right eye (*Figure 1A*) revealed parafoveal pigment clumps with scattered yellowish fleck-like deposits interspersed with areas of retinal pigment epithelial atrophy. The fundus evaluation of the left eye (*Figure 1B*) demonstrated similar though less extensive findings with a prominent area of RPE atrophy in the temporal macula. The peripheral retina was unremarkable in both eyes.

Multimodal imaging

Fundus autofluorescence of both eyes (*Figures 2A and 2B*) revealed densely packed granular areas of intermixed hyperautofluorescence and hypoautofluorescence. Areas of hypoautofluorescence corresponding to areas of RPE atrophy were well-delineated.

Near-infrared reflectance (NIR) imaging

showed foci of hyperreflectivity and hyporeflexivity in both eyes (*Figures 3A and 3B, page 15*). On cross-sectional optical coherence tomography through the fovea of the right eye (*Figure 3A, page 15*), we observed foci of nodular hyperreflectivity at the level of the RPE with disruption of overlying outer retinal laminations. The foveal contour was mildly irregular.

A few areas of hyperreflectivity were found in the outer nuclear layer. Inner retinal laminations were relatively well preserved. Cross-sectional OCT through the fovea of the left eye (*Figure 3B, page 15*) revealed similar hyperreflective deposits at the level of the RPE. There was loss of outer retinal layers in areas of RPE atrophy.

Additional history and diagnosis

Considering these imaging findings, further interrogation of this patient's medication record disclosed a six-year history of pentosan polysulfate sodium (PPS; Elmiron, Janssen Pharmaceuticals) use at a dose of 100 mg t.i.d. She had stopped pentosan three years before onset of her visual symptoms for reasons unrelated to retinal toxicity.

Given her clinical history and constellation of multimodal imaging findings, she was diagnosed with pentosan polysulfate maculopathy (PPSM). She was counseled on Amsler grid monitoring. At follow-up, six months later, the RPE atrophy in both eyes showed mild progression on OCT. Her visual acuity had decreased to 20/400 in the right eye with otherwise stable visual acuity in the left eye.

Pentosan polysulfate maculopathy

PPSM is a recently described clinical entity, first reported in 2018 in a series published by Nieraj Jain, MD, and colleagues describing a novel pigmentary maculopathy observed in six patients with chronic exposure to PPS.¹ Despite recent recognition of its

BIO

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DISCLOSURES: Dr. Gopal has no relevant disclosures.

Dr. Deaner is a consultant to Alimera Sciences, EyePoint Pharmaceuticals and Regeneron Pharmaceuticals.

Dr. Hsu has no relevant relationships to disclose.

potentially toxic effects on the retina, PPS was described structurally first in the 1950s and has been used off-label for various clinical and veterinary indications since the 1980s.²

The U.S. Food and Drug Administration approved pentosan in 1996 under the brand name Elmiron for the relief of bladder pain and discomfort associated with IC.³ IC is a chronic lower urinary tract pain syndrome of unknown etiology characterized by bladder pain, urinary frequency and urgency.³ Urine cultures and other infectious laboratory investigations are negative in these patients. Adult women comprise the vast majority of affected patients. Because of its chronic nature, IC can be functionally debilitating.

Management is symptomatic and often multiarmed, and includes a combination of lifestyle modification, anticholinergic drugs, neuromodulating agents and intravesicular therapy.³ As the only FDA-approved oral agent indicated for IC, PPS is a convenient first- and second-line therapeutic option for patients with IC.

Molecularly, PPS is a semisynthetic heparin-like sulfated polysaccharide. While its exact mechanism of action in IC is uncertain, it's been postulated to coat the glycosaminoglycan layer lining the uroepithelium, reducing bladder wall permeability and offering a mechanical barrier to the irritating effects of urinary toxins.³

The role of PPS in the development of retinal toxicity isn't well elucidated, but authors have hypothesized that it interferes with RPE-photoreceptor homeostasis with resultant aberrant processing of photoreceptor outer segments.²

Clinical and imaging markers of PPSM

Symptomatically, patients with PPSM may present with nyctalopia, prolonged dark adaptation, difficulty reading and metamorphopsia.⁴ Central visual acuity is typically preserved in early stages, but declines with progressive disease.⁵

Fundoscopically, patients demonstrate

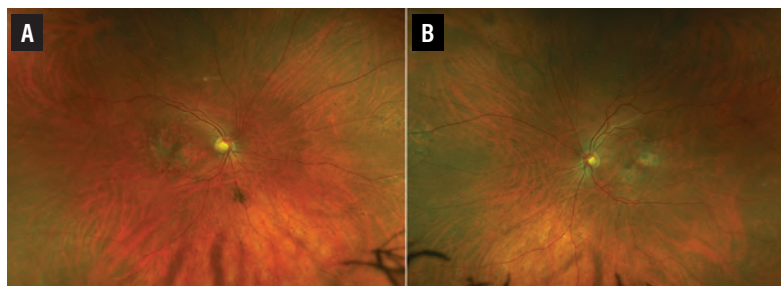


Figure 1. Wide-field pseudocolor fundus imaging of the right (A) and left (B) eyes demonstrate parafoveal pigment clumping interspersed with yellow subretinal deposits and areas of retinal pigment epithelial atrophy.

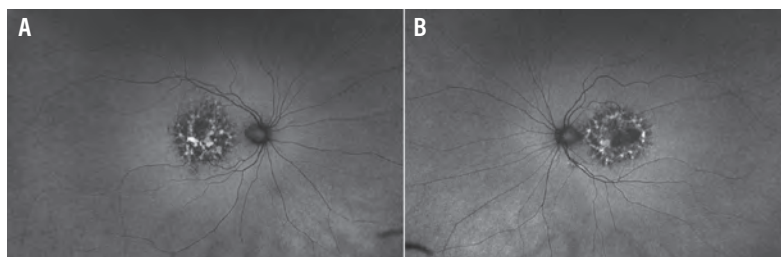


Figure 2. Wide-field fundus autofluorescence imaging of the right (A) and left (B) eyes reveals densely packed granular areas of intermixed hyperautofluorescence and hypoautofluorescence.

hyperpigmented spots in the macula with yellowish subretinal deposits. Patchy areas of paracentral RPE atrophy may accompany more advanced disease with associated central acuity decline if the fovea is involved. Macular findings may be subtle and asymmetric early on. Detection in such cases relies on the use of retinal imaging.

On FAF, eyes with PPSM demonstrate a strikingly dense reticular array of hyperautofluorescent and hypoautofluorescent signal in the parafoveal region. A peripapillary hypoautofluorescent halo may also be noted in cases where the disease extends near the optic disc, which may help distinguish PPSM from other retinal dystrophies.

OCT reveals nodular hyperreflective foci at the level of the RPE with associated shadowing of the underlying choroid, which appear to correspond to the pigmented spots on fundus evaluation. Areas of retinal thinning and RPE atrophy can be readily visualized. No accepted OCT correlate exists for the yellow deposits seen on clinical exam.²

(Continued on page 15)



izervayTM

(avacincaptad pegol
intravitreal solution) 2 mg

INDICATION

IZERVAYTM (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.

NOW APPROVED

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



To learn more and stay up to date,
visit IZERVAYecp.com

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

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

IZERVAY™ (avacincaptad pegol intravitreal solution)

Rx only

Brief Summary: This information is not comprehensive. Visit IZERVAYecp.com to obtain the FDA-approved product labeling or call 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:

IVERIC bio, Inc., An Astellas Company. Parsippany, NJ 07054

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Differential diagnosis

The differential diagnosis of PPSM includes AMD, pattern dystrophies, chronic central serous retinopathy, pachycho-roid pigment epitheliopathy and maternally inherited diabetes and deafness (MIDD) syndrome.² Despite a spectrum of fundoscopic appearance, PPSM can be readily differentiated from other etiologies of pigmentary maculopathy in the appropriate clinical context with the aid of characteristic findings on multimodal imaging.

Risk assessment and monitoring

Risk of retinal toxicity with PPS exposure occurs in a dose-dependent fashion, typically over several years with greater cumulative dose. An electronic health records study within a comprehensive health system identified a PPSM prevalence rate of 12.7 percent in patients with a cumulative PPS dose in the 500-to-999-g range that increased to 41.7 percent in patients exposed to a >1,500-g cumulative dose.⁶

PPSM may progress even after drug discontinuation, as we observed in our patient. Patients are at risk for additional vision-threatening complications, including geographic atrophy, cystoid macular edema and choroidal neovascularization. They should be monitored for development of such.²


No treatment exists for PPSM, highlighting the importance of routine screening and prompt recognition of retinal toxicity in patients prescribed PPS.

In June 2020, the FDA updated the label for PPS in the wake of mounting postmarket evidence of an associated drug-induced pigmentary maculopathy, recommending baseline fundus exam, OCT and FAF within six months of starting therapy and periodically thereafter.⁷

Soon after, the American Urogynecologic Society released a practice advisory recommending prescribers counsel patients on the

possible visual effects of PPS prior to initiation, limit dose and duration of exposure when possible, and help coordinate baseline and routine screening retinal evaluation.⁸ To date, many individuals likely remain undiagnosed or misdiagnosed.

Bottom line

PPSM is a recently described pigmentary maculopathy with potentially visually debilitating effects. Long-term exposure to PPS increases the risk of retinal toxicity, highlighting the importance of patient education, dose monitoring and regular retinal evaluation. Characteristic findings on OCT, NIR and FAF imaging are key in early diagnosis. Further research is needed to better understand the pathophysiology and clinical phenotype of this disease to better aid surveillance and early detection. 

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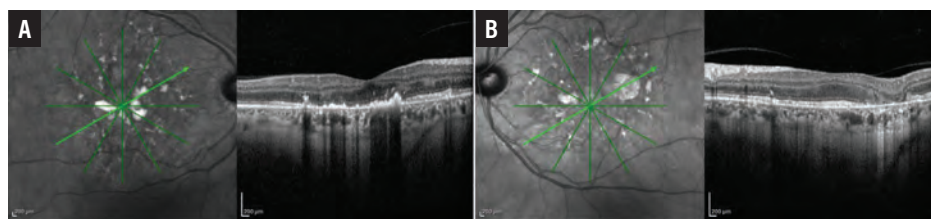


Figure 3. A) Optical coherence tomography of the right eye shows multiple foci of nodular hyperreflectivity at the level of the retinal pigment epithelium with disruption of overlying outer retinal laminations. B) OCT of the left eye shows similar findings with focal loss of the outer retina corresponding to areas of retinal pigment epithelial atrophy.



Managing inflammatory CNVM in uveitis

Solving the diagnostic and treatment challenges of choroidal neovascular membrane in uveitis.

By **Arthi Venkat, MD, and Abdullah Abou-Samra, MD**



Arthi Venkat, MD



Abdullah Abou-Samra, MD

Choroidal neovascular membrane is a common cause of vision loss resulting from disruption in the integrity of Bruch's membrane and the retinal pigment epithelium. A wide array of pathological conditions, such as myopia and macular degeneration, can lead to involvement of such structures and downstream angiogenesis.

Inflammatory etiologies can also cause secondary choroidal neovascular membrane. Inflammatory CNVM can be seen in noninfectious processes such as punctate inner choroidopathy (*Figure*), Vogt-Koyanagi-Harada disease, multifocal choroiditis, sarcoidosis and serpiginous choroiditis. It can also be found in infectious posterior uveitis such as toxoplasmosis,¹ tuberculosis² and presumed ocular histoplasmosis.³

Why it occurs

A complex interplay of inflammatory mediators causes CNVM, including growth factors, interleukins and cytokines with resultant neovascularization and remodeling of the extracellular matrix.⁴ Due to a shift in balance between inhibitory and stimulatory mediators in the retina, the pathway of neovascularization and inflammation can shift to fibrosis and scarring, known as the involutional phase.^{5,6} For this reason, early diagnosis and prompt management are essential to prevent irreversible vision loss.

Diagnostic imaging options

Treatment of CNVM in the setting of infectious uveitides requires treatment of the underlying infectious process in concert with conventional management of CNVM. The remainder of this article will review the management of inflammatory CNVM in the setting of noninfectious uveitis.

In addition to the use of traditional treatment strategies for CNVM, diagnosis and appropriate management of the underlying

uveitic process is important. Appropriate multimodal imaging, including fluorescein angiography, indocyanine green angiography and fundus autofluorescence, can help determine whether the chorioretinal inflammation is active or inactive. Determining the underlying disease activity is crucial because it impacts the best way to manage secondary CNVM.

Inflammatory CNVM can be challenging to diagnose and differentiate from other entities. Uveitic cystoid macular edema can present with intraretinal fluid, subretinal fluid and outer retinal changes on optical coherence tomography that can make it difficult to distinguish from inflammatory CNVM, especially in patients with chronic inflammatory disease. Inflammatory CNVM often presents with subretinal hyperreflective material that can distinguish it from inflammatory CME.

FA can help distinguish between inflammatory pigment epithelial detachment and CNVM, which can often look similar. OCT angiography is another modality that can be helpful in making this distinction. However, in spite of these imaging modalities, differentiating between these two entities can still be difficult.

Treatment options

Inflammatory PED is best treated with steroid therapy or immunomodulatory therapy, while CNVM is best treated with the following treatments:

• **Anti-VEGF therapy.** Multiple case series have demonstrated the utility of anti-VEGF agents for treatment of inflammatory CNVM.⁷ The MINERVA study showed benefit of ranibizumab for secondary CNVM, leading to the approval of ranibizumab by the European Union for the treatment of inflammatory CNVM.

Although no consensus exists on an established treatment protocol for anti-

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DISCLOSURES: Dr. Venkat is a consultant to Apellis Pharmaceuticals and EyePoint Pharmaceuticals.

Dr. Abou-Samra has no relevant relationships to disclose.


Dr. Thomas is a consultant to Allergan/AbbVie, Alimera Sciences, Avesis, EyePoint Pharmaceuticals, Genentech/Roche and Novartis.

