A PUBLICATION BY REVIEW of OPHTHALMOLOGY

RETINA® SPECIALIST

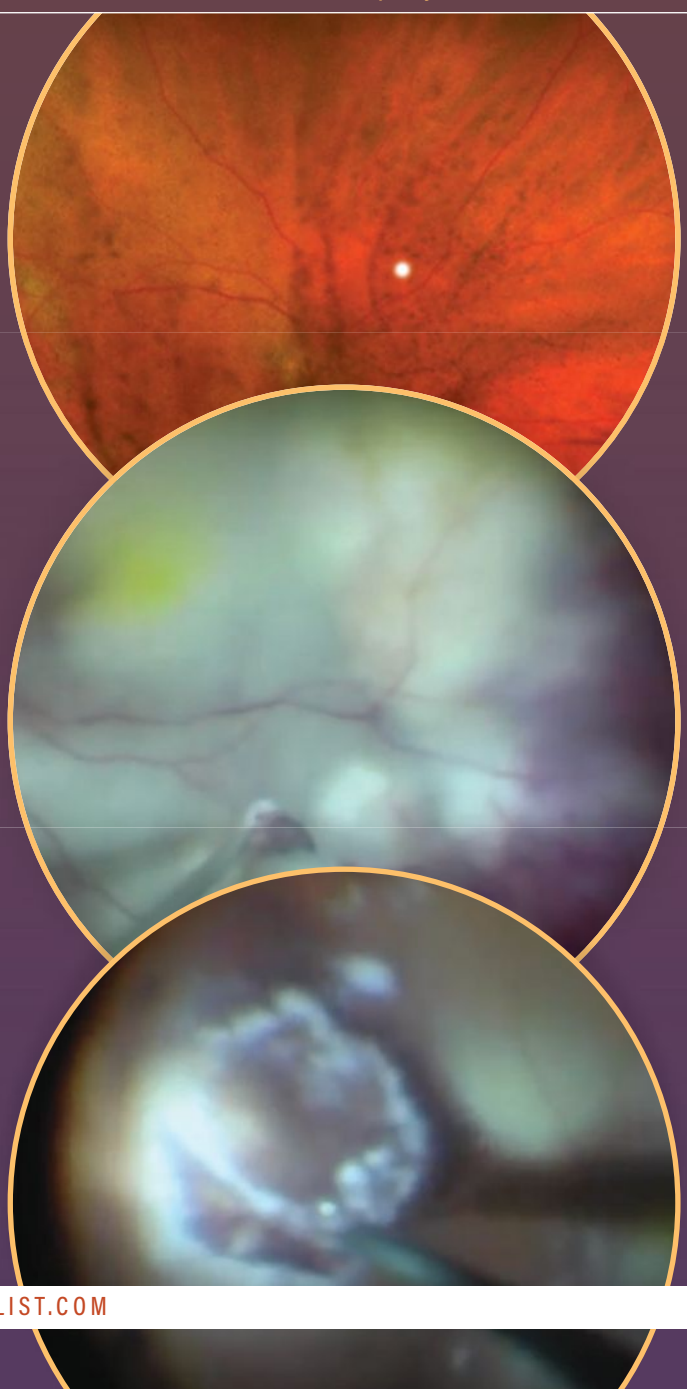
VOL. 9, NO. 3 · MAY/JUNE 2023

New Insights in Imaging

SOLVING THE MASQUERADE OF VITREORETINAL LYMPHOMA

A case-based review of biopsy techniques.

PAGE 21



Also Inside

Online Video

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

Discover continuous calm in uveitis[1]

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

- Proven to reduce uveitis recurrence at 6 and 12 months[1,*]
  At 6 months–18% for YUTIQ and 79% for sham for Study 1 and 22% for YUTIQ and 54% for sham for Study 2 (*P*<.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.

EYEPOINT® PHARMACEUTICALS

480 Pleasant Street, Suite B300, Watertown, MA 02472
02/2023
US-YUT-2300016

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

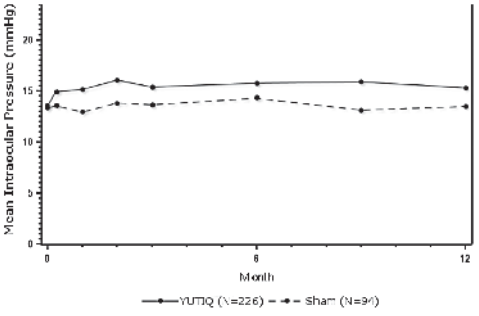
Ocular		
ADVERSE REACTIONS	**YUTIQ (N=226 Eyes) n (%)**	**Sham Injection (N=94 Eyes) n (%)**
Vitreous Hemorrhage	4 (2%)	0
Iridocyclitis	3 (1%)	7 (7%)
Eye Inflammation	3 (1%)	2 (2%)
Choroiditis	3 (1%)	1 (1%)
Eye Irritation	3 (1%)	1 (1%)
Visual Field Defect	3 (1%)	0
Lacrimation Increased	3 (1%)	0
Non-ocular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

Manufactured by:
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EDITORIAL

By Charles C. Wykoff, MD, PhD

Synthetic considerations

For nearly 20 years, we've managed wet AMD with anti-VEGF pharmacotherapies, successfully altering the epidemiology of irreversible blindness in many regions.

Along this road patients have noted, and we have documented, that a large proportion continue to experience progressive vision loss despite adequate exudative control. In many cases this is attributable to the atrophic manifestations of AMD. While unsatisfactory, these conversations used to be simple. "Yes, you are losing vision despite my injections; your wet AMD is well-controlled, but the dry component of the disease is progressing."

With commercial access to therapies that slow GA progression, that conversation must evolve. While I'm discussing GA treatments with many of my patients with wet AMD who have progressive macular atrophy, and using it in some, we have very limited data to guide our recommendations in this scenario.

Exudative AMD in the study eye, past or present, has been exclusionary for all GA trials to date. Fortunately, we have data that the complement inhibitors and anti-VEGF agents can be given safely concurrently to eyes that developed exudative AMD during the trials, but to date that represents only about 140 eyes between the pegcetacoplan and avacincaptad programs combined.

Is the progressive retinal atrophy observed in eyes with nAMD the same phenotype as GA, or is it the same in some eyes but not others? While many have opinions, we desperately need data to guide us. Unfortunately, such data are a long way off. No ongoing trials are incorporating both therapeutics from baseline.

Designing such trials, and most future GA trials for that matter, heralds a host of new challenges—maybe the most important being what control arm to employ. When a Food and Drug Administration-approved therapeutic for a given indication exists, when is it appropriate to use a sham control arm and when is it not?

Diabetic retinopathy pivotal trials have relied on sham control arms despite two FDA-approved agents to treat diabetic retinopathy, grounded on the popular belief that delaying treatment until eyes with nonproliferative DR develop diabetic macular edema or proliferative DR does not irreversibly harm them. (Of note: recent FDA feedback indicate this perspective may be shifting).

However, can the same logic apply to GA, which has an irreversible natural history? One fascinating possibility is the use of a synthetic control arm, a concept being actively applied in oncology but still in its infancy in retina. The idea is to harness large, real-world clinical datasets and use a detailed matching system to identify longitudinal control patients. Validating this approach will be challenging, but possible, especially with an anatomic rather than a functional endpoint. Quite likely, it could accelerate trials in GA and deserves close consideration. RS

Catch AMD Before It's Too Late.

Visible Genomics provides Risk and Progression assessments for Age-related Macular Degeneration (AMD) using patients genetic information and combines it with ocular findings, the patients demographic, and lifestyle risk factors.

- **71% of AMD is tied to genetics** vs. less than 50% for Breast and Colon cancer
- **Empower you and your patients** to make clinical and lifestyle decisions
- Personalize AMD Management based on your **Patient's Individual Risk**
- **Early Identification** of Advanced AMD Risk = Vision Preservation
- **Opportunity to secure** more patients through simple, but critical genetic risk testing

Don't take chances with your patients' vision. If they're over 40, they need to get tested for AMD now. Factors like family history, smoking, high UV exposure, and early symptoms increase their risk. Catching AMD early will save your patient's sight. Don't delay - take action today.

To learn more, contact us at:
Visible Genomics
sales@visiblegenomics.io

Visible GENOMICS

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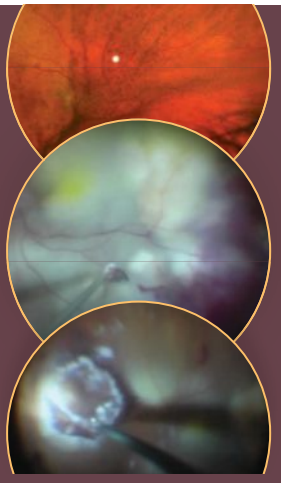
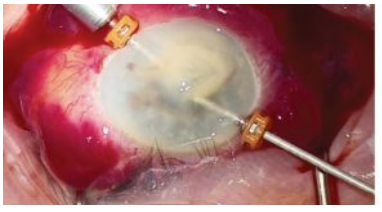
FEATURES

New Insights in Imaging



DEPARTMENTS



NOW APPROVED: the first and only FDA-approved treatment for GA secondary to AMD[1]

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]

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]

AMD=age-related macular degeneration; GA=geographic atrophy; SE=standard error.

Learn more about the SYFOVRE clinical data at SyfovreECP.com/efficacy

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 (mm^2) was measured by fundus autofluorescence (FAF).[1,4]

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

SYFOVRE™ (pegcetacoplan injection) 15 mg / 0.1 mL

Apellis

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

INDICATIONS AND USAGE

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

CONTRAINDICATIONS

Ocular or Periocular Infections

SYFOVRE is contraindicated in patients with ocular or periocular infections.

Active Intraocular Inflammation

SYFOVRE is contraindicated in patients with active intraocular inflammation.