VEGF duration and usage, an international study that looked at 24-month outcomes in treating inflammatory CNVMs either with three monthly anti-VEGF injections followed by *pro re nata* dosing or PRN from the start of therapy showed no difference in outcomes or recurrence rates between the two groups.⁸

• **Oral steroids.** When the underlying uveitis appears active and concurrent CNVM is present, consider oral steroids alongside intravitreal anti-VEGF therapy. Local steroid therapy may also be helpful. Several case series have shown benefit with the use of injectable corticosteroids, including sub-Tenon's⁹ and intravitreal injections.¹⁰

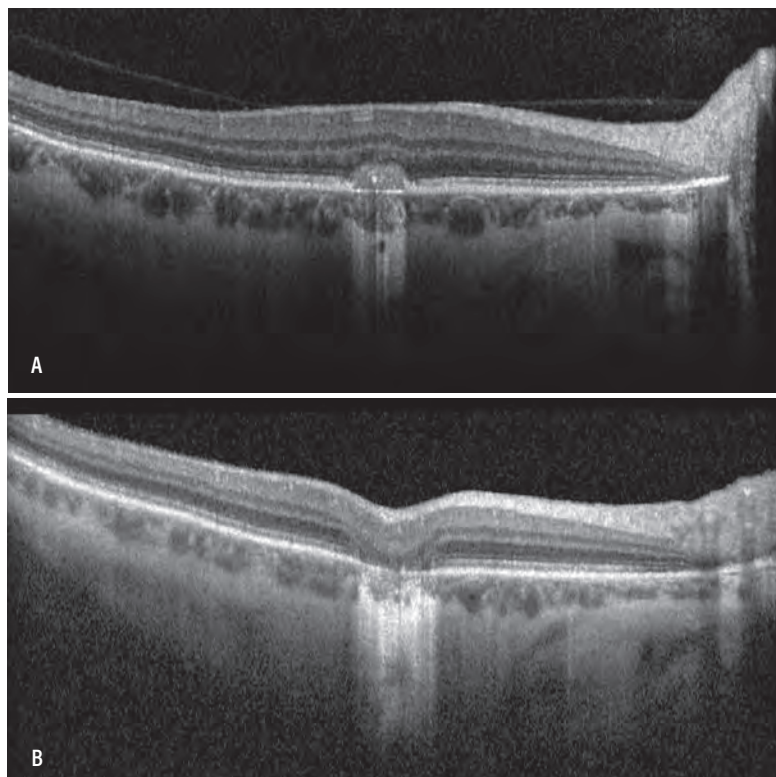
Active uveitis should be controlled and well-managed because incomplete control of inflammation can lead to ongoing CNVM formation despite regular anti-VEGF therapy. In some cases, systemic immunotherapy is needed in concert with ongoing anti-VEGF injections for management of secondary CNVM. Intravitreal immunomodulatory therapy, such as intravitreal methotrexate or rituximab, is another therapeutic option,¹¹ although its use hasn't been validated by larger studies.

Bottom line

Secondary CNVM in the setting of uveitis should be managed by ensuring that the underlying primary inflammatory process is controlled. In the setting of infectious uveitis, this entails appropriate anti-infective therapy in concert with intravitreal anti-VEGF. In the setting of noninfectious chorioretinal inflammation, systemic or local steroid therapy in concert with anti-VEGF can be considered. In some cases, immunomodulatory therapy is needed for durable remission along with ongoing anti-VEGF therapy. 

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A) Optical coherence tomography of the macula of the right eye in a patient with a history of punctate inner choroidopathy showing classic choroidal neovascular membrane (CNVM). B) OCT of the macula of the right eye demonstrating resolution of CNVM and subsequent outer retinal atrophy after intravitreal anti-VEGF therapy.

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How to do intraretinal artery tPA injection

A stepwise approach to intraretinal artery cannulation for injection of tissue plasminogen activator into the central retinal artery.

By Shin Tanaka,
MD, and Kazuaki
Kadonosono, MD



Shin Tanaka, MD

The intraretinal artery cannulation method for injecting tissue plasminogen activator into the central retinal artery may be indicated in cases with early presentation of central retinal artery occlusion.

Patient-level meta-analyses have suggested that early systemic thrombolysis with tissue plasminogen activator (tPA) may be beneficial for management of CRAO embolism or thrombosis when administered within 4.5 hours.¹

Although the European Assessment Group for Lysis in the Eye (EAGLE) trial, which evaluated early intra-arterial delivery of fibrinolysis, didn't demonstrate improved visual outcomes,² others have suggested that conservative treatments are futile¹ and that intra-arterial tPA may have some promise.³ A case series of 13 patients undergoing intraretinal artery cannulation reported no serious surgical complications, with the exception of one case of postoperative vitreous

View the Video

Watch as Dr. Tanaka and Dr. Kadonosono demonstrate their approach to using intraretinal artery cannulation to inject tissue plasminogen activator into the central retinal artery. Scan the QR code or go to <https://bit.ly/VideoPearl-36>



hemorrhage.⁴

Here, we share our approach to intraretinal artery cannulation for injection of tPA in cases of CRAO.

Patient selection and preoperative considerations

Ideal candidates for our approach to intraretinal artery cannulation are patients who have nonarteritic CRAO, visual acuity better than light perception but not exceed-

BIOS

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Dr. Felfeli is an ophthalmology resident at the University of Toronto.

DISCLOSURES: Dr. Tanaka and Dr. Kadonosono have no relevant disclosures.

Dr. Felfeli has no relevant relationships to disclose.

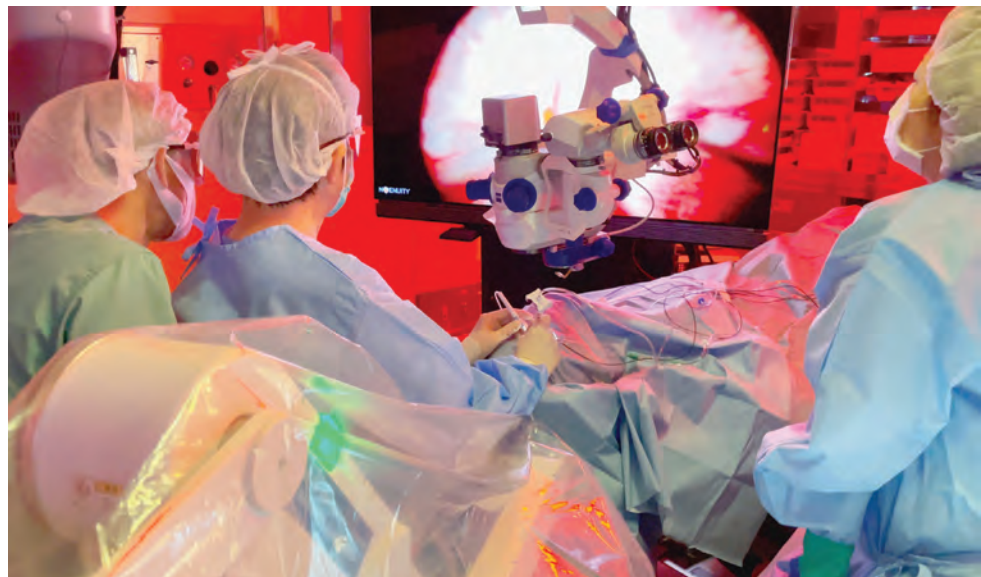


Figure 1. Operating room layout of the three-dimensional heads-up microscope during pars plana vitrectomy for performing the intraretinal artery cannulation for injection of tissue plasminogen activator into the central retinal artery.

ing 20/40 and an onset of symptoms within 48 hours before the initial consultation, preferably sooner.

Those not suitable for the procedure are patients with a history of stroke or head injury within the last three months, those with uncontrolled hypertension and systolic blood pressure >185 mmHg, have a bleeding disorder or have poor baseline visual acuity due to conditions including macular degeneration and proliferative diabetic retinopathy.

One of the most important factors in determining outcomes is likely the delay between symptom onset to reestablishment of perfusion. Because of this, patients should go to the operating room as soon as possible.

Given the risks associated with use of thrombolytic agents, all patients should be informed about the possibility of intracerebral hemorrhage in advance.⁵ Preoperative systolic blood pressure should be maintained in the 120-to-150-mmHg range or lower, so administering antihypertensive drugs may be indicated to minimize risk of intraoperative bleeding.

Surgical approach

We use the three-dimensional heads-up microscope during pars plana vitrectomy (*Figure 1*). This technique is done using a 48-gauge microneedle (Nono cannula, MedOne Corp.) following a core vitrectomy (*Figure 2A*).² During this procedure, the central retinal artery is punctured at the bifurcation where it enters the optic nerve (*Figure 2B*).

After puncture, 0.4 mL of tPA in a solution containing 50 µg/0.1 mL (200 µg total dose) is administered, and the perfusion is maintained for approximately three minutes. At our institution, we infuse the tPA at a pressure of up to 80 psi using the Constellation Viscous Fluid Control Pak syringe (Alcon).

Once the injection is completed, a color change of the vessels to white confirms the tPA has been successfully injected. Pay attention to achieve hemostasis (*Figure 2C*), which may be done using a soft-tipped cannula to

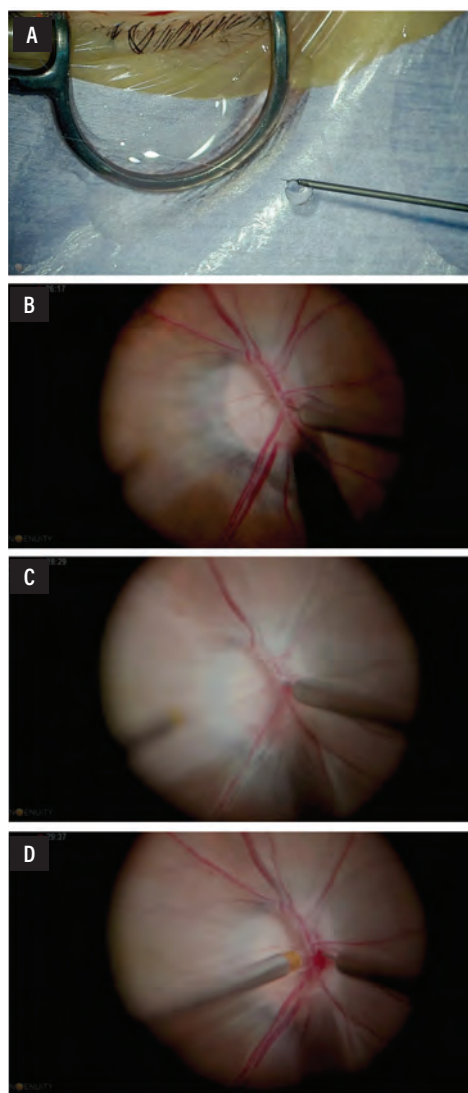


Figure 2. Intraoperative views of our approach to intraretinal artery tissue plasminogen activator (tPA) injection. A) Using a 48-gauge microneedle, the tPA is visualized coming out of the cannula. B) The central retinal artery is punctured at the bifurcation where it enters the optic nerve. C) The vessels change color to white, confirming successful tPA injection. D) Once the injection is completed, any bleeding is aspirated using a soft-tipped cannula bimanually.

aspirate any bleeding at the puncture site (*Figure 2D*).

If you don't notice any improvement in retinal perfusion, you may inject tPA again. However, an increasing number of punctures will result in greater damage to the vessel wall, so achieving hemostasis may become more difficult.

A fluid-air exchange concludes the procedure. *Figure 3* (*page 20*) depicts the outcomes of a case.

Postoperative considerations

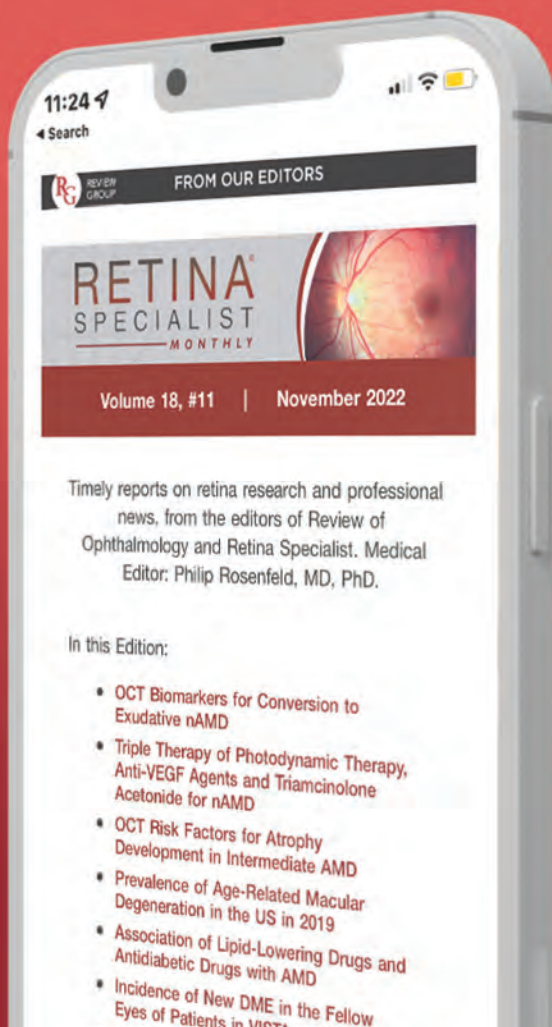
Instruct patients to remain prone over-

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night to prevent postoperative bleeding and to not to engage in strenuous activities. Maintaining blood pressure within a normal range postoperatively is an important consideration. Patients may also be prescribed aspirin (50 mg) daily for two weeks as an anti-platelet drug for reducing the risk of reocclusion.

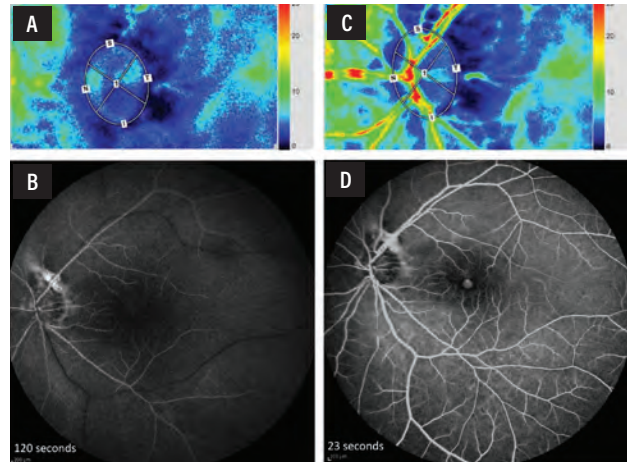


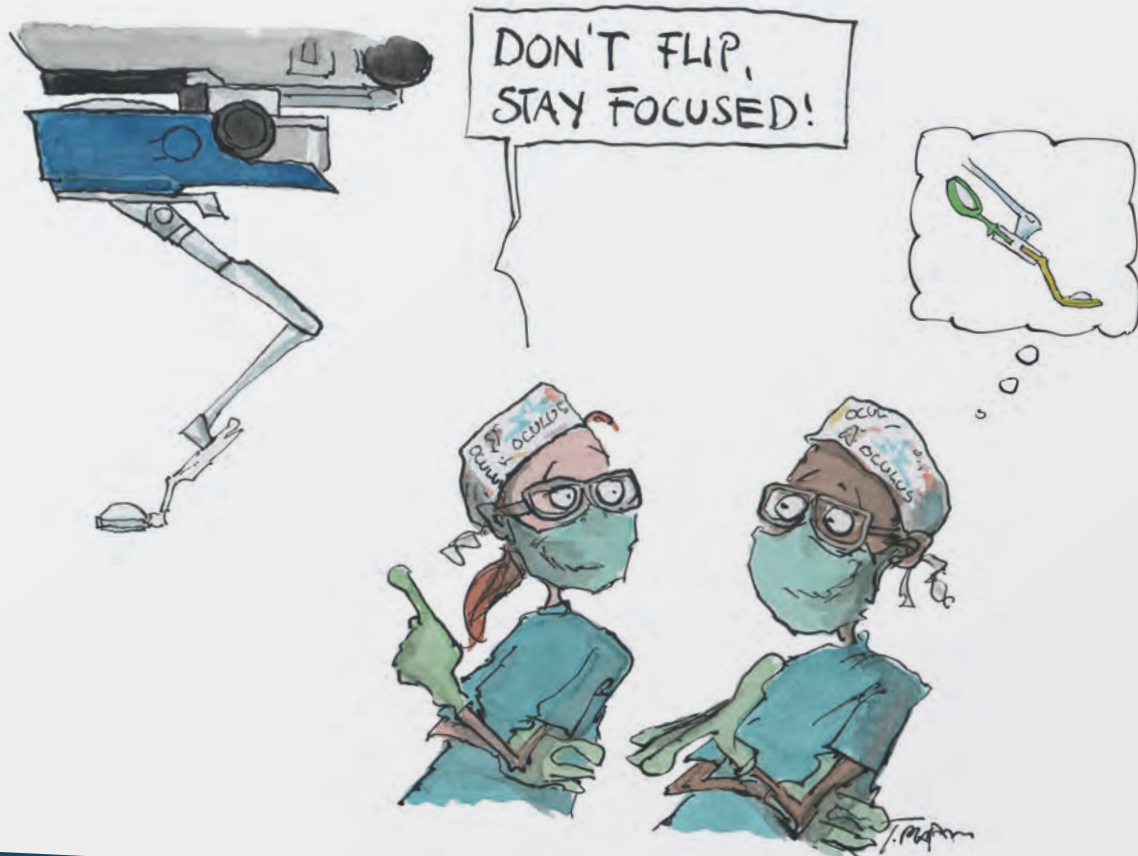
Figure 3. Outcomes of a case of an 84-year-old male with central retinal artery occlusion presenting 48 hours following onset of symptoms. Laser speckle flowgraphy and fluorescein angiography from presentation (A, B) to one week following retinal arterial cannulation with tissue plasminogen activator (tPA, C, D) showed improved retinal perfusion. Mean blur rate of vessel tissue area improved from 2.9 to 14.9. Visual acuity improved from light perception to hand motion at one month. The limited visual improvement in this case likely was due to the retinal ischemic damage from the time elapsed since disease onset to presentation.

Bottom line

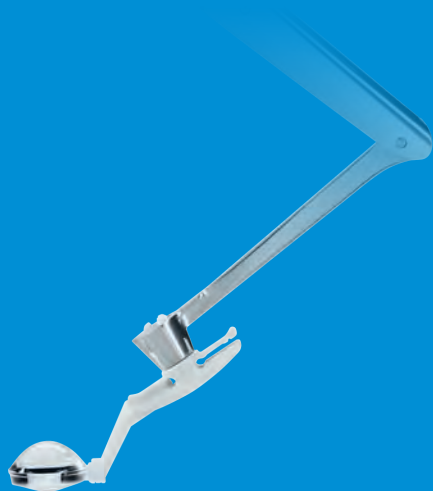
Intraretinal-arterial cannulation may serve as an option for restoring microcirculation in eyes affected by CRAO. Important preoperative and postoperative considerations apply for this procedure. Selecting the appropriate patients is critical. Establishing a system that enables rapid surgery in the treatment of CRAO may also enhance patient outcomes. ^{RS}

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Three looks at how AI may change retinal practice

Artificial intelligence models have shown the potential to decrease disparities in diabetic eye care, personalize management for nAMD treatment and predict outcomes for CRVO.

Take-home points

- » Artificial intelligence-based screening is a promising approach to promote timely detection of referable diabetic retinopathy and decrease disparities in vision loss from diabetes.
- » By tying multiple diagnostic elements together—fluid volume, treatment outcomes, visual acuity and patient symptoms—AI has the potential to use multivariate analysis to determine ideal treatment selection and intervals in neovascular age-related macular degeneration.
- » In patients with central retinal vein occlusion who received six monthly anti-VEGF treatments, a machine-learning model was able to predict 52-week outcomes to help determine *pro re nata* treatment from weeks 24 to 52.

How AI can help address disparities in diabetic eye exams

By Mozhdeh Bahrainian, MD, Tin Yan Alvin Liu, MD, Risa M. Wolf, MD, and Roomasa Channa, MD



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Dr. Channa is an assistant professor of ophthalmology at the University of Wisconsin School of Medicine.

DISCLOSURES: The authors have no relevant relationships to disclose.

Diabetes is a global epidemic and diabetic retinopathy is a major cause of vision loss, particularly among working-aged adults. In 2021, about 9.6 million people had DR in the US and 1.8 million people had vision threatening diabetic reti-

nopathy.¹ Racial/ethnic minorities and socioeconomically disadvantaged individuals with diabetes are at especially high risk of vision loss, and DR is more prevalent among Blacks and Mexican Americans compared to Whites: 39, 34 and 26 percent, respectively.^{2,3}

Screening and early treatment of DR can prevent vision loss in 90 percent of cases.⁴ However, in the United States, at best about 60 percent of people with diabetes receive an annual eye exam.⁵ These rates are consistently lower among racial/ethnic minorities and socioeconomically disadvantaged communities.⁶⁻⁸ Even after adjusting for socioeconomic status and insurance, Hispanics with diabetes are less likely to visit an eye doctor than Whites.⁹

Barriers to provider-based screening

In the United States, referring patients with diabetes to eye-care providers for a diabetic eye exam has been the usual method of screening for DR.

However, patients report many barriers to getting the recommended screening, including the need to make an additional appointment to see an eye doctor, miscommunication about

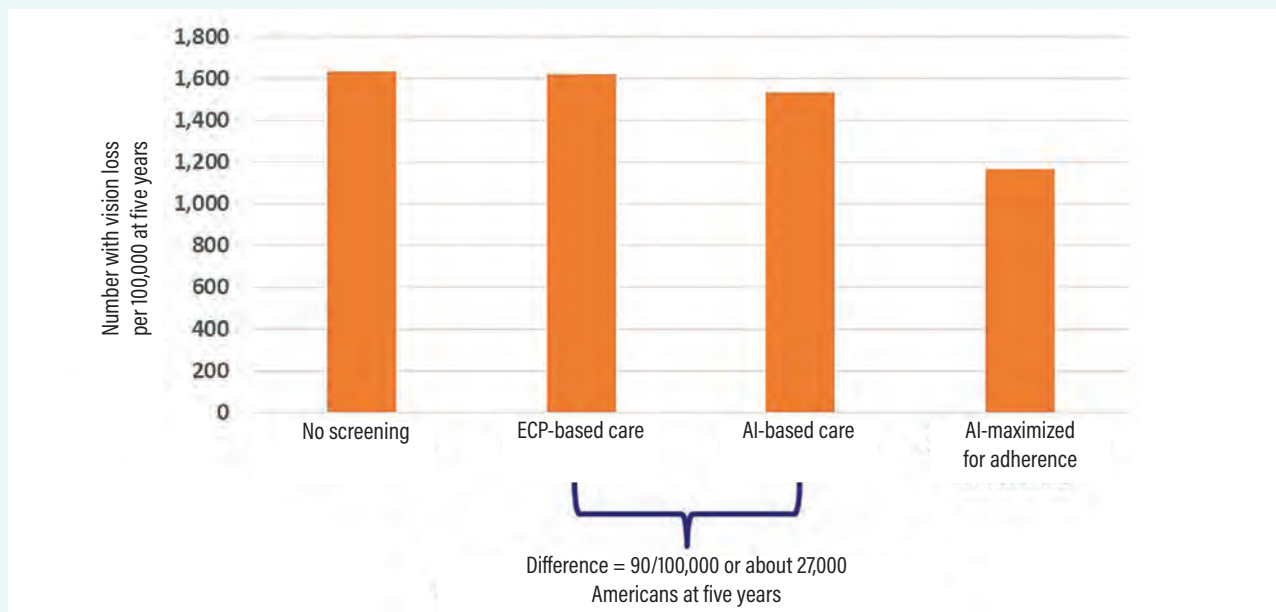


Figure 1. The estimated numbers of patients with diabetes progressing to severe vision loss per 100,000 at five years in various scenarios, as estimated using Markov modeling comparing no-screening, eye-care provider (ECP)-based screening, artificial intelligence-based screening and AI-based screening maximized for adherence. AI-based screening has the potential to prevent vision loss in about 27,000 more Americans with diabetes compared to ECP-based screening. Base case estimates are based on parameters as close to the real world as possible. Maximized for adherence estimates are based on parameters maximized for adherence with screening, follow-up and recommended treatments.

the need for a diabetic eye exam and cost, all of which are accentuated for socioeconomically disadvantaged communities.^{6,10} This method of screening for diabetic eye disease isn't scalable and perpetuates disparities in the much-needed access to diabetic eye care.

How AI may overcome these barriers

Artificial intelligence-based screening is a promising method for detection of referable diabetic eye disease at the primary care provider's office. This is potentially an effective solution as 80 percent of patients with diabetes see their primary care providers, making these visits an excellent opportunity to conduct eye screening.¹¹

This is even more important for our nation's medically underserved patients who often present to Federally Qualified Health Centers (FQHCs)

for their primary care. FQHCs provide care to more than 30 million Americans, including one in three people living in poverty, one in five rural residents and more than 60 percent of racial/ethnic minorities.^{12,13} At this time, 70 percent of FQHCs don't have eye-care providers on site.¹⁴

AI-based diabetic eye screening programs have been associated with improved screening rates as well as follow-up with recommended eye care.¹⁵⁻¹⁷ Importantly, implementation of AI-based eye screening has been shown to improve diabetic eye screening rates across racial/ethnic and socioeconomically disadvantaged groups and has shown the potential to close the current gaps in diabetic eye care.¹⁸⁻²¹

Existing autonomous AI platforms

Three autonomous AI platforms have been approved by the U.S. Food

and Drug Administration for diabetic eye testing. They are:

- **IDx-DR system**, now known as LumineticsCore (Digital Diagnostics), was cleared by the FDA in 2018. The system has demonstrated an 87.4-percent sensitivity, 89.5-percent specificity and 96-percent imageability for detecting more-than-mild DR (mtmDR),²² defined as Early Treatment Diabetic Retinopathy Study level of 35 or higher.
- **EyeArt system** (Eyenuk) was cleared by the FDA in 2020 to detect mtmDR and vision-threatening diabetic retinopathy (vtDR). It has shown 96-percent sensitivity, 88-percent specificity and 97-percent imageability for detecting eyes with mtmDR, and 97-percent sensitivity and 90-percent specificity for detecting vtDR,²³ defined as ETDRS level of 53 or

higher, but not equal to 90 and/or presence of clinically significant macular edema (CSME).

- **AEYE Health's AI-based system** for detection of mtmDR, which demonstrated a 93-percent sensitivity and 91.4-percent specificity for detecting mtmDR.²⁴

Challenges in adopting AI-based eye screening

While uptake of AI-based eye screening in specialized pediatric endocrine clinics improved screening rates to over 90 percent, screening uptake in adult primary care clinics remains about 60 percent.¹⁹

Multiple factors are likely to affect AI-based screening uptake in the clinic and a team-based approach is required to address these barriers.²⁵ These factors include lack of clarity regarding reimbursement and multiple competing demands in adult primary-care clinics with limited resources.

The CPT code 92229 was approved in 2021 to reimburse for “imaging of retina for detection or monitoring of disease; point-of-care autonomous analysis and report.”²⁶ As awareness regarding this code increases, more clinics may be able to realize the return on investing in AI-based screening for diabetic eye disease.

Implementation strategies using established frameworks, incorporating the needs of multiple stakeholders, are needed to address implementation barriers and optimize the initial and sustained uptake of AI-based screening.