WARNINGS AND PRECAUTIONS

Endophthalmitis and Retinal Detachments

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

Neovascular AMD

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

Intraocular Inflammation

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

Increased Intraocular Pressure

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

ADVERSE REACTIONS

Clinical Trials Experience

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

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

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

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

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

PM: SYFOVRE monthly; PEOM: SYFOVRE every other month

*The following reported terms were combined:

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

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

Punctate keratitis included: punctate keratitis, keratitis

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

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

USE IN SPECIFIC POPULATIONS

Pregnancy

Risk Summary

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

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

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

Lactation

Risk Summary

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

Females and Males of Reproductive Potential

Contraception

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

Pediatric Use

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

Geriatric Use

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

PATIENT COUNSELING INFORMATION

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

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

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

SYF-PI-17Feb2023-1.0

2/23 US-PEGGA-2200163 v2.0

Study reports potential of OCT to identify vascular damage in severe COVID-19

Optical coherence tomography may be a key diagnostic tool for evaluating vascular damage in severe COVID-19, according to the author of a small study that demonstrated OCT's potential to identify a biomarker in patients who've had severe COVID-19.

The cross-sectional study, published online in *Nature Scientific Reports*,[1] evaluated 61 eyes in 31 people who had no other comorbidities such as diabetes or heart disease—20 of whom had COVID-19 and 11 healthy controls used for comparison, senior study author William R. Freeman, MD, distinguished professor and director of the Jacobs Retina Center at the University of San Diego in La Jolla, Cailf., tells *Retina Specialist Magazine*.

The major implication of the study is more about understanding the etiology of COVID-19 and why some patients remain sick with it and less about how it impacts vision, Dr. Freeman says. OCT "may be a way to evaluate the damage that the virus has done to the blood vessels," he says.

"One of the mysteries of COVID-19 is, how does the virus damage all the organs in the body?" Dr. Freeman says. "People talk about long COVID, which is now becoming epidemic; people get COVID-19, but they don't fully recover and a lot of them are very disabled. How does it happen?"

Study results

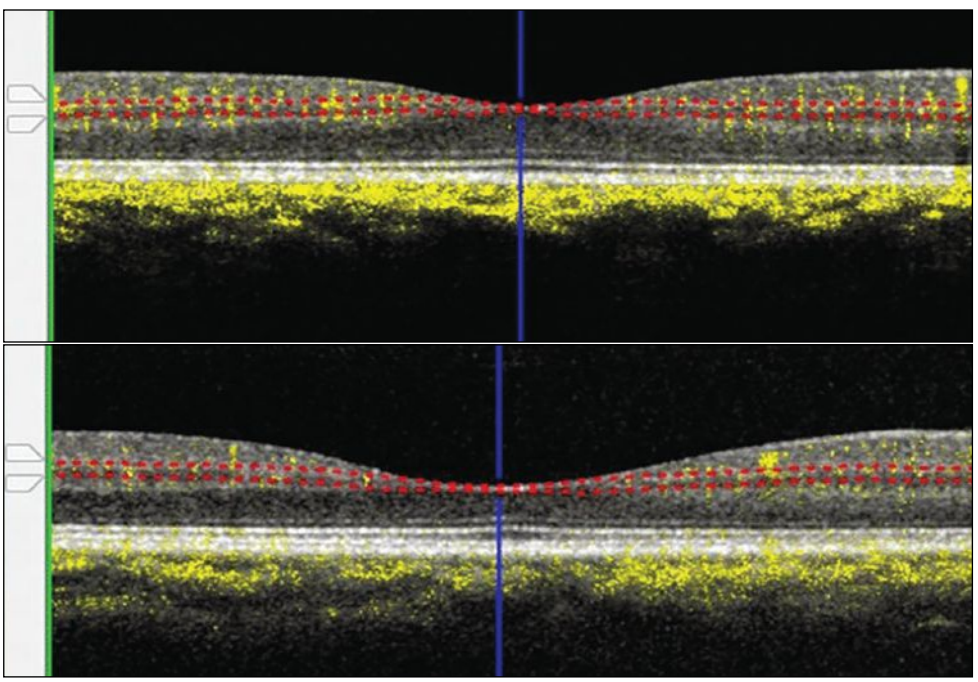
The study found that severe COVID-19 patients had significantly lower mean vessel density from the three inner retinal layers evaluated (24.20, least square mean) than mild COVID-19 patients (26.18, p=0.0057) and controls (26.28, p=0.004). Vessel density in mild COVID-19 patients didn't differ significantly from normal participants (p=0.87). The analysis used pooled data from the three measured inner retinal layers.

The severe COVID-19 patients demonstrated the following findings from the three specific measured retinal layers:

- Significantly decreased retinal volume in the outer 3 mm of the macula (p=0.02).
- Significantly lower total retinal vessel density (p=0.0004 and 0.0057 in controls and the mild COVID-19 group, respectively).
- Significantly lower intermediate (*Figure*) and deep capillary plexuses (p<0.05).

William R. Freeman, MD

"So it seems that it's not only a viral pneumonia that typically resolves, but the virus damages the blood vessels in many organs in the body," Dr. Freeman says. "In ophthalmology—in retina—we're able to visualize microscopic vessels, living vessels, measure



Representative optical coherence tomography images of the intermediate capillary plexus slab of a patient without COVID-19 (top) and one with severe COVID-19 demonstrate corresponding vessel densities of 33 and 18 percent, respectively. (Open access from Kalaw FGP, Warter A, Cavichini M, et al. Retinal tissue and microvasculature loss in COVID-19 infection. Sci Rep. 2023;13:5100. Published online March 29, 2023.)

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the blood flow into those vessels in living patients to an accuracy that's not possible anyplace else in the body."

That's because of OCT. The study patients had a comprehensive opthalmologic examination that included retinal imaging obtained from spectral-domain OCT and evaluation of retinal vessel density with OCT angiography.

OCT may solve the mystery

This may mean that ophthalmologists are uniquely positioned to evaluate COVID-19-related vascular changes, Dr. Freeman says.

He notes that pulmonologists have reported that COVID-19 causes vascular damage to the lungs and that multiple reports have been published of COVID-19 patients who've had reduced cognition. "That is felt to be potentially due to damage in the vessels in the brain," Dr. Freeman says.

However, there's no readily available way to image those vessels, he adds. "OCT may be a way to evaluate the damage that the virus has done to the blood vessels," he says. "The eye, and the retina, is a window into the brain and into the microcirculation everywhere."

What's unique about this study was that it enrolled only COVID-19 patients that had no previous comorbidities, Dr. Freeman says. "This is the first observation, I would stress: that with all the problems with the other studies, we eliminated the confounding problems," he says. "We believe the loss of the vessels in the retinal tissues is real. It's objectively seen on scans."

This doesn't mean that retinal changes brought on by COVID-19 impact visual acuity. "This is not causing visual symptoms because they're relatively small changes and there's a lot of redundancy in the retina. You can lose a few cells and you'll still see," he says.

"You're not going to go blind from this, but it is an objective marker. It's a scan that can be done on a nondilated patient and this may tell us who's likely to get long COVID and who will have COVID complications," Dr. Freeman says.

Future research should aim to repeat the study, he says. "This was a difficult study to do because you have to eliminate people with other underlying conditions."

Dr. Freeman has no relevant relationships to disclose.

– Richard Mark Kirkner

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IN BRIEF

The Food and Drug Administration approved **Mydcombi** (tropicamide/phenylephrine, **Eyenovia**) 1%/2.5% for inducing short-term mydriasis for diagnostic procedures. Mydcombi is the first drug approved using the **Optejet** device.

Endogena Therapeutics reports completing patient enrollment ahead of schedule in its Phase I/IIa trial **of EA-2353** for retinitis pigmentosa. The trial has enrolled 14 patients.

The FDA accepted the supplemental Biologics License Application for additional indication for **Vabysmo** (faricimab-svoa, **Genentech/Roche**): macular edema following retinal vein occlusion.

The FDA approved an Investigational New Drug application submitted by **Atsena Therapeutics** for a Phase I/II clinical trial of the gene therapy **ATSN-201** for X-linked retinoschisis.

The FDA granted Breakthrough Device Designation for the **Prima System** (**Pixium Vision**), a subretinal, miniature photovoltaic wireless implant, for dry age-related macular degeneration.

Slithering toward the fovea

How multimodal imaging aids in the crucial differentiation of serpiginous choroiditis from serpiginous-like choroiditis.

By Asad Durrani, MD, and Jason Hsu, MD

Asad Durrani, MD

Jason Hsu, MD

A 46-year-old male presented for second opinion of blurred vision in the left eye. The patient had an ocular history of poor vision in the right eye for many years. He had no relevant medical history.

Examination findings

The patient's visual acuity was counting fingers in the right eye and 20/25 in the left. Intraocular pressures were within normal limits in both eyes. Anterior segment examination was significant for trace nuclear sclerosis in both eyes. The anterior chamber and anterior vitreous were notably quiet bilaterally.

Fundus examination of the right eye (*Figure 1A*) demonstrated clear vitreous without vitritis. The optic nerve was flat with sharp margins. Circumpapillary and contiguous to the disc, there was a large helicoid area of chorioretinal atrophy with intermixed hyperpigmentation involving the entire macula. The vessels were of normal course and caliber without sheathing and the periphery was unremarkable.

Fundus examination of the left eye (*Figure 1B*) also demonstrated clear vitreous without vitritis. The optic nerve head was flat with sharp margins. Circumpapillary and contiguous to the disc was a helicoid area of chorioretinal atrophy, smaller than the right eye, with intermixed hyperpigmentation abutting, but not involving, the fovea.

The left eye also showed an area of hypopigmentation along the inferior arcade at the edge of chorioretinal atrophy in the left eye. The vessels were of normal course and caliber without sheathing and the periphery was unremarkable.