Potential impact of AI-based screening

Our team developed a simulation to estimate vision loss prevented using eye-care provider vs. AI-based screening. The model showed that if AI were

to replace the current eye-care provider-based system of screening, severe vision loss could be prevented in 90/100,000 individuals with diabetes at five years (*Figure 1, page 22*). This translates to at least 27,000 Americans over five years, assuming 34 million Americans have diabetes.²⁷

This effect is likely to increase because the number of people with diabetes is projected to grow. Furthermore, this effect can be multiplied manifold if AI-based eye screening is adapted to local needs and downstream aspects of care, such as follow-up with recommended eye care and strategies to promote adherence with metabolic control and ophthalmic follow-up, are optimized.

Bottom line

Artificial intelligence-based screening is a promising approach to promote timely detection of referable diabetic retinopathy and decrease disparities in vision loss from diabetes. **RS**

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How AI with home-based OCT may change the nAMD treatment paradigm

By Miguel Busquets, MD



Dr. Busquets is a partner with Retina Associates of Kentucky and chairman of Technology and Innovation Committee/EyeCare Partners.

DISCLOSURE: Dr. Busquets is a consultant, principal investigator and paid speaker for Notal Vision.

Home-based optical coherence tomography partnered with artificial intelligence represents a paradigm shift for high-frequency monitoring of neovascular age-related macular degeneration in that it gives retina specialists a tool that they can use to personalize management to each patient's tolerance for fluid.

As longer-acting treatments evolve, retina specialists are trying to find ways to optimize treatment intervals. Tracking fluid on a daily basis with home-based OCT combined with AI to analyze findings has the potential to be a powerful tool to do so.

We recently reported on a study that investigated AI-derived fluid volume trajectories in nAMD patients using daily monitoring with the Notal Vision Home OCT (NVHO).¹ The purpose was to evaluate fluid dynamics during the reactivation-to-time-of-treatment and treatment-to-response intervals and to analyze the impact treatment delay had on treatment response (*Figure 2*). Our patient data demonstrated strong heterogeneity both in fluid recurrence and resolution patterns.

Tracking fluid daily

The best way to optimize treatment intervals is to track fluid daily. Adding AI modules and platforms to analyze and quantify fluidics amplifies our assessment capabilities.

As retina specialists, we need to take that information and correlate it with vision and patient symptoms to determine what the ideal interval is. We illustrated this point with two cases: one patient who required very tight management of fluid and another who could tolerate large amounts of sub-retinal fluid and still maintain 20/20 vision.

We generally have no way of knowing whether patients, like the one in our second example, would maintain good vision. However, with NVHO we could determine that the patient tolerated a certain level of fluid, allowing for greater flexibility with dosing intervals. That patient could have gone five to six weeks without needing another injection. But using today's standard of care without the information NVHO can generate, the patient

would have been brought in monthly.

This type of approach is significant in the era of extended treatment regimens. It's a matter of patient convenience and access because it means not bringing patients into the clinic who don't need injections and freeing up clinic time for patients who do need them. Payers also are demanding this level of efficiency, creating a constant tug-of-war for retina specialists.

Quantifying treatment responses

In our study, we manually annotated phases of fluid volume trajectory, which resulted in 35 reactivations and 48 responses from 54 patients and 57 eyes. Expert graders manually segmented reactivation and resolution periods. The study quantified treatment response for two groups: patients treated within seven days of recurrence; and patients treated after seven days from the time of recurrence.

The mean (standard deviation) reactivation phase duration was 12 (10) days with a mean fluid increase rate of 12 (18) nL/day. The mean response phase duration was 11 (8) days with a mean fluid reduction rate of 8 (9) nL/day.

When we divided the events according to treatment timing, measured as <1 week or >1 week from the begin-

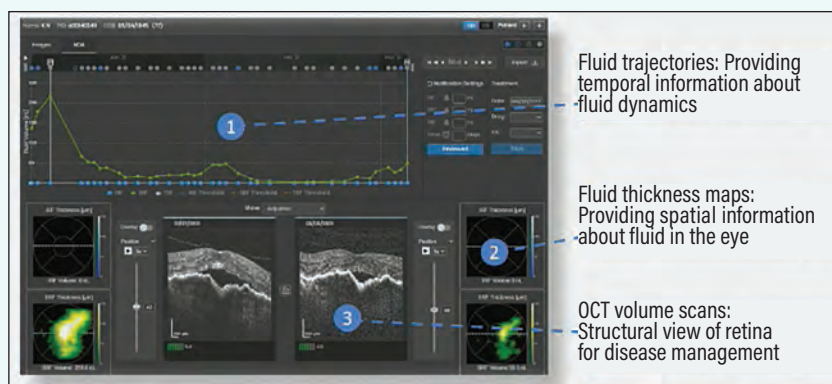


Figure 2. A Home OCT screen view of three measures that provide insights into fluid trends. (Courtesy Notal Vision)

ning of the reactivation phase, the groups had a significant difference in mean volume at treatment [36 vs. 139 nL ($p<0.003$)], as well as in mean time to fluid resolution [4.7 vs. 13.6 days ($p<0.02$)]. The mean area under the curve was 76 and 769 nL-days ($p<0.00001$) for treatment timing, respectively.

Machine learning is being used to identify the presence or absence of fluid. Based on our findings, AI outperforms human readers in this regard. AI can further improve our evaluation process by not only assessing the pres-

ence or absence of fluid, but also fluid volume over time, which provides a new parameter for evaluating patients with exudative disease. Tracking fluid volume, and not only its presence or absence, along with the central subfield thickness adds a new dimension to our diagnostic repertoire.

The next steps in the use of this technology may include the incorporation of multivariate analyses and predictive modeling. Can AI extrapolate that information into an ideal treatment algorithm for a patient that involves interval selection and drug selection?

Based on research, it certainly has the potential.

Bottom line

By tying multiple diagnostic elements together—fluid volume, treatment outcomes, visual acuity and patient symptoms—AI has the potential to use multivariate analysis to determine ideal treatment selection and interval. This may be the next level of AI utilization. ^{RS}

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How machine-learning models may improve management of CRVO

By Yasha Modi, MD



Dr. Modi is a retina and uveitis specialist and an associate professor of ophthalmology at NYU Langone Health.

DISCLOSURES: Dr. Modi is a consultant for Alimera Sciences, Allergan/AbbVie, Apellis Pharmaceuticals, Astellas Pharma, DORC, EyePoint Pharmaceuticals, Genentech/Roche, Thea Pharma, Regeneron Pharmaceuticals and Zeiss.

Machine learning in retina is in its infancy. Food and Drug Administration approval exists only for the screening of diabetic retinopathy, and there are no prognostic-focused algorithms. For this technology to become meaningful to physicians, machine-learning (ML) functionality will need to scale up to provide diagnostic and prognostic insights across a host of retinal diseases. This effort will involve validating diagnostic accuracy across different disease states as well as for prognostic guidance within each disease state.

We reported on a recent collaborative project aimed to provide a proof

of concept on prognostic capabilities of ML using a robust Phase III randomized clinical trial (RCT) data set, COPERNICUS AND GALILEO.¹ The trials evaluated 2-mg aflibercept for the treatment of macular edema due to central retinal vein occlusion. Patients received monthly treatment for the first six months and then were transitioned to a *pro re nata* approach.

The transition from monthly to PRN treatment allowed us to create and test an algorithm to predict one-year outcomes. Could the algorithm predict visual acuity or change in VA? Could it predict central subfield thickness or dosing frequency during the PRN arm and could it provide insights

into what weights are being assessed in these predictions?

Project objectives

It's certainly unusual to use a Phase III dataset as the model to train an artificial-intelligence algorithm. This is, in part, due to the small dataset size.

However, unlike large real-world datasets that tend to have large amounts of missing data or incorrect information (e.g. data carried forward in the electronic medical record), RCT data have a very high accuracy. This can potentially amplify the signal-to-noise ratio, which can be diluted in incomplete or inaccurate datasets.

COPERNICUS and GALILEO (n=351) randomized patients 3:2 to treatment vs. sham. The studies obtained extensive baseline demographics, medical characteristics including laboratory values and multiple post-baseline outcomes for each patient.

Using a random forest model, we opted to evaluate the following parameters: absolute best-corrected visual acuity and BCVA change at week 52; change in CST at week 52; and intravitreal aflibercept injection dosing frequency from week 24 through week 52.

(Continued on page 31)

WET AMD EYE

ANTI-VEGF

Therapy yields better long-term VA results when wet AMD detected with good VA¹

FELLOW EYE

20/79 VA

Mean VA of fellow eyes at wet AMD diagnosis according to real-world data¹

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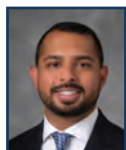
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Lessons from Protocol AA for UWF imaging in DR

How to use the DRCR Retina Network roadmap for ultra-widefield imaging to evaluate eyes with nonproliferative diabetic retinopathy.

By Venkatkrish M. Kasetty, MD, Harnaina Baines and Dennis M. Marcus, MD



Venkatkrish M. Kasetty,
MD



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Dennis M. Marcus, MD

Take-home points

- » Ultra-widefield (UWF) imaging allows us to capture approximately 82 percent of the retinal area, significantly greater than the 30 to 35 percent captured in the standard Early Treatment Diabetic Retinopathy Study seven-field images. This allows us to capture predominantly peripheral lesions, defined as lesions primarily outside the ETDRS standard images.
- » The presence of predominantly peripheral lesions on UWF fluorescein imaging, but not on UWF color photos, is associated with a higher risk of diabetic retinopathy progression in eyes with nonproliferative diabetic retinopathy.
- » Eyes with a higher UWF fluorescein angiographic nonperfusion index are more likely to experience diabetic retinopathy worsening.
- » UWF fluorescein angiography provides key information to clinicians and diabetic patients and helps better predict risk for diabetic retinopathy worsening and to help determine follow-up intervals for monitoring.

When the Diabetic Retinopathy Severity Score was first established more than 30 years ago, it was based on imaging findings predominantly in the posterior pole, so the mid-peripheral and peripheral retina typically weren't imaged.¹ Advancements in retinal imaging, such as ultra-widefield imaging, have enabled capturing more retinal area in a single image,² but the DRSS hasn't been updated to account for these imaging modalities.

To help incorporate these imaging advancements, the DRCR Retina Network initiated Protocol AA, a four-year multicenter prospective observational study to evaluate the ability of UWF fundus photography and fluorescein angiography in assessing the risk of retinopathy progression in treatment-naïve nonproliferative diabetic retinopathy eyes. Here, we discuss the findings of DRCR Protocol AA and its applicability to clinical practice.

From posterior pole to the periphery

Since 1991, the DRSS from the Early Treatment Diabetic Retinopathy Study has been the established system for grading the severity and progression of diabetic retinopathy in clinical trials and epidemiologic studies.

The ETDRS used film seven-standard field fundus photos that captured approximately 30 to 35 percent of the retinal area, predominantly capturing the posterior pole.¹ Previous DRCR Retina Network studies validated agreement between the DRSS clinical exam and film seven-standard field fundus photos, as well as between digital and film seven-standard field images.^{3,4}

UWF imaging, centered on the fovea extending anteriorly to the vortex veins in all four quadrants, captures approximately 82 percent of the retinal area, including the peripheral retina (*Figure 1*).⁵ Thus, UWF imaging allows us to identify peripheral

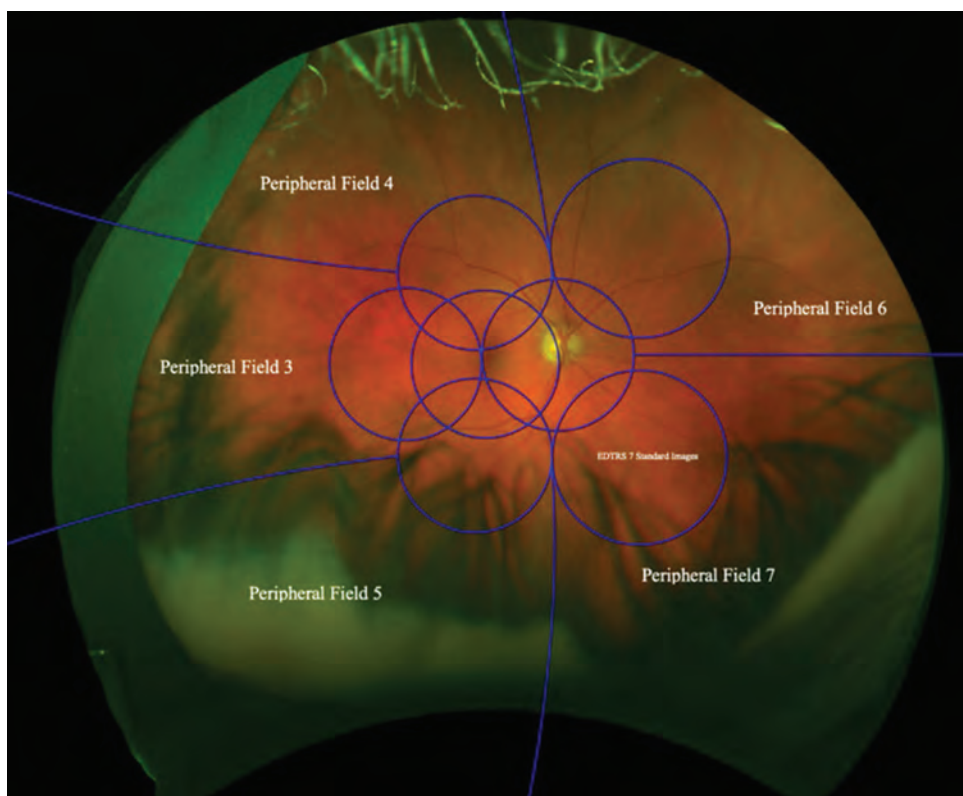


Figure 1. Ultra-widefield color fundus photo of a right eye demonstrating the Early Treatment Diabetic Retinopathy Study seven-standard-field images (blue circles) and peripheral fields 3 to 7. (Courtesy DRCR Retina Network)

lesions outside the standard EDTRS fields and better assess DR lesions.