Imaging results

Optical coherence tomography of the macula showed preserved inner retinal laminations with large areas of outer retinal atrophy and retinal pigment epithelium migration the right eye (F*igure 2A, page 12*) and outer retinal atrophy in the nasal macula with preserved inner and outer retinal lamination subfoveally and in the temporal macula in the left eye (*Figure 2B, page 12*).

Fundus autofluorescence demonstrated dense hypoautofluorescence in the area of chorioretinal atrophy in the right eye (*Figure 3A, page 13*) and dense hypoautofluorescence in the area of chorioretinal atrophy with an adjacent area of hyperautofluorescence along the inferior arcade in the left eye (*Figure 3B, page 13*).

Fluorescein angiogram showed a large window defect in the area of chorioretinal atrophy with interspersed hypofluorescence

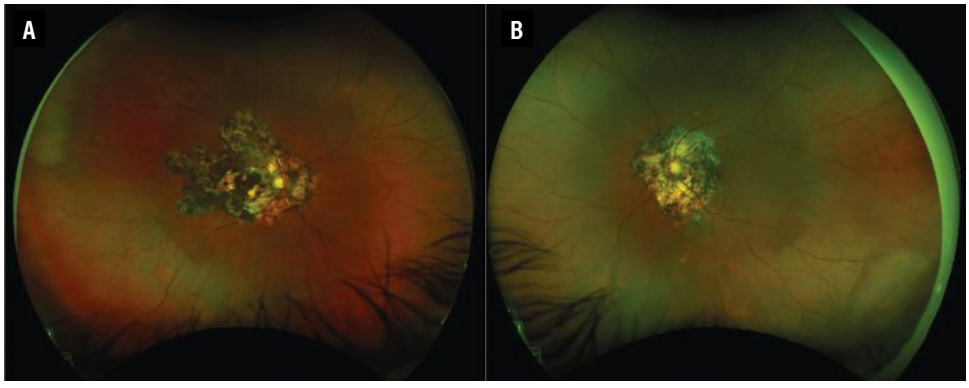

Figure 1. Pseudocolor fundus imaging demonstrates bilateral helicoid chorioretinal atrophy emanating from the disc.

BIO

Dr. Durrani is a first-year vitreoretinal surgery fellow at Mid Atlantic Retina/Wills Eye Hospital, Philadelphia.

Dr. Hsu is an attending physician at Mid Atlantic Retina and the Retina Service of Wills Eye Hospital.

DISCLOSURES: Dr. Durrani and **Dr. Hsu** have no relevant financial relationships to disclose.

from blockage due to hyperpigmentation and hyperfluorescence from the choroidal vasculature of the right eye (*Figure 4A*) and a similar pattern of fluorescence in the area of chorioretinal atrophy with an area of late leakage along the inferior arcade concerning for disease activity in the left eye (*Figure 4B*).

Additional history and diagnosis

Given the classic appearance, we obtained a limited laboratory work-up. A negative QuantiFERON Gold test ruled out serpiginous-*like* choroiditis. We diagnosed serpiginous choroiditis with an acute flare in the left eye. Another provider had already prescribed maintenance therapy with adalimumab (Humira, AbbVie) and mycophenolate, so we started high-dose oral steroids to manage his acute flare.

Serpiginous choroiditis

Serpiginous choroiditis is a bilateral chronic inflammatory disease of the RPE and choriocapillaris that often recurs despite appropriate treatment. This is a rare cause of posterior uveitis, estimated to cause less than 5 percent of all posterior uveitides.[1] The disease typically effects middle-aged adults without any gender predilection.[2]

The etiology of serpiginous choroiditis remains unknown. Proposed etiologies include an association with human leukocyte antigen (HLA)-B7, given the increased frequency of this HLA type in patients with serpiginous choroiditis, herpetic disease or an immune response to retinal S-antigen, a protein found in the membrane of the photoreceptor outer segments.[3]

Serpiginous choroiditis is often asymmetrical. Patients typically present with vision loss in one eye. The lesions in this disease start in the peripapillary region and spread in a helicoid or snake-like manner into the macula and mid-periphery. These lesions have a leading edge that, once resolved, leave chorioretinal atrophy with interspersed hypopigmentation and hyperpigmentation on funduscopic examination.

Vitreous inflammation is minimal or absent. Fundus autofluorescence and fluorescein angiography are helpful ancillary imaging modalities to assess disease activity at the atrophy margins.[4] OCT can help monitor for juxtafoveal or foveal involvement, which leads to rapid loss of visual acuity.

Differential diagnosis

The differential diagnosis includes serpiginous-like choroiditis, persistent placoid maculopathy, ampiginous choroiditis and acute multifocal posterior placoid pigment epitheliopathy.

It's crucial to differentiate serpiginous choroiditis from serpiginous-*like* choroiditis secondary to tuberculosis.[5] Serpiginous-like choroiditis tends to present with multifocal or placoid lesions in the posterior pole with vitritis and anterior chamber reaction.[6] Often, the lesions in serpiginous-like choroiditis aren't contiguous with the disc as in serpiginous choroiditis. Patients with serpiginous-like choroiditis secondary to tuberculosis require antituberculosis drug therapy. A QuantiFERON Gold test is mandatory before initiating steroid or immunosuppression therapy in cases of serpiginous choroiditis.

Treatment and long-term prognosis

The natural history of serpiginous choroiditis includes multiple recurrences with

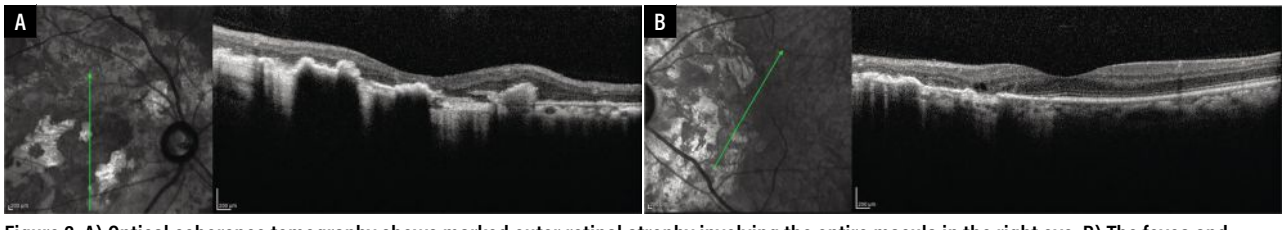

Figure 2. A) Optical coherence tomography shows marked outer retinal atrophy involving the entire macula in the right eye. B) The fovea and temporal macula in the left eye are spared.

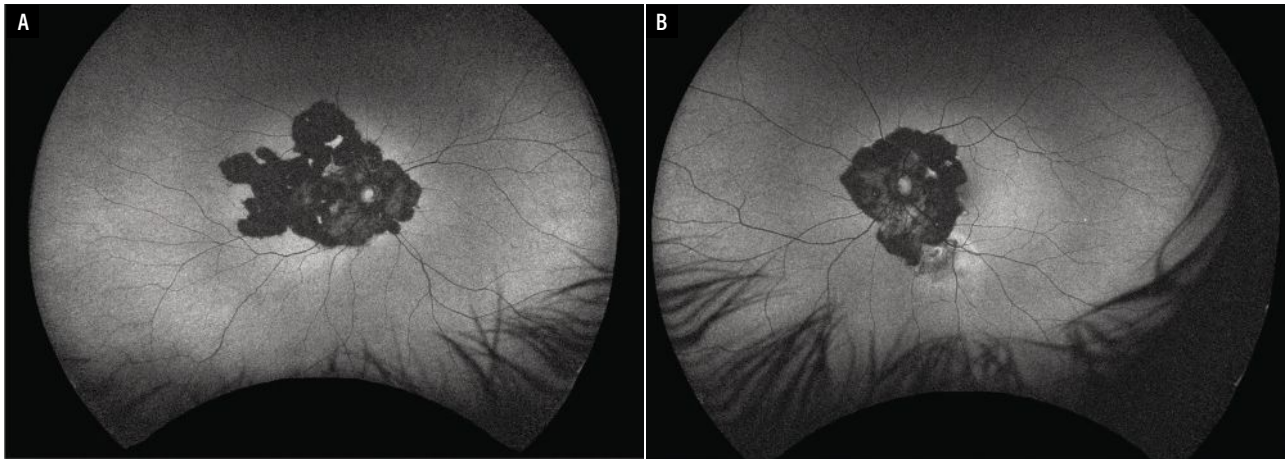

Figure 3. Fundus autofluorescence reveals dense hypofluorescence in both eyes with a leading edge of hyperfluorescence in the left eye (B) concerning for activity.

eventual foveal involvement. The mainstay of treatment involves immunosuppressive therapy with steroid-sparing agents to prevent vision loss.

No agreed-upon best treatment exists for this challenging disease. Multiple regimens have been proposed, including systemic steroids alone or systemic steroids combined with agents such as azathioprine, mycophenolate, cyclophosphamide, chlorambucil or anti-tumor necrosis factor (TNF) agents.[7-8] These agents have various side effects, ranging from mild to severe or life-threatening. For this reason, consultation with a rheumatologist is often recommended when treating this condition.