Additionally, UWF fluorescein angiography allows us to identify peripheral non-perfusion, microaneurysm leakage, neovascularization and vascular leakage.²

When diabetic lesions, such as hemorrhages, microaneurysms, intraretinal microvascular abnormalities and venous beading, are located primarily outside the standard EDTRS seven-field photos, they're termed predominantly peripheral lesions.⁶ Previous small and short-term studies have demonstrated that PPL may be predictive of higher risk of DR progression.^{2,7-13}

UWF color and FA PPLs

DRCR Protocol AA enrolled 388 patients and analyzed 544 eyes. Forty-one and 46 percent of eyes had PPLs on base-

line UWF color photos and UWF FA, respectively. The most common PPLs were hemorrhages/microaneurysms.

Of the 542 eyes with gradable UWF color and FA photography, 16, 20 and 25 percent had PPLs present on color photos, FA, and both color photos and FA, respectively. Therefore, grading of PPL on UWF FA and color photos was discordant. Thirty-nine percent of eyes had no PPLs on either UWF color photos or FA. The most common location for PPLs were in Fields 3, 4 and 6 (*Figure 1*).

Based on grading of the masked UWF color photos, 45, 40, 26 and 43 percent of eyes with baseline mild, moderate, moderately severe and severe NPDR, respectively, demonstrated a two-or-more step increase in DRSS over four years.

While DR progression wasn't as expected based on baseline DRSS status as deter-

BIOS

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DISCLOSURES: Dr. Kasetty, Ms. Baines have no relevant disclosures.

Dr. Marcus disclosed relationships with Regeneron, Genentech/Roche, Regeneron Pharmaceuticals, Clearside Biomedical, Annexon Biosciences, Apellis Pharmaceuticals, Vial, Coherus BioSciences, Vantage Biosciences, Amgen, Ionis, Xplore, Mylan, Opthea, Iveric Bio, Outlook Therapeutics, Hengenix, Graybug Vision, Topcon, Gyroscope Therapeutics, Roche, Xplore, Kodiak Sciences, Oculus, Alexion and Ocular Therapeutix.

mined on UWF color photos, any DRSS worsening was seen in 31, 37, 43 and 56 percent of eyes with mild, moderate, moderately severe, and severe NPDR with baseline grading of ETDRS photographs.

DRCR Protocol AA found no significant relationship between the baseline presence of UWF color PPLs and two-or-more-step worsening in DRSS (38 percent of eyes with baseline color PPLs vs. 43 percent without). However, eyes with baseline UWF FA PPLs had a significantly greater risk of two-or-more-step worsening in DRSS (50 percent for eyes with baseline UWF FA PPLs vs. 31 percent without UWF FA PPLs).

The primary outcome of DRCR Protocol AA was to determine if PPLs predicted a two-or-more-step increase in the DRSS or required treatment for DR. Overall, the trial demonstrated that baseline UWF FA PPLs were associated with greater risk of DR worsening. These eyes were found to have a 70 percent greater risk of DR progression compared to eyes without UWF FA PPLs over four years. Baseline UWF

color PPLs weren't found to be predictive of DR worsening.⁶

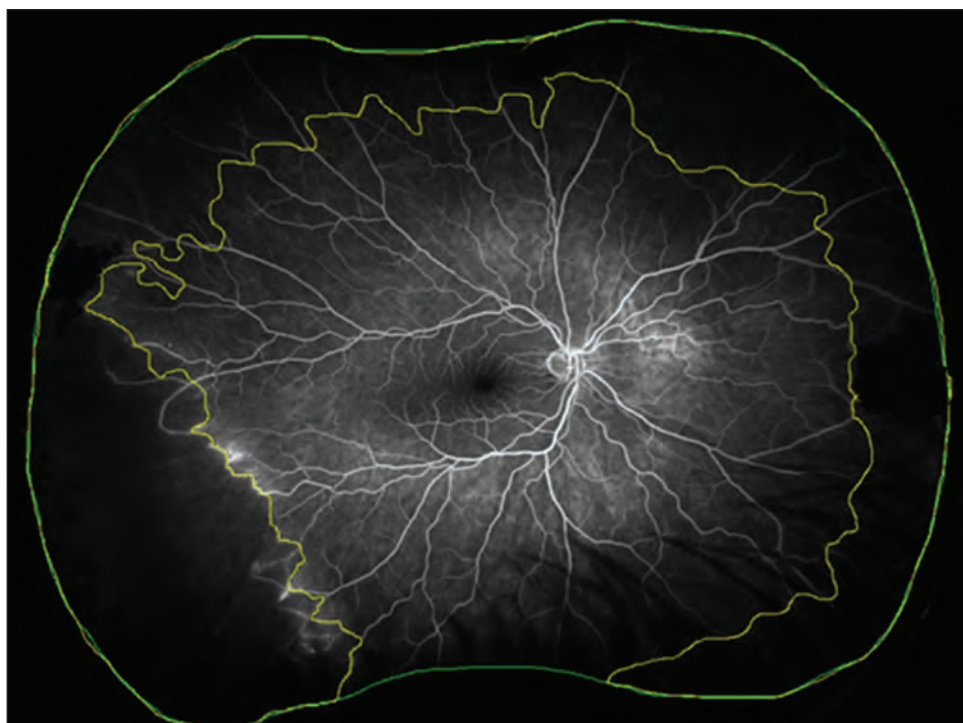
Retinal non-perfusion

DRCR Protocol AA also analyzed the retinal nonperfusion area (NPA) and nonperfusion index (NPI) measured on UWF FA (*Figure 2*). NPI was defined as NPA (mm^2) divided by total gradable area (mm^2). Of the 508 eyes with gradable baseline UWF FA nonperfusion, 9 percent had no nonperfusion.

Eyes with a greater area of nonperfusion were more likely to have type 1 diabetes, a longer duration of diabetes, higher baseline DRSS score and higher amounts of UWF FA PPLs.

Similar to the PPL analysis, the primary outcome of the NPA/NPI analysis was the proportion of eyes with two-or-more-step worsening in DRSS or required treatment for DR over four years. Twenty-six percent of eyes with no baseline nonperfusion met this primary outcome. However, 43, 38 and 46 percent of eyes in the low, medium and high nonperfusion subgroups, respec-

Figure 2: Ultra-widefield fluorescein angiography demonstrating total gradable area (mm^2 , within the green line) and area of nonperfusion (mm^2 , between the yellow and green lines). Nonperfusion index is calculated as the ratio of the area of nonperfusion to the total gradable area. (Courtesy DRCR Retina Network)





FEATURE


AI in retina

tively, met the primary outcome.

Eyes with higher NPI were associated with a higher risk of progression to PDR. Other risk factors associated with higher rate of DR worsening were higher NPI in the posterior pole and midperiphery, ETDRS fields 6 and 7, and the superior, inferior and nasal extended periphery (Figure 2).¹⁴

Bottom line

Protocol AA provides us a foundation for using UWF color fundus photography and FA when evaluating eyes with NPDR. Over four years, PPLs on UWF FA and NPI can be used as markers to identify eyes that are more likely to have DR progression. While longer-term results are unknown, it's likely that these markers portend worse DR prognosis at longer intervals as well.

These eyes should be monitored closely for evidence of progression and patients should be appropriately counseled. While historically FA wasn't routinely used in eyes with NPDR, the use of UWF FA may help us better predict and counsel NPDR patients for DR progression and to determine appropriate monitoring intervals. 

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How machine-learning may improve CRVO management
(Continued from page 26)

ML model showed a high degree of accuracy

The model was trained using 80 percent of the dataset (n=159) to learn and refine outcome predictions. The remaining dataset (n=39) was used to establish validation and performance metrics of the ML models. The models used patient data for 47 baseline features, including demographics and laboratory values, and 13 postbaseline factors up to 24 weeks.


The ML model predicted absolute BCVA at week 52 with 87-percent accuracy, mainly driven by BCVA at weeks 16, 20 and 24. In a patient-to-patient comparison, the absolute BCVA at week 52 was 4.5 to 4.6 letters larger for every 5-letter increase in absolute BCVA at weeks 16, 20 or 24.

For predicting BCVA change at week 52, the model demonstrated 76-percent accuracy. The patient-to-patient comparison found a 1.7-letter less gain in BCVA at week 52 for every 5-letter increase in baseline BCVA. In contrast, there was a 1.3 letter greater gain in BCVA at week 52 for every 5-letter increase in BCVA at weeks 20 and 24, respectively.

The ML model also was able to predict change in CST from baseline at week 52 with high accuracy (r=0.76). The key predictive factors were baseline CST and BCVA. Interestingly, however, the algorithm wasn't able to reliably detect absolute CST at week 52.

The ML model predicted PRN injection frequency from weeks 24 through 52 with an 83-percent accuracy, with CST at baseline and at week four serving as the key drivers. The patient-to-patient comparison showed the odds of receiving two or fewer PRN injections was 10 percent less likely for every 50-μm increase in baseline CST. The odds of receiving two or fewer PRN injections was 20 percent less likely for every 50-μm increase in CST at week four.

Bottom line

This proof-of-concept model demonstrated that reasonable predictions can be made on small but clean datasets. Certainly, the accuracy of this algorithm could be improved using additional datasets and building on its framework. ML models have the potential to assist us when we're discussing prognosis with patients with CRVO. 

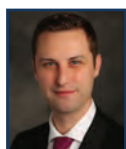
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ILM peeling sans forceps: Is it time to make the switch?

Internal limiting membrane peeling with forceps is the gold standard, but cutter-based methods are safe, effective and potentially more efficient.

By Scott D. Walter, MD, MSc, with Simon D. Archambault, MD, MSc



Scott D. Walter, MD, MSc



Simon D. Archambault, MD, MSc

Take-home points

- » Vitrectomy with internal limiting membrane peeling is the most commonly performed macular surgery for patients with epiretinal membranes and macular holes
- » Traditionally, the ILM is removed with ILM forceps using a "pinch and peel" technique. Some surgeons use a second instrument to initiate the ILM rhexis before peeling with forceps
- » Our research has shown that cutter-based membrane peeling is a safe and effective alternative to conventional forceps-based peeling
- » In our experience, the adoption of cutter-based membrane peeling can lead to reduced operating times and lower case costs in the ambulatory surgical center setting

BIOS

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DISCLOSURES: **Dr. Walter** disclosed relationships with Allergan/AbbVie, Bausch + Lomb, Castle Biosciences, EyePoint Pharmaceuticals, Genentech/Roche, Novartis, Regeneron Pharmaceuticals, Apellis Pharmaceuticals and Spark Therapeutics.

Dr. Archambault has no relevant relationships to disclose.

More than 20 percent of the U.S. population will develop epiretinal membranes by the sixth and seventh decades of life.¹ A complete or partial posterior vitreous detachment typically precedes membrane formation, leaving hyaloid remnants and activated hyalocytes on the macular surface which serve as the scaffold for membrane formation.²

Pars plana vitrectomy with internal limiting membrane peeling has become the gold standard procedure for treatment of full-thickness macular holes (FTMH) and epiretinal membranes (ERM).^{3,4} ILM peeling has been shown to improve success rates for FTMH closure⁵ and reduce postoperative ERM recurrence.⁶

The existing gold standard for ILM peel involves the use of ILM forceps, but a number of techniques have emerged that forgo the use of forceps. This article will explore alternative approaches for performing ILM

peel for FTMH and ERM.

The ILM is a type IV collagen membrane on the macular surface, produced by the footplates of Müller glia, that thickens over time. These age-related changes at the vitreoretinal interface are believed to contribute to the pathogenesis of vitreoretinal interface disorders such as FTMH and ERM.^{7,8}

Standard ILM peeling with forceps

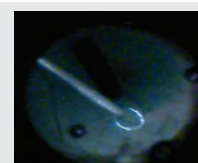
The standard procedure involves performing a three-port pars plana vitrectomy to remove the vitreous body and, if neces-

View the Video

Watch as Dr. Walter demonstrates his cutter-based approach for performing internal limited mem-



brane peeling. Scan the QR code or go to <https://bit.ly/RetSpec-ILMpeel-Video-3-2023>



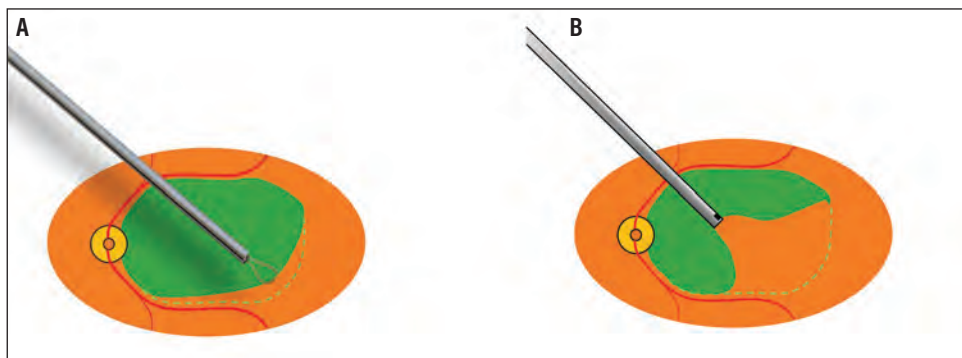


Figure 1. Examples of internal limiting membrane peeling approaches used in patients in our consecutive case series of cutter-based membrane peeling. A) The first patient with successful closure of a large full-thickness macular hole. B) Successful removal of an epiretinal membrane in the last patient in the series. Both patients had clinically significant improvements in visual acuity, macular volume and central subfield thickness at one month postoperatively vs. baseline.

sary, surgically inducing a posterior vitreous detachment to remove cortical vitreous from the macular surface. Chromovitrectomy is performed with a vital dye, such as indocyanine green or Brilliant Blue, to stain the ILM.

The ILM is peeled to remove ERMs and other tractional forces acting on the macular surface. Classically, the surgeon creates the ILM rhexis using either ILM forceps (“pinch and peel”) or a second instrument, such as a Finesse Flex Loop (Alcon) or Tano Diamond Dusted membrane scraper (Bausch + Lomb). The surgeon then completes the ILM peel using forceps to manually peel and remove ILM fragments from the eye.⁸

Alternative approaches to ILM peeling

Several vitreoretinal surgeons have previously described techniques for ILM peeling without the use of forceps. Both Tim Murray, MD, MBA, and Goran Petrovski, MD, PhD, have independently reported cases of ILM peeling using only the vacuum aspiration function of the vitrectomy probe.⁹ Recently, Carl Awh, MD, developed a new instrument (Awh MVP Micro Vacuum Pick, Katalyst Surgical) specifically designed for ILM peeling by vacuum aspiration.¹⁰ In all these reports, the patients had anatomical and functional improvements without iatrogenic retinal damage.

Evolution of my technique

The Finesse Flex Loop has always been my preferred instrument for creating the ILM rhexis. After initiating the ILM rhexis, I used to switch to an ILM forceps to peel and remove the ILM fragments.

However, like my colleagues,⁹⁻¹⁰ I recently discovered that ILM peeling can be performed with ease and efficiency using the vacuum aspiration function of the vitrectomy handpiece. This technique has several apparent advantages. Most importantly, they include the ability to peel and remove ILM tissue without removing instruments from the eye.

As cutter-based membrane peeling became my preferred technique, Dr. Archambault and I wanted to examine the practicality, safety and efficacy of cutter-based membrane peeling compared with conventional forceps-based peeling. We hypothesized that this technique could minimize the number of instrument exchanges, potentially reducing surgical time and the risk of intraoperative complications.

We conducted a retrospective chart review to compare patient outcomes between the different peeling techniques for patients undergoing vitrectomy with ILM peeling. We first presented our results last year at the 50th annual meeting of the American Society of Retina Specialists in New York City.¹¹

Several vitreoretinal surgeons have described techniques for ILM peeling without forceps. In all these reports, the patients had anatomical and functional improvements without iatrogenic retinal damage.

You may feel somewhat clumsy when starting with the cutter-based technique, but in my experience the learning curve was very short because we already perform many of the required maneuvers during other vitreoretinal surgeries.

Surgery time reduced 10 minutes

Between April 2020 and December 2021, I performed 92 consecutive vitrectomies with ILM peeling for FTMHs (n=30, 32 percent) and ERMs (n=62, 68 percent) at a single ASC in Connecticut. Baseline demographics, visual acuities, macular volumes (MV) and central subfield thicknesses were similar between the two groups. We followed the patients for a minimum of three months postoperatively (*Figure 1, page 33*).

For all the operations, I used a 25-gauge vitrectomy platform (Constellation Vision System; Alcon) and “heavy” ICG for ILM staining. I initiated the ILM rhexis using a Finesse Flex Loop. The only modifications to the procedure were whether the ILM peeling was done using the ILM forceps (n=12) or a 25-gauge vitrectomy probe (“cutter”) (n=80).

Total surgical time was the primary outcome of our study. We found that cutter-based membrane peeling significantly reduced the total operative time by an average of 10 minutes ($p=0.001$).

Safety and efficacy outcomes

Knowing that cutter-based membrane peeling could significantly reduce surgical time, we sought to establish the safety and efficacy of this technique.

Patients in both groups had significant improvements in visual acuity ($p=0.001$), macular volume ($p=0.001$) and CST ($p=0.001$) three months postoperatively compared to preoperative values. In addition, the cutter-based technique resulted in high rates of single-operation anatomic success (>96 percent).

We reported no intraoperative complications, such as iatrogenic macular holes, retinal breaks, retinal detachments or choroidal detachments, in either group. There was only one case of postoperative RD in the cutter-based group after three months, which is less than the expected 2-to-3-percent cumulative incidence of RD observed in large claims-based studies of vitrectomy with ILM peeling.¹²

Tips and tricks for cutter-based peeling

You may feel somewhat clumsy when starting with the cutter-based technique. Peeling and manipulating the ILM with the cutter will require new coordination and movements. However, in my experience the learning curve was very short because we already perform many of the required maneuvers during other vitreoretinal surgeries. Here are key steps in the procedure.

● **Initiating the peel.** I typically initiate the peel using a Finesse Flex Loop to create a 90-to-180-degree curvilinear ILM rhexis along the inferotemporal arcade (*Figure 2A*). To engage the ILM flap with the vitrectomy handpiece, turn the cutter off. Position the cutter directly in front of or behind the rhexis edge with the port aimed towards the middle of the flap.

● **Increasing the vacuum.** Next, use proportional foot pedal control to increase the vacuum until the ILM tissue occludes the port. Once the port is occluded, the vitrectomy handpiece will function like closed forceps as long as a moderate level of vacuum aspiration is maintained (*Figure 2B*).

● **Peeling maneuvers.** Peeling can be done using a variety of simple maneuvers, including lateral movements of the cutter, vertical movement of the cutter, rotation of the cutter port and/or adjusting the amount of vacuum aspiration.

● **Coordinating cutter maneuvers.** Exercise caution when coordinating cutter maneuvers with increasing proportional vacuum because you can easily tear the flap if the suction is too great.

● **Releasing traction.** Take care when releasing traction on the fovea. With low aspiration, carefully rotate the cutter port or gently “tug back” with the probe, to tease the ILM off the fovea. Once all traction has been released from the fovea, the remaining 180 degrees of the ILM rhexis can be completed with full aspiration.

This technique has helped me save time and reduce my ASC instrument costs. I was glad to see that my patients have had excellent anatomic and visual outcomes without

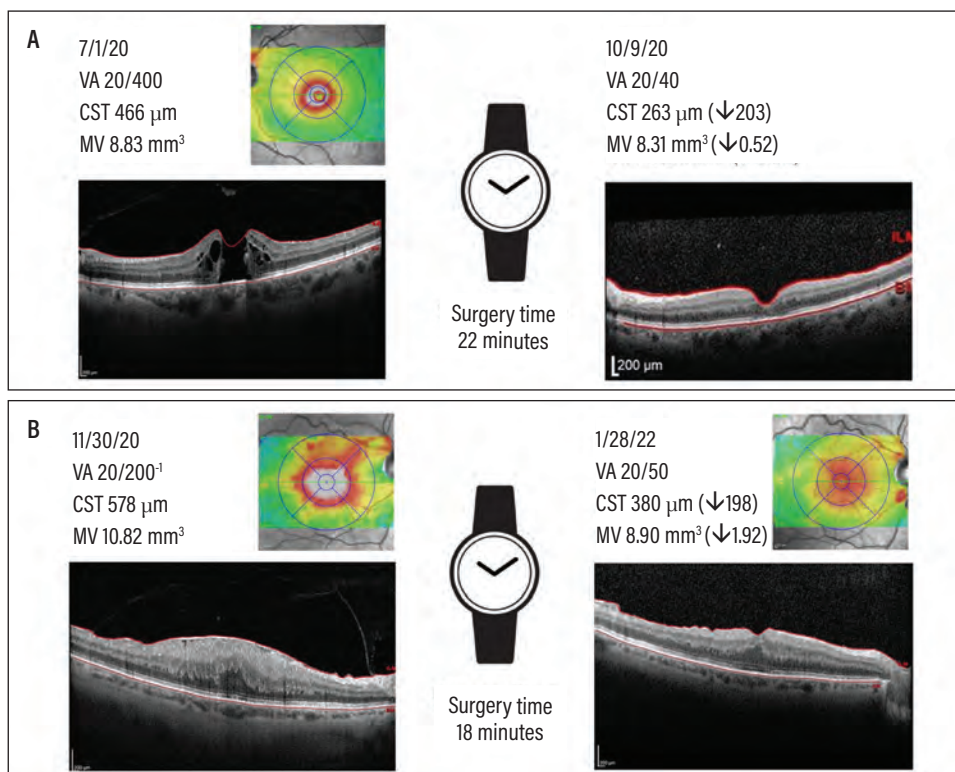


Figure 2. A two-step technique for internal limiting membrane peeling without forceps. A) We use a flexible loop scraper to create a 180-degree rhexis of the ILM along the arcades. B) The ILM flap is then peeled using the vitrectomy probe on aspiration mode to release all traction on the fovea. Once the ILM rhexis is completed, the amputated ILM flap is aspirated into the port. Key: VA = visual acuity; CST = central subfield thickness; MV = macular volume.

sacrificing safety. I no longer use ILM forceps except in special circumstances, such as for ILM peeling under perfluorocarbon liquid. Over the past three years, I've completed hundreds of cases, using ILM forceps on only four occasions. There's also no doubt that the decreased operative time contributes to increased patient satisfaction.

Bottom line

Based on our study, we believe that cutter-based membrane peeling is a safe and effective alternative to forceps-based peeling. This technique can reduce operative time and surgical case costs while providing the same high quality of patient care. ^{RS}

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Based on our findings, we believe that cutter-based membrane peeling is a safe and effective alternative to forceps-based peeling. It can reduce operative times and surgical case costs while providing the same quality of patient care.

Metformin's potential impact on AMD prevention

Multiple observational studies have shown the potential of the antidiabetic in the management of age-related macular degeneration.



John Moir



Reem Gonnah, MD



Madeleine Yehia, MD



Dimitra Skondra, MD, PhD

By John Moir, Reem Gonnah, MD, Madeleine Yehia, MD, and Dimitra Skondra, MD, PhD

Take-home points

- » Age-related macular degeneration is a leading cause of blindness worldwide, but current therapeutic tools for preventing or slowing progression are limited.
- » Metformin is an oral medication commonly used to treat type 2 diabetes. It's well-tolerated, broadly available, and has been suggested to have anti-aging properties, which make it an appealing possible candidate in the management of AMD.
- » Data from population-level studies demonstrate that metformin may reduce the risk of developing AMD, although conflicting data surround this point.
- » Further studies, especially prospective clinical trials, are warranted to determine the potential role of metformin in preventing or delaying AMD progression.

BIOS

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DISCLOSURES: Mr. Moir, Dr. Gonnah and Dr. Yehia have no relevant disclosures.

Dr. Skondra disclosed relationships with Biogen, Allergan/AbbVie, Focusscope, LaGrippe Research, Keywest Health, Lumina and Trinity Life Sciences.

Intravitreal anti-VEGF agents have revolutionized the treatment of wet age-related macular degeneration, but treatment options for the dry form have remained scarce.¹ Retina specialists have been largely restricted to recommending AREDS2 vitamins and minerals to prevent progression to advanced AMD along with recommending pertinent lifestyle interventions, such as smoking cessation.²

This year, the Food and Drug Administration approved two treatments for treatment of dry AMD: intravitreal pegcetacoplan (Syfovre, Apellis Pharmaceuticals), which was shown to mildly slow the progression of geographic atrophy;³ and, more recently, avacincaptad pegol (Izervay, Iveric Bio/Astellas), which demonstrated a statistically significant reduction in GA progression.⁴

However, no medication is known to prevent disease progression regardless of staging. This is a notable shortcoming, con-

sidering that the dry AMD accounts for approximately 90 percent of all AMD cases and can slowly progress to GA, which causes permanent central vision loss.

Furthermore, wet AMD accounts for 80 to 90 percent of all blindness related to AMD. However, treatments with recurrent injections may present uncomfortable burdens to patients, and few if any interventions exist to prevent or delay conversion to wet AMD.⁵

Hence, an ideal medication would prevent the onset of AMD entirely or prevent its progression to advanced and debilitating stages of disease, all while offering safety and ease of use to patients. That has inspired some researchers to evaluate the potential of using metformin for management of AMD.

Metformin's expanding use

Metformin is a first-line oral medication

for treating type 2 diabetes. In recent years, its off-label use has expanded for treating polycystic ovarian syndrome, gestational diabetes and prediabetes, and for managing the metabolic effects from antipsychotic medications.⁶ Part of this growing therapeutic range is attributable to its benign side-effect profile. Metformin isn't associated with a risk of hypoglycemia and is generally well-tolerated.⁶

Also emerging is evidence of metformin's potential geroprotective properties. Metformin may have an anti-aging effect through its interactions with age-related cellular pathways, and its use has been shown to decrease mortality from dementia, cancer and cardiovascular disease.⁷

Metformin's beneficial anti-aging associations, expanding therapeutic use and safety profile have inspired researchers to explore its possible connections with AMD.

Possible mechanism for metformin in AMD

While the pathogenesis of AMD is multifactorial and isn't completely characterized, complement, angiogenic, oxidative stress, lipid, extracellular matrix and inflammatory pathways all contribute.⁸ Metformin may interact with these pathways to modulate prevention or delay the progression of AMD through several plausible mechanisms.

Metformin acts through activation of AMP-activated protein

kinase (AMPK), which is responsible for inhibition of glucose production in hepatocytes.⁹ AMPK downregulates mammalian target of rapamycin (mTOR), a kinase that plays a key role in aging, and inhibition of mTOR can extend the lifespan of mammalian model organisms.¹⁰

Through AMPK-dependent and independent pathways, metformin also reduces levels of reactive oxygen species and pro-inflammatory cytokines while enhancing autophagy and delaying stem cell aging.¹¹ These findings help to explain metformin's purported anti-aging properties.

Within retinal tissue, metformin exhibits antiangiogenic and anti-inflammatory properties,¹² protects against oxidative stress¹³ and augments autophagy-mediated removal of damaged RPE cells.¹⁴

Given the considerable overlap between the pathways on which metformin acts and the pathways responsible for the development of AMD, researchers have turned their attention to observational studies to determine whether metformin may protect against AMD.

Implications of the available evidence

Retina specialists should understand how metformin's effects differ in non-diabetes patients.



Three points warrant this additional analysis:

- Prior studies have either exclusively included patients with diabetes or a combination of patients with and without diabetes, making it difficult to parse the effect of metformin from the effect of diabetes on AMD risk.
- Metformin can be taken safely by patients who don't have diabetes.
- As Andrea Blitzer, MD, and colleagues at the University of Chicago demon-

The observational evidence supporting the potential of metformin in AMD

While evidence supporting the use of metformin to prevent age-related macular degeneration is mixed from observational studies, a trend has begun to emerge that it may have protective properties against AMD development. Over the past four years, these nine different studies of varying methodologies and sizes have supported that trend.