Systemic corticosteroids, periocular steroids and/or intravitreal steroids may be necessary to rapidly control the disease when it recurs or threatens the fovea. Despite aggressive immunosuppression, many patients will experience a decline in visual acuity due to eventual foveal involvement. A small number of patients also may experience vision loss due to secondary choroidal neovascular membrane formation.[9]

Bottom line

Serpiginous choroiditis is a rare cause of posterior uveitis characterized by bilateral inflammation of the retinal pigment epithelium and choriocapillaris that frequently recurs despite aggressive immunosuppression. The helicoid chorioretinal atrophy emanating from the optic nerve is characteristic of this disease. Fundus autofluorescence is an excellent imaging modality to monitor for recurrence. Rule out serpiginous-like choroiditis secondary to tuberculosis infection because the management of this related entity is antibiotic therapy. RS

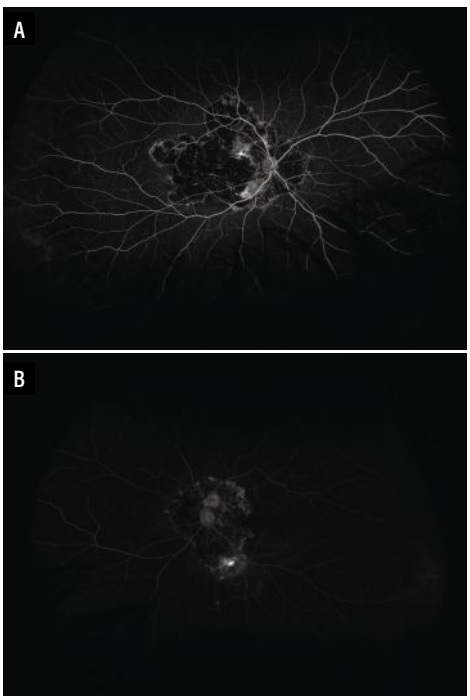

Figure 4. A) Fluorescein angiogram in the right eye showed a window defect with inactive choroiditis. B) The left eye demonstrated a window defect with an area of active leakage along the inferior arcade.

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Department Editor ***Akshay S. Thomas, MD, MS***

Birdshot chorioretinopathy: What's new

An update on diagnosis and treatment, including the role of multimodal imaging and combination therapy.

By Arman Mosenia, MD, MSE, and Eric Crowell, MD, MPH

Arman Mosenia, MD, MSE

Eric Crowell, MD, MPH

BIOS

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Dr. Crowell is an assistant professor of ophthalmology at Dell Medical School, clinical director of UT Health Austin's Mitchel and Shannon Wong Eye Institute and the Ascension Seton Network ophthalmology specialty service chief for Texas.

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DISCLOSURES: Dr. Mosenia and **Dr. Crowell** have no relevant disclosures.

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

Birdshot chorioretinopathy is a chronic, bilateral, posterior uveitis characterized by multifocal, cream-colored choroidal lesions in the posterior pole and mid-periphery at the level of retinal pigment epithelium or deeper layers.[1,2]

Birdshot chorioretinopathy (BSCR) is a T-cell mediated autoimmune disorder that's strongly associated with human leukocyte antigen (HLA) A29. More than 85 to 95 percent of affected patients test positive for this allele.[3–5] BSCR primarily affects individuals of northern European descent ages 40 to 60.6 years.

Patients typically present with floaters, flashes, loss of peripheral vision and nyctalopia. However, the most common chief complaint is decreased visual acuity.[6] Diagnosis can be delayed significantly because BSCR has vague symptomatology and an insidious early course with stable vision loss despite significant tissue loss. [7]

Diagnosis and monitoring

While BSCR is diagnosed clinically, examination findings, diagnostic testing and multimodal imaging all can play an important role in identifying patients who require further evaluation and monitoring of treatment.

Clinical findings

On exam, you can expect to find mild to no anterior chamber inflammation and no to moderate vitritis.[8] Retinal vascular leakage may be the only noticeable finding early on, while the characteristic multifocal, cream-colored or yellow-orange, oval or round lesions emerge from around the optic nerve later in the disease course (*Figure 1*).

Cystoid macular edema, vascular attenuation, subretinal neovascularization and optic nerve atrophy may accompany advance-stage BSCR.[9] Vision loss is more notable in later stages and correlates highly with macular edema or photoreceptor loss secondary to diffuse retinal damage.[9,10]

Visual acuity and fields

Studies have demonstrated a robust correlation between VA at disease onset and long-term visual prognosis, emphasizing the importance of prompt diagnosis and treatment of BSCR.[9]

Besides the symptoms described, patients can experience significant visual field defects despite well-preserved central VA, including diffuse constriction, paracentral scotomas and blind spot enlargement.[11]

Visual electrodiagnostic testing

Electrodiagnostic testing is one of the oldest diagnostic modalities of BSCR. In earlier stages of BSCR, testing may reveal a disproportionate decrease in B-wave amplitude relative to A-wave amplitude.

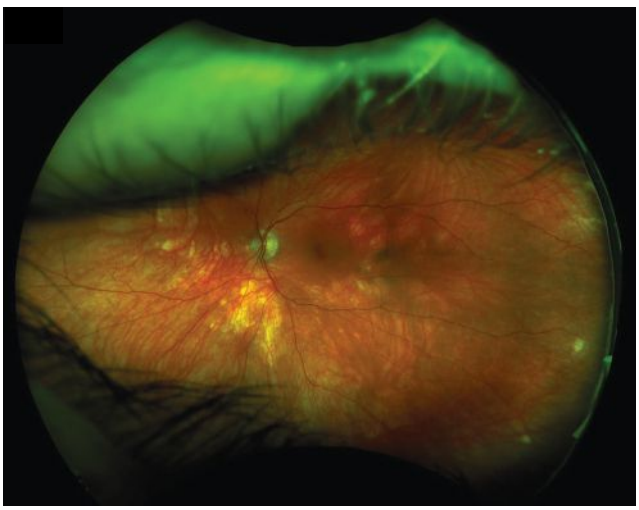


Figure 1. Fundus examination reveals creamy hypopigmented ovoid lesions in the peripapillary and midperipheral region.

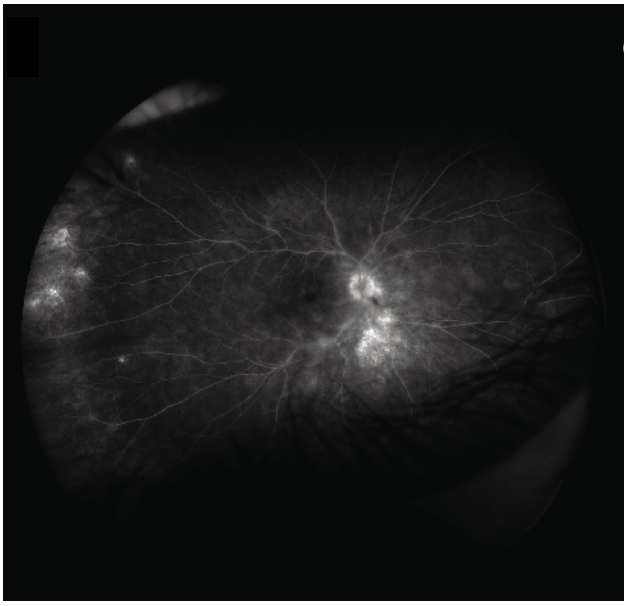


Figure 2. Fluorescein angiography demonstrates leakage of the retinal vessels and optic disc, along with angiographic macular edema.

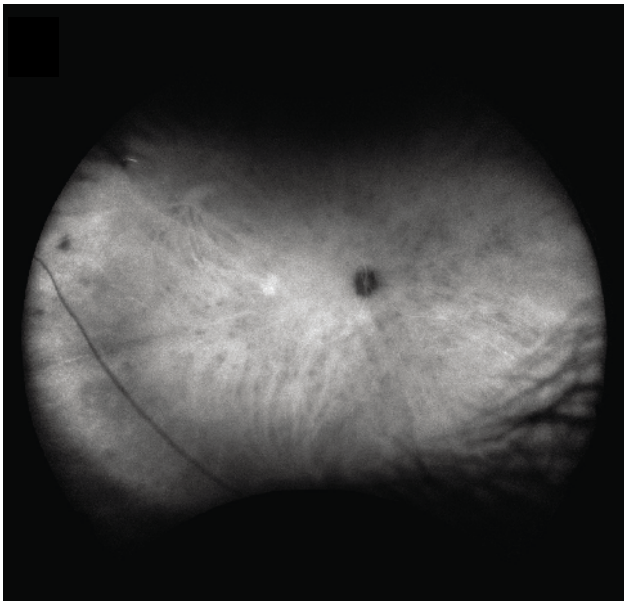


Figure 3. Indocyanine green angiography demonstrates hypofluorescent lesions throughout the choroid, some corresponding to the lesions seen on color fundus photography.

As the disease progresses, changes to the inner retinal function of the cone and rod systems present with a delayed cone mediated 30 Hz flicker on electroretinograms, which is the most sensitive electrodiagnostic test for assessing and monitoring BSCR.[12] Nevertheless, electrodiagnostic testing is time-consuming and isn't readily available in most clinics.

Multimodal imaging

Small birdshot lesions represent areas of focal inflammation and cause abnormalities on various types of imaging, which can be monitored over time. Fluorescein angiography is the gold-standard imaging study for evaluating vascular abnormalities, including vascular leakage or hypoperfusion (*Figure 2*).[13] Additionally, FA may reveal macular edema and hyperfluorescent choroidal lesions.

Indocyanine green angiography is more sensitive than FA and fundoscopy in revealing choroidal lesions (*Figure 3*), especially early in the disease course.[14] Optical coherence tomography provides a less-invasive alternative for monitoring BSCR.

In addition to revealing the choroidal lesions and macular edema, it can be used to quantify retinal thinning and loss of the third highly reflective band, both of which have been associated with worse visual outcomes.[13,15]

The highly reflective band is a linear band found at the photoreceptor level. OCT angiography can identify abnormal flow signals, similar to those seen on ICGA.[16] Hyporeflectivity in the macular and peripapillary regions on enhanced-depth OCT, which enables the analysis of deeper choroidal levels, is another common finding in BSCR; it has been reported in up to 64 percent of patients.[17]

More recently, retina specialists have used FA to reveal important information about retinal health in BSCR. Particularly, peripapillary confluent hypoautofluorescence is shown to be present in 73 percent of eyes and is associated with chronicity and severity of BSCR.[18] Authors have also reported linear hypoautofluorescence streaks along the retinal vessels and an arcuate pattern of hypoautofluorescence at the posterior pole.[18,19]

Monitoring treatment

Imaging and diagnostic tools are also valuable in the treatment and monitoring of BSCR. They facilitate treatment decisions, such as determining the need to escalate or de-escalate care.