- **Emily Brown, MD, and colleagues** at the University of Florida were the first group to perform an observational study of the association between metformin and AMD.²¹ In a case-control study of 1,947 cases of incident AMD and 5,841 controls, they found exposure to metformin decreased the odds of developing any AMD (odds ratio [OR]=0.58; 95% confidence interval [CI]=0.43-0.79).
- **A retrospective cohort study** in Taiwan corroborated this finding among 68,205 patients with type 2 diabetes.¹⁶ In a propensity score-matched sample, those exposed to metformin were less likely to develop any AMD (hazard ratio [HR]=0.57; 95% CI=0.52-0.63). The researchers found a significant trend of lower hazard of AMD development with increasing total and average daily dosing of metformin.
- **A cross-sectional retrospective study** of 3,120 diabetes patients at the University of California, San Francisco found that patients taking metformin were less likely to have any AMD (OR=0.70; 95% CI=0.55-0.88), including dry AMD only (OR=0.59; 95% CI=0.46-0.77).²²
- **In a nationwide case-control study** in the United States that featured more than 300,000 AMD cases and 300,000 matched controls, Andrea Blitzer, MD, and colleagues at the University of Chicago found that metformin reduced the odds of any AMD development (OR=0.94; 95% CI=0.92-0.96).¹⁵ This protective effect showed the greatest benefit at lower doses, particularly cumulative doses of 1 to 270 g and 271 to 600 g over a two-year period. Notably, the study showed a protective effect in diabetes patients without retinopathy (OR=0.93; 95% CI=0.91-0.95) but not in diabetes patients with diabetic retinopathy.
- **A small retrospective cohort study** of 324 patients diag-

nosed with type 2 diabetes in Beijing reported that metformin users were less likely to develop any AMD (OR=0.24; 95% CI=0.13-0.42) and early AMD (OR=0.18; 95% CI=0.10-0.33), but not less likely to develop late AMD (OR=0.43; 95% CI=0.18-1.04).¹⁷ This study also observed a significant trend of decreasing odds of AMD with both prolonged duration of exposure and higher cumulative doses of metformin. However, the small size was a major drawback that severely limited subgroup analysis of AMD stage and metformin dosing.

- **A large retrospective cohort study** of 1 million U.S. patients with diabetes found that active use of metformin conferred an increased hazard of dry AMD (HR=1.08; 95% CI=1.04-1.12).¹⁸ Meanwhile, prior use of metformin decreased the hazard of dry AMD (HR=0.95; 95% CI=0.92-0.98). These researchers additionally reported that the quartile with the lowest dosage of metformin had a decreased hazard of dry AMD (HR=0.95; 95% CI, 0.91-0.99). Comparably, those in the highest dosage quartile had an increased hazard of dry AMD (HR=1.07; 95% CI=1.01-1.13).
- **A retrospective cohort study** of 173,689 patients with type 2 diabetes in the United Kingdom found no effect on AMD development in patients prescribed metformin compared to patients prescribed other antidiabetic medications only (HR=1.02; 95% CI=0.92-1.12).²³
- **A nested case-control study** of 2,330 cases of incident AMD and 23,278 matched controls in Korea found no association of metformin with any AMD (OR=1.15; 95% CI=0.91-1.45) or wet AMD (OR=1.03; 95% CI=0.80-1.34), but an increased association with dry AMD (OR=1.62; 95% CI=1.02-2.60).¹⁹
- **A cohort study of the prospective, Europe-based Rotterdam Study**, which included 11,260 participants, reported that metformin was associated with a lower odds of developing AMD (OR=0.69; 95% CI=0.49-0.98).²⁴ This analysis showed that increasing years of treatment or greater daily dosing didn't further decrease AMD risk. The prospective nature of this study is an important strength relative to the retrospective design of other similar observational studies.

strated, metformin wasn't protective in patients with diabetic retinopathy, which is generally associated with more severe diabetes.¹⁵

With these points in mind, it's possible that metformin may have the greatest benefit in patients who don't have diabetes.

Inconsistencies in observational studies


Data behind metformin dosing is still unclear and has been described inconsistently in observational studies. Some studies have described a protective effect with metformin that's enhanced with greater dosing.^{16,17} Others have reported an optimal effect at lower doses.^{15,18} This point requires further investigation as well.

Lastly, only one study has reported the impact of metformin separately on dry and wet AMD.¹⁹ Metformin may modulate disease activity differently in these two forms due to unique aspects of their pathogenesis.

It's crucial to understand if metformin protects against GA, considering its severe and irreversible visual burdens, and if metformin protects against the rapidly progressive wet AMD—both shortcomings in the current literature. An ongoing phase II clinical trial of metformin in nondiabetic patients with GA will shed light on its ability to prevent progression of this debilitating and advanced form of AMD.²⁰

Bottom line

While it's too early to discern whether metformin will ultimately have a role in the management of AMD, results from multiple observational studies across North America, Europe and Asia are encouraging.

In conjunction with a plausible mechanism that preclinical studies have uncovered, sufficient evidence from observational studies has amassed to warrant testing of metformin in prospective clinical trials. We should eagerly await the results of these trials as they could have the potential to further revolutionize treatment of this debilitating disease. 

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It's crucial to understand if metformin protects against GA, considering its severe and irreversible visual burdens, and if it protects against the rapidly progressive wet AMD—both shortcomings in the current literature.

Trial updates in GA, MacTel type 2 and DME

Four ASRS abstracts look at ANX007, pegcetacoplan, encapsulated cell therapy and tarcocimab.

Abstracts selected by
Charles C. Wykoff,
MD, PhD, Chief
Medical Editor

Reporting by staff
.....



The ARCHER study demonstrated C1q inhibition had a distinct neuroprotective effect, along with consistent visual function benefits, although it didn't show any significant change in lesion growth area.

The 41st annual scientific meeting of the American Society of Retina Specialists in Seattle was abuzz with reports of retinal vasculitis cases in patients treated with pegcetacoplan (Syfovre, Apellis Pharmaceuticals), but that didn't derail the multitude of trial readouts that characterize the meeting.

Here, we share four abstracts that are worth a second look.



ARCHER trial of novel ANX007 antibody fragment

The ARCHER study evaluated the efficacy and safety of intravitreal ANX007 (Annexon Biosciences), a novel antibody fragment that binds to C1q, inhibiting activation of the classical complement pathway, in geographic atrophy secondary to age-related macular degeneration.¹ The primary endpoint of the double-masked, sham-controlled study was comparison of the rate of change in GA lesion growth at 12 months between ANX007 and sham.

The study used three arms: sham monthly or every other month (n=89), and ANX007 5 mg monthly (n=89) or every other month (EOM, n=92).

Jeffrey Heier, MD, director of the vitreo-retinal service, Ophthalmic Consultants of Boston, reported ANX007 didn't significantly reduce lesion area compared to sham. GA change from baseline at 12 months was 2.15 mm² for sham, 2.02 mm² for monthly treatment (-6.2 percent, p=0.526) and 2.12 mm² for every-other-month (EOM) treatment (-1.3 percent, p=0.896).

The study showed ANX007 provided significant dose-dependent protection from vision loss. Sham patients had a rate of 21.3 percent of ≥15-letter loss at 12 months vs. 5.6 percent for monthly ANX007 (p=0.0021) and 10.9 percent for EOM treatment (p=0.055). The pooled average for the treatment group was 8.3 percent (p=0.0024).

Treated patients also demonstrated signif-

icant time-dependent protection from ≥15-letter loss, with risk reductions of 72 percent vs. sham in the monthly arm (p=0.006) and 48 percent in the EOM arm (p=0.064).

The study also evaluated protection from vision loss in foveal and nonfoveal involvement. In foveal patients, the proportions with persistent ≥15-letter loss through 12 months were 25 percent for sham, 5.9 percent for monthly ANX007 and 18.4 percent for EOM treatment. In nonfoveal patients, the percentages were 17.8, 5.3 and 2.3, respectively.

Dr. Heier said ANX007 treatment was "generally well-tolerated," although adverse events were higher in the treatment group vs. sham: 4.5 and 4.3 percent of the monthly and EOM patients had choroidal neovascularization vs. 3.4 percent of sham. The treatment arms had low rates of endophthalmitis—one in the monthly and two in EOM arms—and intraocular inflammation—two and one, respectively. One case of retinal vascular occlusion was reported in the EOM arm. The sham arms had none of these complications.

The study demonstrated C1q inhibition had a distinct neuroprotective effect, along with consistent visual function benefits, although it didn't show any significant change in lesion growth area. A six-month follow-up is ongoing and the company is planning for regulatory discussions with the Food and Drug Administration and a Phase III trial.

Dr. Heier is a consultant to Annexon.



GALE extension study shows increasing efficacy

The GALE open-label extension study evaluated the long-term efficacy data through 30 months of pegcetacoplan (Syfovre, Apellis Pharmaceuticals) and through five years based on data modeled from the 24-month OAKS and DERBY trials.² GALE (n=782) enrolled 83 percent of patients from OAKS and DERBY in the following arms: continued monthly pegceta-

coplan treatment (n=241); continued EOM treatment (n=268); and sham crossed over to monthly (n=129) or EOM (n=144) pegcetacoplan.

Notably, Nathan Steinle, MD, a vitreoretinal specialist with California Retina Associates in San Luis Obispo, said the 30-month GALE results failed to find any reports of occlusive or nonocclusive retinitis or vasculitis.

The study also showed that reductions in GA lesion growth after 30 months of continuous pegcetacoplan treatment progressed over time. At six months, the monthly arm had a 19 percent reduction and the EOM arm a 17 percent reduction vs. sham. In the modeled 30-month results, that gap had grown to 39 percent for monthly treatment and 32 percent for EOM. The overall reduction at 30 months was 24 percent for monthly and 21 percent for EOM ($p<0.0001$).

In patients with nonsubfoveal lesions, the difference was even more pronounced: 31 percent for monthly and 26 percent for EOM vs. sham ($p<0.0001$).

Dr. Steinle addressed the postmarket reports of intraocular inflammation, namely retinal vasculitis, after pegcetacoplan injection. No infectious endophthalmitis cases were reported in the first six months of GALE, and the rate of IOI in treated patients across OAKS, DERBY and GALE was 0.26 percent. In the interim, Apellis linked the cases of retinal vasculitis to the 19-gauge filter needle in certain injection kits and recommended retina specialists discontinue use of the kits in favor of kits with an 18-gauge needle instead.

Dr. Steinle is a consultant to and investigator for Apellis.



CNTF implant shows promise for treating MacTel type 2

Revakinagene tarorectel, also known as NT-501 (Neurotech Pharmaceuticals), is first-in-class encapsulated cell therapy that's surgically implanted into

the vitreous cavity via a capsule anchored to the sclera to produce sustained levels of ciliary neurotrophic factor (CNTF). Emily Chew, MD, of the National Eye Institute, reported on two Phase III studies evaluating the treatment in patients with macular telangiectasia type 2 (MacTel) vs. sham treatment.³

The NTMT-03-A and NTMT-03-B trials were identically designed and randomized patients 1:1 to NT-501 (n=58 and 59, respectively) or a sham procedure in the study eye (n=57 and 54). Inclusion criteria were ages 21 to 80 years and an ellipsoid zone break between 0.16 and 2 mm² and BCVA of ≥ 54 letters.

The primary endpoint was rate of change in the area of EZ loss from baseline to month 24. Secondary efficacy outcomes were aggregate sensitivity of microperimetry within the EZ line break area and monocular reading speed at month 24. Secondary safety outcomes were the proportion of patients with a ≥ 15 -letter loss in BCVA at any visit or one or more treatment-related serious adverse events.

In the A study, the treatment arm had a 0.074 mean change in EZ area loss vs. 0.170 for the sham arm ($p<0.0001$). The disparity in absolute size of EZ area loss at 24 months was similar, with a difference of -0.096 for treatment vs. sham ($p<0.0001$), leading to a 56.4-percent reduction in retinal degeneration for the treatment arm.

In the B study, the gaps between the treatment and sham arms were closer: 0.116 vs. 0.164 for mean change from baseline in EZ area loss at 24 months ($p<0.0001$); -0.048 difference in EZ area loss ($p<0.0210$); and a 29.2-percent reduction in retinal degeneration.

For the secondary endpoint of aggregate retinal sensitivity loss from baseline, the A trial demonstrated a mean change of 25.27 vs. 43.02 in the treatment vs. sham arms ($p=0.0199$), but the B trial showed no significant differences between the two arms.

The treatment arms in both studies had

The GALE study also showed that reductions in GA lesion growth after 30 months of continuous pegcetacoplan treatment progressed over time. Overall reduction at 30 months was 24 percent for monthly and 21 percent for EOM.

While GLEAM and GLIMMER didn't meet their primary endpoint, tarcocimab did demonstrate strong durability. Despite its development being discontinued, efforts are underway to better understand the incidence of cataracts.

significantly higher levels of treatment-emergent adverse events (TEAEs), with 90 (n=52) and 93 percent (n=55) of NT-501 patients in the A and B trials vs. 60 (=34) and 41 percent (n=76) for the sham arms.

In terms of ocular TEAEs related to CNTF, 17 percent of treated patients in the A trial (n=10) and 24 percent in the B trial (n=14) had delayed dark adaptation, and 17 (n=10) and 14 percent (n=8), respectively, had miosis. One sham patient in the B trial had delayed dark adaptation.

Treatment with NT-501 preserved photoreceptors through 24 months in both trials, Dr. Chew said, demonstrating safety and efficacy for treatment of MacTel.

Dr. Chew has no relevant disclosures.