Corticosteroids are the mainstay initial treatment in BSCR. Immunosuppressive therapy, in combination with steroids, has advantages in preserving visual function and reducing the adverse effects associated with high-dose corticosteroids compared with corticosteroid therapy alone.[20]

Calcineurin inhibitors, which inhibit T-cell signaling, and antimetabolites are typically the first immunosuppressive treatments clinicians consider. Mycophenolate mofetil has been shown to be more effective compared to other antimetabolites in treating posterior uveitis and panuveitis.[21] However, a randomized clinical trial of methotrexate and mycophenolate mofetil revealed statistically insignificant higher treatment success in methotrexate for posterior and panuveitis in general.[22]

Stepping up to biologics

In most patients who respond to concomitant immunosuppressive therapy, corticosteroids can be successfully tapered and possibly discontinued.[23] However, if patients don't respond to conventional immunosuppressive therapies, then stepping up to biologics is indicated.

Tumor necrosis factor (TNF)-alpha inhibitors, such as infliximab (Remicade, Janssen) and adalimumab (Humira, AbbVie), have been reported to be effective in treating some forms of refractory uveitis, including BSCR.[24–26]

Patients treated with adalimumab demonstrated VA improvement and had successful tapering of concomitant immunosuppressive therapy. However, complete disease remission with adalimumab alone can be challenging.[26] Some authors have reported successful use of other classes of biologics, but current evidence for their use in BSCR is limited.[27]

If patients don't respond to immunosuppressive therapies, stepping up to biologics is indicated. TNF-alpha inhibitors, such as infliximab and adalimumab, have been effective in treating some forms of refractory uveitis.

Localized steroid administration

Local steroid injections are often indicted in patients who have persistent macular edema despite systemic therapy. In patients who can't tolerate or don't respond adequately to systemic therapy, local therapy with intravitreal corticosteroid implants can be a viable option. The intravitreal 0.59 mg fluocinolone implant (Retisert, Bausch + Lomb) is a well-described treatment for uveitis. It exerts its effect locally and may spare the side effects of systemic immunosuppression.

Based on the Multicenter Uveitis Steroid Treatment (MUST) trial, patients with uveitis who receive systemic therapy and intravitreal implants have similar visual outcomes for up to 4.5 years of treatment.[28] However, after seven years, systemic therapy was associated with better visual outcomes.[29]

In BSCR particularly, steroid implants have been associated with an intraocular pressure response more robust than seen in patients with other types of uveitis. Up to 40 percent of patients can need filtering surgery, and all of them will need to undergo cataract surgery.[30,31]

Long-term treatment and outcomes

Treatment success with immunosuppression after one year of therapy has been reported at 67 to 90 percent.[23] Single- or dual-agent immunosuppression has been successfully used to control BSCR while sparing steroid use to minimize systemic side effects. Steroid sparing, defined as successfully tapering the prednisone dose to ≤ 7.5 mg, is generally considered safe for long-term use and can be achieved within six months.

One recent study suggested that up to 90 percent of patients with BSCR can achieve steroid sparing, and as many as 75 percent can completely discontinue steroid use.[23] However, more than 40 percent of patients can have reactivation of BSCR during tapering, requiring the use of a second immunosuppressive therapy.

(Continued on page 18)

Two-trocar approach to endophthalmitis

A minimalist technique for enhancing surgical outcomes for acute endophthalmitis in pseudophakic eyes.

By Miguel Cruz-Pimentel, MD, and Efrem D Mandelcorn, MD, FRCSC

Miguel Cruz-Pimentel, MD

Efrem D. Mandelcorn, MD, FRCSC

Patients with endophthalmitis can have a poor outcome after pars plana vitrectomy, particularly when the vitreous cavity has been manipulated significantly. Minimal vitrectomy[1] is recommended to prevent further complications, such as surgically induced necrotizing scleritis[2,3] and scleral abscess.[4]

In pseudophakic eyes where the anterior chamber is filled with debris, we recommend using a minimalist two-trocar approach. This technique starts by placing two trocars in the anterior chamber. The first trocar is placed for the infusion line after the infusion that can be opened under direct visualization.

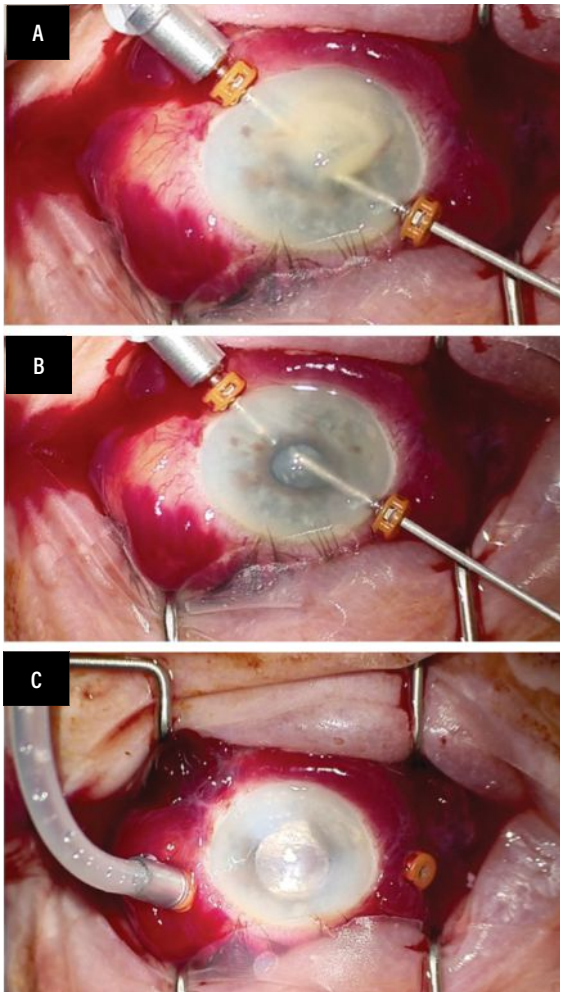
The second trocar cannula is placed in the anterior chamber through which the vitrector is placed to remove the anterior chamber plaque and to collect a first sample for culture and sensitivity (*Figure A*).

By placing the infusion in the anterior chamber, you can avoid complications from the infusion placement through the pars plana, which include infusion-induced choroidal detachments, particularly given the poor visibility in these cases.

Placing the two trocars

Once the view improves from the anterior chamber washout, two trocars are placed in the superior quadrants to start the posterior vitrectomy in order to collect a second sample from the mid-vitreous cavity.

After this, a core vitrectomy is undertaken. Once there's a clear view of the posterior pole, the vitrectomy can be stopped (*Figure B*).



The two-trocar approach. A) The first is used for the infusion line, the second to introduce the vitrector after it's inserted into the anterior chamber to clean the debris and to collect a first sample for culture and sensitivity. B) Stop the vitrectomy when you get a clear view of the posterior pole. C) Leaving the vitreous cavity filled with 50-50 air and balanced salt solution will ensure the two superior sclerotomies close appropriately and keep the intravitreal antibiotics in the vitreous cavity away from the trocars.

View the Video

Drs. Cruz-Pimentel and Mandelcorn demonstrate their two-trocar approach to treating endopthalmitis in pseudophakic eyes. Available at: bit.ly/VideoPearl-34

BIOS

Dr. Cruz-Pimentel is a vitreoretinal fellow at the University of Toronto.

Dr. Mandelcorn is an associate professor of ophthalmology at the University of Toronto.

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

DISCLOSURES: The authors and **Dr. Felfeli** have no relevant relationships to disclose.

The posterior pole membrane peeling or peripheral vitreous shave is deliberately avoided, given the high risk of retinal tear and detachment in these cases. The infusion line can be removed from the anterior chamber trocar and then placed via the pars plana in the superior temporal quadrant trocar. A partial air-fluid exchange can be done, leaving the vitreous cavity filled with 50 percent air and 50 percent balanced salt solution. Intravitreal antibiotics are then injected in the vitreous cavity.

Leaving the vitreous cavity filled with 50-50 air and BSS will ensure that the two superior sclerotomies close well. At the same time, it will keep the intravitreal antibiotics into the vitreous cavity away from the trocars, preventing any efflux of these medications through the sclerotomies. This step will ensure you administer the full dose and that nothing escapes through the trocars (*Figure C, page 17*).

Bottom line

The minimalist two-trocar approach can avoid complications in pseudophakic eyes with endophthalmitis, such as spreading the infection toward the sclera, causing surgically induced scleritis, scleral abscess and choroidal effusion from placing the infusion into the suprachoroidal space in cases of thick choroid. RS

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Birdshot chorioretinopathy: What's new

(Continued from page 16)

Once steroid tapering happens, it may be necessary to continue treatment with higher-dose immunosuppressive therapy for at least two years before tapering the immunosuppressive agents to decrease the risk of relapse after remission.[23]

Bottom line

Diagnosing BSCR can be challenging because of its gradual onset and ambiguous symptoms. Several diagnostic methods and imaging techniques exist for the treatment of BSCR, each with its own set of benefits and drawbacks at different stages of the illness.