Tarcocimab fails to meet trial endpoint

Tarcocimab tedromer, also known as KSI-301 (Kodiak Sciences), is an anti-VEGF biopolymer conjugate that had been evaluated in four different indications. The GLEAM and GLIMMER Phase III trials evaluating tarcocimab for noninferiority to aflibercept in diabetic macular edema failed to meet their primary endpoint. Development of the drug is being discontinued.

The trials (n=917) randomized patients 1:1 to tarcocimab every eight to 24 weeks after three monthly loading doses or aflibercept q8 weeks after five monthly loading doses. About 90 percent of patients in each treatment arm completed the trial to week 64.

In GLEAM, the mean letter change from baseline to week 64 was 10.3 (standard deviation 8.1) vs. 6.4 (8.8) for aflibercept and tarcocimab, respectively. In GLIMMER, the change was 12.2 (10.1) vs. 7.4 (11.2).

In the tarcocimab patients, 74 percent had at least one five-to-six-month interval between treatments. The median number of injections in both trials through week 64 was five with tarcocimab and 10 for aflibercept.

Retinal thickness outcomes were also similar between the treatment arms. In GLEAM, the mean change in central subfield thickness

measured on optical coherence tomography was 151.6 (127.1) μm for tarcocimab and 142.8 (135.1) μm for aflibercept. In GLIMMER, those respective outcomes were 190.9 (154.7) μm and 159 (135.6) μm .

For ocular adverse events (OAE), tarcocimab patients had significantly higher rates of cataract—19.4 percent (n=89) vs. 8.7 percent (n=40) in the pooled analysis of both studies.

The mean BCVA change curve trajectories of tarcocimab and aflibercept trended upward until week 36, when they started to separate, when the tarcocimab curve trended downward. The higher rates of cataract in the tarcocimab arms emerged after 36 weeks.

Rates of any OAE were 48 percent (n=220) in the pooled tarcocimab arms and 34.9 percent (n=160) in the aflibercept arms. Rates of intraocular inflammation were low in both treatment groups and endophthalmitis rates were similar between both treatment and sham groups. Neither study had any cases of IOI with vasculitis or vascular occlusion.

When pseudophakic patients were separated out, the BCVA and OCT CST outcomes were more evenly matched between the tarcocimab (n=108) and aflibercept (n=112) arms.

While GLEAM and GLIMMER didn't meet their primary endpoint, tarcocimab did demonstrate strong durability, Dr. Wykoff said. However, cataracts compromised the drug's vision outcomes. Despite its development being discontinued, efforts are underway to better understand the incidence of cataracts.

Dr. Wykoff is Chief Medical Editor of Retina Specialist Magazine and a consultant to and investigator for Kodiak Sciences. 

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Laurent Kodjikian

**Rationale for Early-Switch and First-Line Dexamethasone
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Pharma marketing and social media

Some thoughts on avoiding the pharmaceutical digital marketing group-think.

By Jayanth Sridhar, MD



Jayanth Sridhar,
MD

Sermo and LiveWorld recently published results of a survey of more than 200 physicians and more than 50 pharmaceutical marketers that demonstrated the impact social media may ultimately have on physician prescribing patterns.¹

Nearly all of the marketers (94 percent) said that social media was a critical channel for reaching health-care providers. And 57 percent of physicians said that their initial perception of a medication had been previously changed by social media content.

Along the same lines, 90 percent of the marketers stated that social media was a formal component of their 2023 budget, with half of these budgets increasing yearly.

A natural progression

This shouldn't surprise us, nor should we condemn it. While direct-to-patient marketing via social media raises a host of legal and ethical questions,² one could simply view the transition to more digital interactions between pharma and physicians as natural, complementing previously compliant office visits, interfacing at conferences and mail communications.

Still, it's incumbent for physicians—and, in the case of this column, retinal specialists specifically—to think carefully about how we source our information on social media.

According to the previously mentioned survey, physicians choose other physicians as influencers based on, in equal parts, their credentials, their knowledge of a topic and their relatable content. While these factors seem like good reasons to put more trust in a key opinion leader (KOL), none of them necessarily correlate with scientific accuracy and merit when evaluating new medications. Despite this, KOL influencers have become a major part of pharmaceutical strategy, with 56 percent of the marketers surveyed saying they're including influencers in their 2023 plans.

Some ground rules

Responsibility goes two ways, both for the information provider and the recipient. For physicians who are KOL influencers (or who are budding digital KOLs, cultivating a careful social media presence to build their personal brands), it's reasonable to lay out a few basic ground rules.

First, all physicians posting information related to a drug or trial results should be open about any financial disclosures. It's a requirement for continuing medical education programs and should be part of the transparency between all of us as colleagues.

Second, physicians should understand that while friending or connecting with our pharma partners is inbounds and part of today's modern world, they should take care to vet and take responsibility for any information before they repost and retweet drug or device content.

Finally, separate church and state. Leave patients out of the fray. If connecting on a platform with patients (for example, a practice Facebook page), it's almost certainly inappropriate to post content promoting a specific product, given the concerns about direct-to-patient pharmaceutical marketing.

Bottom line

Social media has democratized the retina specialist's ability to become a KOL and build their personal brand in rapid-fire fashion. For those interested in embracing this opportunity, let's do it in a mindful, professionally respectful manner that follows ethical standards so we don't fall prey as a community to pharmaceutical digital marketing group-think. **RS**

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1. Survey Finds 57% of U.S. physicians have changed their perception of a medication as a result of info on social media [press release]. New York, NY; Sermo and LiveWorld; February 15, 2023. Available at: <https://www.businesswire.com/news/home/20230215005061/en/Survey-Finds-57-of-U.S.-Physicians-Have-Changed-Their-Perception-of-a-Medication-as-a-Result-of-Info-on-Social-Media>
2. Sridhar J. Current digital direct-to-consumer advertising—The tip of the iceberg. *JAMA Ophthalmol*. 2022;140:642-643.

BIO

Dr. Sridhar serves as *Retina Specialist Magazine's* Social Media Ambassador. He's an associate professor of clinical ophthalmology at Bascom Palmer Eye Institute, Miami.

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



Transgene shows restorative properties in nAMD

4D-150 is an intravitreal dual transgene genetic medicine that expresses both aflibercept and a mRNAi sequence that inhibits intracellular expression of VEGF-C.

An intravitreal transgene genetic medicine designed to activate production of two proteins to maintain vision and central subfield thickness in age-related macular degeneration has been shown to reduce treatment burden of intravitreal anti-VEGF treatments by up to 81 percent through nine months, according to recent results from a Phase I/II trial.¹

The PRISM trial of 4D-150 (4D Molecular Therapeutics) evaluated three different doses and found that the highest dose— 3×10^{10} (3e10) vector genes (vg)/eye—was most effective at maintaining best-corrected visual acuity and CST through 36 weeks. The Phase II dose-expansion phase of PRISM (n=50) for patients with neovascular AMD has completed enrollment.

4D-150 is composed of a novel primate-evolved, proprietary, intravitreal vector, R100, and a transgene payload that expresses both aflibercept and a VEGF-C inhibitory interference mRNA (RNAi). The dual transgene payload inhibits four angiogenic factors that drive nAMD and diabetic macular edema: vascular endothelial growth factors A, B and C and placental growth factor.

Here, Arshad M. Khanani, MD, MA, answers questions about 4D-150 and the PRISM clinical trial. Dr. Khanani is managing partner at Sierra Eye Associates in Reno, Nevada, and clinical associate professor at the University of Nevada, Reno School of Medicine. He's a consultant to and receives research funding from trial sponsor 4D Molecular Therapeutics.

Q In your own words, what's the mechanism of action of 4D-150?

A This is a novel, low-dose, intravitreal, in-clinic transgene therapy that uses a primate-evolved R100 capsid that takes the dual transgene payload for aflibercept and interference mRNA for vascular endothelial

growth factor C. This is a single intravitreal injection that's designed to provide sustained delivery of anti-VEGF to control nAMD and diabetic macular edema.

Q How does this differ from other investigative gene therapies?

A Currently, the most advanced gene therapy program for nAMD is RGX-314 (Regenxbio), which is delivered via a subretinal injection in the operating room and expresses a transgene for a protein similar to ranibizumab. It's also being evaluated in nAMD using an in-clinic suprachoroidal injection. Another gene therapy vector being evaluated is intravitreal ADVM-022, or ixo-vec (Adverum Biotechnologies). This uses a novel AAV.7m8 vector that's designed to express a transgene for aflibercept. 4D-150 is the only gene therapy program using a dual transgene to treat nAMD.

Also, 4D-150 uses a much lower dose than the other gene therapy programs. Currently, the highest dose in the 4D-150 program is 3e10 vg/eye. This is important because there maybe a direct correlation between dose and risk of inflammation when it comes to intravitreal gene therapy.

Q What can you tell us about the design of the PRISM trial?

A The Phase I/II trial investigated safety and clinical activity of 4D-150 in previously treated patients with nAMD in two phases: dose-exploration and dose-expansion. In the dose-escalation phase, patients received 3e10 vg/eye. Five patients were treated, and because the efficacy was promising, the dose was actually lowered. The trial studied three different doses in the dose-exploration phase, with five patients in each dosing group: 6e9 (6×10^9 vg/eye), 3e10 and 1e10 (1×10^{10} vg/eye).

In the dose-expansion phase, the 3e10 and 1e10 doses have been taken forward.

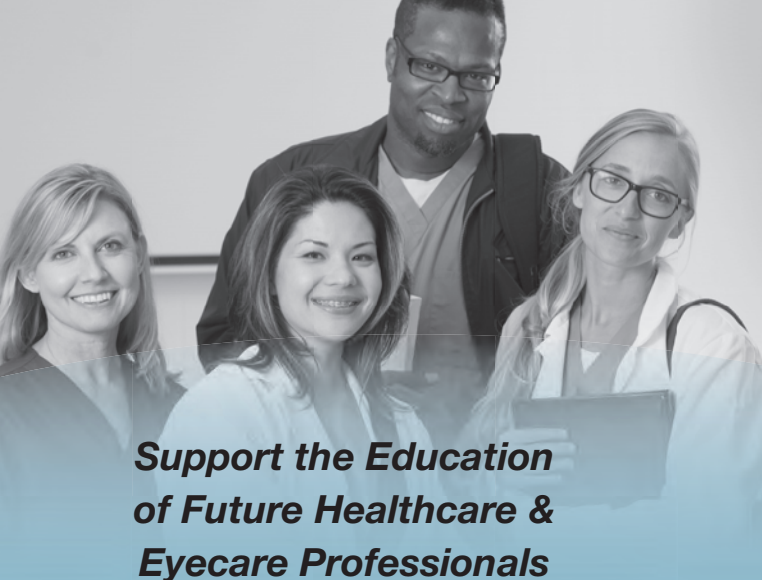
With **Arshad M. Khanani, MD, MA**



BIO

Dr. Khanani is managing partner, director of clinical research and fellowship director at Sierra Eye Associates in Reno, Nevada, and clinical associate professor at the University of Nevada, Reno School of Medicine.

DISCLOSURES: Dr. Khanani disclosed relevant relationships with 4D Molecular Therapeutics, Adverum Biotechnologies and Regenxbio.



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ABOUT RICK

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**CLINICAL
TRIAL
CLOSEUP**

Patients are randomized in 2:2:1 to one of those two doses or aflibercept injections every eight weeks. Fifty patients are enrolled in the dose-expansion phase. It's worth noting that patients received a 20-week prophylactic topical corticosteroid taper.

The primary endpoint is incidence and severity of adverse events. The secondary endpoints are reduction in annualized injection frequency, the need for supplemental aflibercept, and change in BCVA and CST from baseline.

Q What can you tell us about the latest readout from PRISM?


A Intravitreal 4D-150 was safe and very well-tolerated out to 36 weeks. No dose-related toxicities and no treatment-related SAEs were reported. Fourteen of 15 participants in Phase I/II had no intraocular inflammation. One patient had vitreous cells that resolved without treatment. No cases of hypotony or low intraocular pressures were reported.

We saw durable clinical activity in all three cohorts up to week 36, with up to an 81-percent reduction in the mean annualized injection frequency in the high-dose 3e10 group. The reduction in 1e10 was 64 percent and in 6e9 it was 77 percent. Four of five patients in the 3e10 cohort were injection-free, as were two of five in cohort two (1e10) and one of five in cohort three (6e9).

We've seen stable or improved BCVA and CST after treatment. These are previously heavily treated patients, so we don't expect them to have improvements in BCVA and CST after treatment with 4D-150.

Q Where potentially would this treatment fit in the retina-specialist toolbox?

A As a single in-clinic intravitreal gene therapy injection, it would be accessible to a large patient population. It appears to be safe so far and if that continues to be the case, we would be able to use this option broadly in patients after approval.

For patients who need frequent injections—monthly or every two months or even every three months—4D-150 could potentially help to eliminate the need for injections or decrease the burden. 

REFERENCE

1. Kay CN, et al. Interim results of the Phase 1/2 PRISM trial evaluating 4D-150, a dual-transgene intravitreal genetic medicine for neovascular (wet) age-related macular degeneration. Paper presented at American Society of Retina Specialist 41st annual scientific meeting; Seattle, WA; July 29, 2023.

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

SYF-PI-17Feb2023-1.0

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7/23 US-PEGGA-2200163 v3.0

SYFOVRE[®]

(pegcetacoplan injection)
15 mg / 0.1 mL

GA unravels so much
**SAVE RETINAL TISSUE
BY SLOWING
PROGRESSION**¹⁻³

**SYFOVRE achieved continuous reductions
in mean lesion growth rate* vs sham
pooled from baseline to Month 24^{1,4}**

Monthly	Every Other Month (EOM)
OAKS trial (mm ²): (3.11 vs 3.98) 22%	OAKS trial (mm ²): (3.26 vs 3.98) 18%
DERBY trial (mm ²): (3.28 vs 4.00) 18%	DERBY trial (mm ²): (3.31 vs 4.00) 17%

**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

The CMS-assigned permanent J-code for
SYFOVRE is J2781—effective 10/1/23¹

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

ADVERSE REACTIONS

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

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

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 (mm²) 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.

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