Treatment involves a combination of oral steroids and immunosuppressive therapy to address inflammation, with most patients successfully reducing steroid use over time. Effective management of BSCR requires ongoing monitoring, even after the patient has successfully stopped immunosuppression therapy. RS

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Start With EYLEA From the First Injection in Wet AMD

EYLEA® (aflibercept) Injection For Intravitreal Injection

Demonstrated maintenance of vision

- **≈95% of patients maintained their vision** (<15 ETDRS letters lost) with EYLEA at Year 1 (primary endpoint)[1]
  – VIEW 1 (n=605); VIEW 2 (n=615)[1,*]

Effective regardless of fluid status

- Vision outcomes in patients **with and without early persistent fluid** (*post hoc* subgroup analysis)[3,†]

Long-term vision outcomes

- EYLEA maintained **+7.1 letters of BCVA gain at Year 4** in the VIEW 1 extension study (n=323)[2]

Broad national coverage

- 75% of lives have access to EYLEA first line, covering **239 million lives nationwide**[4,‡]

When You See Wet AMD, Consider EYLEA First Line

LEARN MORE at hcp.eylea.us

VIEW 1 and VIEW 2 Clinical Trial Designs: Two multicenter, double-masked clinical studies in which patients with Wet AMD (N=2412; age range: 49-99 years, with a mean of 76 years) were randomized to receive: 1) EYLEA 2 mg Q8W following 3 initial monthly doses; 2) EYLEA 2 mg Q4W; 3) EYLEA 0.5 mg Q4W [not an approved dose]; or 4) ranibizumab 0.5 mg Q4W. Protocol-specified visits occurred every 28 (±3) days. In both studies, the primary efficacy endpoint was the proportion of patients with Wet AMD who maintained vision, defined as losing <15 letters of visual acuity at Week 52, compared with baseline.[1]

VIEW 1 Extension Clinical Trial Design: Prospective, open-label, single-arm, multicenter, long-term safety and tolerability study of patients who completed VIEW 1 through Week 96 (n=323; mean age: 79 years). All patients received EYLEA 2 mg on a modified quarterly dosing schedule (maximum treatment interval: Q12W) that was later amended to dosing at least Q8W through Week 212. The primary endpoint was the safety and tolerability of EYLEA.[3]

*Includes patients from both EYLEA Q4W and Q8W treatment arms. EYLEA was clinically equivalent to ranibizumab.

†Early persistent fluid (intraretinal [cystic] or subretinal) was defined as presence of fluid at the first 4 visits (baseline, Week 4, Week 8, and Week 12) after having received 3 initial monthly injections (baseline, Week 4, and Week 8) as seen on TD-OCT.

‡Data represent payers across the following channels as of January 2023: Medicare Part B, Commercial, Medicare Advantage, and VA. Individual patient coverage is subject to patient's specific plan.

IMPORTANT SAFETY INFORMATION

CONTRAINDICATIONS

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

WARNINGS AND PRECAUTIONS

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

ADVERSE REACTIONS

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

INDICATIONS

EYLEA® (aflibercept) Injection 2 mg (0.05 mL) is indicated for the treatment of patients with Neovascular (Wet) Age-related Macular Degeneration (AMD), Macular Edema following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), and Diabetic Retinopathy (DR).

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. February 2023. **2.** Kaiser PK, Singer M, Tolentino M, et al. Long-term safety and visual outcome of intravitreal aflibercept in neovascular age-related macular degeneration: VIEW 1 extension study. *Ophthalmol Retina*. 2017;1(4):304-313. doi:10.1016/j.oret.2017.01.004 **3.** Jaffe GJ, Kaiser PK, Thompson D, et al. Differential response to anti-VEGF regimens in age-related macular degeneration patients with early persistent retinal fluid. *Ophthalmology*. 2016;123(9):1856-1864. doi:10.1016/j.ophtha.2016.05.016 **4.** Data on file. Regeneron Pharmaceuticals, Inc.

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4W, every 4 weeks; Q8W, every 8 weeks; Q12W, every 12 weeks; TD-OCT, time domain–optical coherence tomography.

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EYLEA®
(aflibercept) Injection
For Intravitreal Injection

BRIEF SUMMARY—Please see the EYLEA full Prescribing Information available on HCP.EYLEA.US for additional product information.

1 INDICATIONS AND USAGE
EYLEA is a vascular endothelial growth factor (VEGF) inhibitor indicated for the treatment of patients with:

Neovascular (Wet) Age-Related Macular Degeneration (AMD), Macular Edema Following Retinal Vein Occlusion (RVO), Diabetic Macular Edema (DME), Diabetic Retinopathy (DR).

4 CONTRAINDICATIONS

4.1 Ocular or Periocular Infections
EYLEA is contraindicated in patients with ocular or periocular infections.

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

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

5 WARNINGS AND PRECAUTIONS

5.1 Endophthalmitis and Retinal Detachments
Intravitreal injections, including those with EYLEA, have been associated with endophthalmitis and retinal detachments [*see Adverse Reactions (6.1)*]. Proper aseptic injection technique must always be used when administering EYLEA. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay and should be managed appropriately [*see Patient Counseling Information (17)*].

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

5.4 Thromboembolic Events
There is a potential risk of arterial thromboembolic events (ATEs) following intravitreal use of VEGF inhibitors, including EYLEA. ATEs are defined as nonfatal stroke, nonfatal myocardial infarction, or vascular death (including deaths of unknown cause). The incidence of reported thromboembolic events in wet AMD studies during the first year was 1.8% (32 out of 1824) in the combined group of patients treated with EYLEA compared with 1.5% (9 out of 595) in patients treated with ranibizumab; through 96 weeks, the incidence was 3.3% (60 out of 1824) in the EYLEA group compared with 3.2% (19 out of 595) in the ranibizumab group. The incidence in the DME studies from baseline to week 52 was 3.3% (19 out of 578) in the combined group of patients treated with EYLEA compared with 2.8% (8 out of 287) in the control group; from baseline to week 100, the incidence was 6.4% (37 out of 578) in the combined group of patients treated with EYLEA compared with 4.2% (12 out of 287) in the control group. There were no reported thromboembolic events in the patients treated with EYLEA in the first six months of the RVO studies.

6 ADVERSE REACTIONS
The following potentially serious adverse reactions are described elsewhere in the labeling:
- Hypersensitivity [*see Contraindications (4.3)*]
- Endophthalmitis and retinal detachments [*see Warnings and Precautions (5.1)*]
- Increase in intraocular pressure [*see Warnings and Precautions (5.2)*]
- Thromboembolic events [*see Warnings and Precautions (5.4)*]

6.1 Clinical Trials Experience
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in other clinical trials of the same or another drug and may not reflect the rates observed in practice.
A total of 2980 adult patients treated with EYLEA constituted the safety population in eight phase 3 studies. Among those, 2379 patients were treated with the recommended dose of 2 mg. Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment. The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

Neovascular (Wet) Age-Related Macular Degeneration (AMD). The data described below reflect exposure to EYLEA in 1824 patients with wet AMD, including 1223 patients treated with the 2-mg dose, in 2 double-masked, controlled clinical studies (VIEW1 and VIEW2) for 24 months (with active control in year 1).
Safety data observed in the EYLEA group in a 52-week, double-masked, Phase 2 study were consistent with these results.

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

	Baseline to Week 52		Baseline to Week 96	
Adverse Reactions	**EYLEA (N=1824)**	**Active Control (ranibizumab) (N=595)**	**EYLEA (N=1824)**	**Control (ranibizumab) (N=595)**
Conjunctival hemorrhage	25%	28%	27%	30%
Eye pain	9%	9%	10%	10%
Cataract	7%	7%	13%	10%
Vitreous detachment	6%	6%	8%	8%
Vitreous floaters	6%	7%	8%	10%
Intraocular pressure increased	5%	7%	7%	11%
Ocular hyperemia	4%	8%	5%	10%
Corneal epithelium defect	4%	5%	5%	6%
Detachment of the retinal pigment epithelium	3%	3%	5%	5%
Injection site pain	3%	3%	3%	4%
Foreign body sensation in eyes	3%	4%	4%	4%
Lacrimation increased	3%	1%	4%	2%
Vision blurred	2%	2%	4%	3%
Intraocular inflammation	2%	3%	3%	4%
Retinal pigment epithelium tear	2%	1%	2%	2%
Injection site hemorrhage	1%	2%	2%	2%
Eyelid edema	1%	2%	2%	3%
Corneal edema	1%	1%	1%	1%
Retinal detachment	<1%	<1%	1%	1%

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

Macular Edema Following Retinal Vein Occlusion (RVO). The data described below reflect 6 months exposure to EYLEA with a monthly 2 mg dose in 218 patients following central retinal vein occlusion (CRVO) in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following branch retinal vein occlusion (BRVO) in one clinical study (VIBRANT).

Table 2: Most Common Adverse Reactions (≥1%) in RVO Studies

	CRVO		BRVO	
Adverse Reactions	**EYLEA (N=218)**	**Control (N=142)**	**EYLEA (N=91)**	**Control (N=92)**
Eye pain	13%	5%	4%	5%
Conjunctival hemorrhage	12%	11%	20%	4%
Intraocular pressure increased	8%	6%	2%	0%
Corneal epithelium defect	5%	4%	2%	0%
Vitreous floaters	5%	1%	1%	0%
Ocular hyperemia	5%	3%	2%	2%
Foreign body sensation in eyes	3%	5%	3%	0%
Vitreous detachment	3%	4%	2%	0%
Lacrimation increased	3%	4%	3%	0%
Injection site pain	3%	1%	1%	0%
Vision blurred	1%	<1%	1%	1%
Intraocular inflammation	1%	1%	0%	0%
Cataract	<1%	1%	5%	0%
Eyelid edema	<1%	1%	1%	0%

Less common adverse reactions reported in <1% of the patients treated with EYLEA in the CRVO studies were corneal edema, retinal tear, hypersensitivity, and endophthalmitis.

Diabetic Macular Edema (DME) and Diabetic Retinopathy (DR). The data described below reflect exposure to EYLEA in 578 patients with DME treated with the 2-mg dose in 2 double-masked, controlled clinical studies (VIVID and VISTA) from baseline to week 52 and from baseline to week 100.

Table 3: Most Common Adverse Reactions (≥1%) in DME Studies

	Baseline to Week 52		Baseline to Week 100	
Adverse Reactions	**EYLEA (N=578)**	**Control (N=287)**	**EYLEA (N=578)**	**Control (N=287)**
Conjunctival hemorrhage	28%	17%	31%	21%
Eye pain	9%	6%	11%	9%
Cataract	8%	9%	19%	17%
Vitreous floaters	6%	3%	8%	6%
Corneal epithelium defect	5%	3%	7%	5%
Intraocular pressure increased	5%	3%	9%	5%
Ocular hyperemia	5%	6%	5%	6%
Vitreous detachment	3%	3%	8%	6%
Foreign body sensation in eyes	3%	3%	3%	3%
Lacrimation increased	3%	2%	4%	2%
Vision blurred	2%	2%	3%	4%
Intraocular inflammation	2%	<1%	3%	1%
Injection site pain	2%	<1%	2%	<1%
Eyelid edema	<1%	1%	2%	1%

Less common adverse reactions reported in <1% of the patients treated with EYLEA were hypersensitivity, retinal detachment, retinal tear, corneal edema, and injection site hemorrhage.
Safety data observed in 269 patients with nonproliferative diabetic retinopathy (NPDR) through week 52 in the PANORAMA trial were consistent with those seen in the phase 3 VIVID and VISTA trials (see Table 3 above).

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy
Risk Summary
Adequate and well-controlled studies with EYLEA have not been conducted in pregnant women. Aflibercept produced adverse embryofetal effects in rabbits, including external, visceral, and skeletal malformations. A fetal No Observed Adverse Effect Level (NOAEL) was not identified. At the lowest dose shown to produce adverse embryofetal effects, systemic exposures (based on AUC for free aflibercept) were approximately 6 times higher than AUC values observed in humans after a single intravitreal treatment at the recommended clinical dose [*see Animal Data*].
Animal reproduction studies are not always predictive of human response, and it is not known whether EYLEA can cause fetal harm when administered to a pregnant woman. Based on the anti-VEGF mechanism of action for aflibercept, treatment with EYLEA may pose a risk to human embryofetal development. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
All pregnancies have a background risk of birth defect, loss, or other adverse outcomes. The background risk of major birth defects and miscarriage for the indicated population is unknown. In the U.S. general population, the estimated background risk of major birth defects and miscarriage in clinically recognized pregnancies is 2-4% and 15-20%, respectively.

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

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

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

Infertility
There are no data regarding the effects of EYLEA on human fertility. Aflibercept adversely affected female and male reproductive systems in cynomolgus monkeys when administered by intravenous injection at a dose approximately 1500 times higher than the systemic level observed in adult patients with an intravitreal dose of 2 mg. A No Observed Adverse Effect Level (NOAEL) was not identified. These findings were reversible within 20 weeks after cessation of treatment.

8.4 Pediatric Use
The safety and effectiveness of EYLEA have been demonstrated in two clinical studies of pre-term infants with ROP. These two studies randomized pre-term infants between initial treatment with EYLEA or laser. Efficacy of each treatment is supported by the demonstration of a clinical course which was better than would have been expected without treatment.

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

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

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

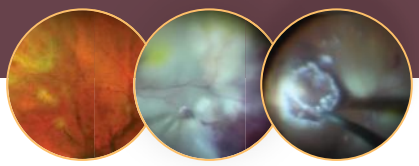
REGENERON®

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

Issue Date: 02/2023
Initial U.S. Approval: 2011

Based on the February 2023 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.23.02.0006



New Insights in Imaging

Solving the masquerade of vitreoretinal lymphoma

A case-based review of biopsy techniques from vitreous sampling to more invasive approaches.

By Abel Hamdan, MD, Danny A. Mammo, MD, Sunil K. Srivastava, MD and Sumit Sharma, MD

Take-home points

- As a masquerade syndrome, vitreoretinal lymphoma presents multiple diagnostic challenges, including atypical clinical presentations, which may include a misleading initial response to steroids and false-negative biopsies.
- Definitive diagnosis allows for targeted therapy. Vitreoretinal surgeons have several methods available to them to acquire diagnostic tissue, including vitreous biopsies, fine needle aspiration biopsies, retinal/subretinal biopsies and sequencing technologies.
- Retinal and subretinal pigment epithelium biopsies are more likely to provide a definitive diagnosis and retinal specialists should consider them during the initial diagnostic procedures in highly suspicious cases.
- Adjunct multimodal imaging and an effective collaboration with cytopathology can't be overemphasized to maximize diagnostic yield.

Vitreoretinal lymphoma presents multiple diagnostic challenges because of its atypical clinical presentation, which may include misleading initial response to steroids and false-negative biopsies. As a masquerade syndrome, vitreoretinal lymphoma requires a high suspicion and reliance on good cytopathology for a definitive diagnosis.

Clinicians have historically used vitreous biopsies and fine-needle aspiration biopsies (FNAB) to diagnose inflammatory, neoplastic or infectious ocular diseases in the posterior segment because these methods provide good accessibility and a low likelihood of complications.[1-8]

Nonetheless, when vitreous sampling or FNAB is inconclusive, more invasive techniques, such as retinal or subretinal pigment epithelium biopsies, may be warranted. Here, we present two cases that demonstrate the utility of these techniques.

Case 1: Worsening floaters and dry AMD

A general ophthalmologist saw an 82-year-old White phakic male for chronic worsening floaters in both eyes. His ocular history included non-neovascular age-related macular degeneration in both eyes and a right posterior vitreous detachment. His medical history was significant for prostate cancer status post-radiation and resection.

Visual acuity on initial presentation was 20/30 OU. The slit lamp exam demonstrated no anterior chamber or vitreous cells. Optical coherence tomography imaging at this time demonstrated drusen and rare subretinal deposits we interpreted to be consistent with drusen.

The patient had subsequent cataract surgery in the right eye. While on a topical steroid taper during the postoperative course, he was referred to the retina service for new white lesions in the right eye.

Decline in VA. Visual acuity declined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BIOS

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DISCLOSURES

Dr. Hamdan has no relevant relationships to disclose.

Dr. Mammo served on an advisory board for Alimera Sciences.

Dr. Srivastava disclosed relationships with Bausch + Lomb, Regeneron Pharmaceuticals, Novartis, jCyte, Adverum Biotechnologies, Zeiss, EyePoint Pharmaceuticals and Eyevensys.

Dr. Sharma disclosed relationships with Allergan/AbbVie, EyePoint, Clearside Biomedical, Bausch + Lomb, Genentech/Roche, Regeneron, RegenxBio, Apellis IONIS, Santen and Gilead.

rapidly from 20/50 to 20/500 within two weeks. Slit lamp and fundus examinations were significant for 3+ vitreous cell OD in clumps/sheets with superotemporal retinal whitening and elevation (*Figure 1A*). OCT demonstrated RPE thickening and hyperreflective subretinal infiltrates (*Figure 1B*). Inflammatory and infectious lab workups were unremarkable. A brain MRI showed no lesions.

A diagnostic pars plana vitrectomy was performed with only vitreous biopsy. Cytology and flow cytometry revealed no malignant cells. However, suspicion remained high for vitreoretinal lymphoma.

Neurological symptoms worsen. A full-thickness retinal biopsy was scheduled, although before the patient returned to the operating room, he developed worsening neurological symptoms and was admitted, whereupon a new brain MRI (just two weeks after the prior) demonstrated multifocal areas of bilateral signal abnormality suspicious for primary CNS lymphoma.

Lumbar puncture with cerebrospinal fluid studies were inconclusive. These new findings prompted an even higher suspicion of vitreoretinal lymphoma. The patient's primary-care team helped clear him to undergo an additional diagnostic vitrectomy with a full thickness retinal/RPE biopsy.

At the time of this surgery, his fundus appearance had worsened significantly (*Figure 1C*). The vitreous aspirate was inconclusive again, yet pathology of the subretinal (*Figure 1C*) and retinal and sub-RPE tissue (*Figure 1D*) revealed aggressive large B-cell non-Hodgkin's lymphoma. The patient was started on systemic rituximab and methotrexate. Within two weeks he was transferred to the intensive-care unit for increasing lethargy, and was later transferred to hospice.

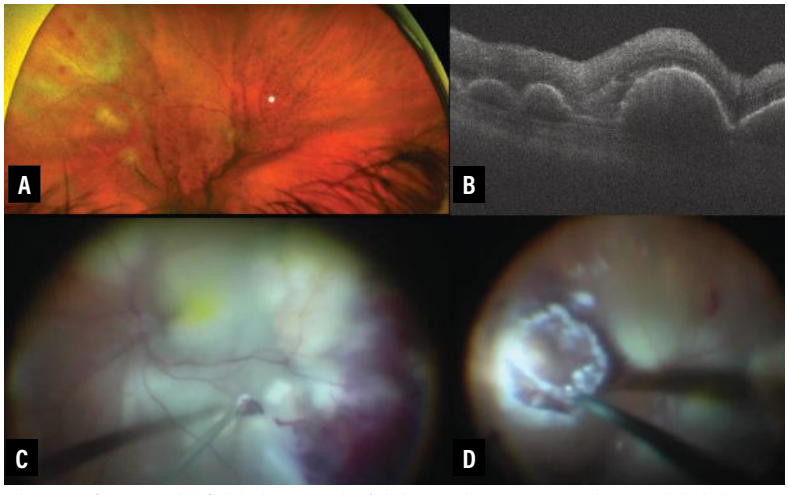


Figure 1. A) Optos widefield photograph of right eye demonstrates vitreous debris in clumps and sheets with superotemporal subretinal whitening and elevated lesions. B) Optical coherence tomography through the lesions demonstrates retinal pigment epithelium thickening and hyperreflective subretinal infiltrates. C) At the time of pars plana vitrectomy, the fundus appearance had significantly worsened with large areas of subretinal whitening and elevation. A subretinal aspiration biopsy is visualized with the 25-gauge cutter. D) Visualization of a full-thickness retinal and sub-RPE biopsy.

Case 2

A 42-year-old male with no significant medical history presented through an outside referral with a decline in vision OS to 20/400. A diagnostic vitrectomy by an outside provider was negative.

He presented with 1+ vitreous cells, clumps of vitreous debris, subretinal macula deposits, inferotemporal retinal whitening, vascular sheathing, and peripheral exudates (*Figure 2A*). OCT OS demonstrated ellipsoid zone mottling and subretinal hyperreflective deposits, which were greatest temporally.

Fundus autofluorescence demonstrated mostly hypoautofluorescence with some areas of hyperautofluorescence. Fluorescein angiography demonstrated significant vascular leakage around the subretinal lesions and greater leakage in the area of full-thickness retinal involvement inferotemporally with peripheral nonperfusion. Outside lab testing for syphilis antibodies and tuberculosis (QuantiFERON Gold) were negative. A brain MRI was also normal.

Intraoperative OCT showed full-thickness retinal involvement without significant subretinal/RPE involvement (*Figure 2B*). Despite the previous negative diagnostic vitrectomy at the outside hospital, these findings gave rise to a higher suspicion for vitreoretinal lymphoma, requiring a repeat diagnostic vitrectomy with full-thickness

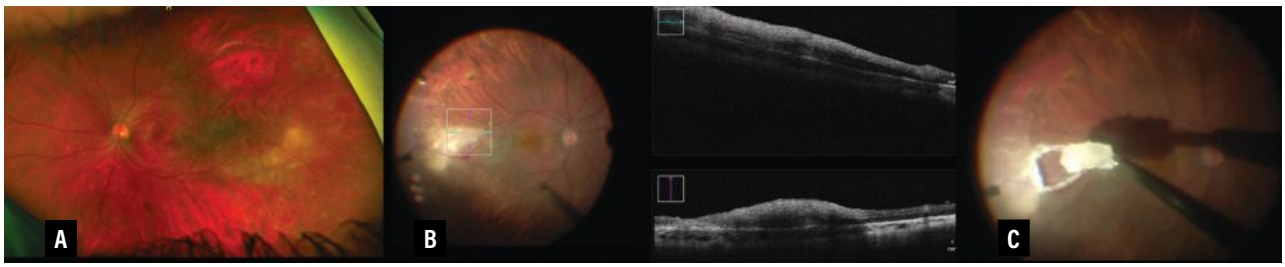


Figure 2. A) Optos widefield photograph of the left eye demonstrates vitreous debris, subretinal macular deposits, inferotemporal retinal whitening, vascular sheathing and peripheral exudates. B) Intraoperative optical coherence tomography shows full-thickness retinal involvement without significant subretinal/retinal pigment epithelium involvement. C) We performed a full-thickness retinal and sub-RPE biopsy.

retinal/RPE biopsy.

The vitreous aspirate was negative on cytology and flow cytometry for a malignant process. In contrast, the full-thickness retinal and RPE biopsy (*Figure 2C*) revealed evidence of a large B-cell non-Hodgkin's lymphoma. The patient returned to his outside institution with the tissue-proven diagnosis and began systemic and local chemotherapy.

Vitreous collection with PPV or FNAB

Vitreoretinal surgeons have several methods available for acquiring diagnostic tissue, including vitreous biopsies, FNABs and retinal/subretinal biopsies.

Because of its relatively low invasiveness, vitreous collection continues to be a standard diagnostic procedure for inflammatory disorders affecting the posterior segment.[5] Vitreous can be acquired through a PPV or a FNAB. It's typically done as a primary surgery and, theoretically, carries a decreased risk of complications compared to retinal/choroidal biopsies.[5]

In PPV, the vitreous sample is collected through aspiration into a syringe across a broken aspiration line while the cutter is activated.[5] In contrast, FNAB involves insertion of a needle and syringe through the pars plana. FNAB isn't recommended primarily for vitreous aspirate because of insufficient cellularity, although it could be a reasonable option for retinal, RPE or choroidal biopsy.[5]

Vitreous samples can be obtained in both undiluted and diluted forms for cytology and flow cytometry, respectively. Other options include polymerase chain reaction (PCR, MYD88 or viral), cytokine rearrangement, metagenomic sequencing, and microbial/fungal microscopy and culture.[1,6]

Fixate extracted cells quickly. Cells extracted from the vitreous should be quickly fixated or placed in tissue culture because they're susceptible to rapid degeneration. We greatly encourage effective collaboration with a cytopathologist.[5] We immediately place the sample into fixative to reduce the risk of cellular degeneration, followed by prompt transportation directly to the cytopathology lab.

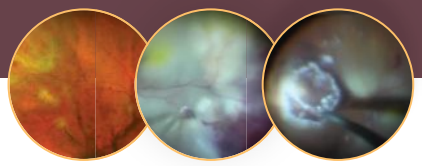
Postoperative complications associated with vitreous biopsies include false-negative results, hemorrhage, retinal detachment, needle-tract seeding and endophthalmitis.[5]

Retinal/choroidal biopsies

One of the most common indications for retinal/choroidal biopsies is atypical uveitis refractory to treatment, especially when a rare neoplastic or infectious etiology is suspected. In highly suspicious cases, full-thickness biopsies can also be considered during the initial diagnostic procedure.[1,2] These cases often have inconclusive vitreous biopsies, brain MRI studies and lumbar punctures, further requiring a definitive diagnosis to initiate treatment. Retinal/choroidal biopsies may either provide a definitive diagnosis or at least exclude infectious and malignant causes to enable more targeted therapy.[1,2]

Key steps for retinal/choroidal biopsies. Retinal/choroidal biopsies begin with a vitreous sample through a PPV, as we described.[5] Perform endodiathermy of the retinal vessels surrounding the biopsy after

A common indication for retinal/choroidal biopsies is atypical uveitis refractory to treatment. These cases often have inconclusive vitreous biopsies, brain MRI studies and lumbar punctures.



completing the vitrectomy and then define the biopsy site with a diode laser and/or full-thickness diathermy. Curved horizontal scissors, vertical scissors, pneumatic vertical scissors or a small-gauge vitreous cutter may be used to remove the tissue.

Postdissection, leave a small segment of retina attached at the base so the tissue isn't lost due to fluidic changes. Create or extend a full-thickness sclerotomy. Forceps, grasping at the tissue base, enable withdrawal of the specimen through the sclerotomy. A fluted, large-bore needle attached to suction or a syringe are alternative options for extraction.

Encircling the biopsy site. You may encircle the biopsy site with additional endolaser and long-acting gas or silicone oil tamponade if needed.[5] We tend to aim for the thickest part of the lesion and avoid large vessels when performing direct aspiration biopsy with the cutter. We also raise the intraocular pressure and introduce the cutter at a low cut rate to help prevent hemorrhage. Complications associated with these approaches include cataract, retinal detachment, vitreous hemorrhage, choroidal hemorrhage, proliferative vitreoretinopathy and endophthalmitis.[5]

We hypothesize that by the time a lesion develops, the disease course is more chronic. Given the fragility and necrosis of vitreous lymphocyte cells, the vitreous yield may decline with time.

Our biopsy experience

Resembling our experiences, other cases of false-negative vitreous studies have been reported, with definitive diagnoses later confirmed using retinal/RPE biopsies.[1,2,4,9] In our recently completed single-center retrospective study, 51 patients had diagnostic vitrectomies suspicious for vitreoretinal lymphoma, 39 of which were positive (76.5 percent). Of these, 29 were vitreous-positive (three of which were retinal and/or subretinal biopsy [RSRB]-positive). The remaining 10 positive biopsies were noted to be vitreous negative but RSRB positive. We performed 14 RSRB, 13 of which were positive for vitreoretinal lymphoma (92 percent).

Most interestingly, 21 patients had retinal, subretinal and/or sub-RPE lesions on their initial visit, 13 of whom (62 percent) had a negative vitreous biopsy. This suggests that if patients present with clear lesions, the vitreous specimen may have a lower cytopathological yield.

The average time from symptom onset to diagnosis was 7.45 months among all patients. However, patients who tested positive only on RSRB tended to present at a later stage than patients with positive vitreous biopsies. Among RSRB-positive but vitreous-negative patients, the time to diagnosis was 8.56 months. For patients with positive vitreous biopsy, the average time to onset was 5.07 months (p=0.002).

A more chronic disease course?

We found no differences in vitreous haze scores between the two groups. We hypothesize that by the time a lesion develops, the disease course is more chronic. Given the fragility and necrosis of vitreous lymphocyte cells, the vitreous yield may decline with time. We used two different RSRBs techniques in our study: cutting/aspiration with a vitrector; or bimanual dissection with scissors and forceps. We performed 10 RSRBs with a cutting/aspiration technique with the vitreous cutter and four with a dissection technique with retinal scissors.

Importantly, only two postoperative retinal detachments occurred in the series, both in RSRB patients utilizing the cutting/aspiration technique. We used follow-up PPV with gas-tamponade in both for reattachment.

How we choose a biopsy technique

With these findings in mind, we highly consider RSRB for suspicious cases at time of primary diagnostic vitrectomy to expedite diagnosis and treatment.[9]

Biopsy methods may differ depending on provider preference and experience. We prefer PPV due to our comfort with the procedure and our preference for a definitive diagnosis at the time of initial surgery.

Ocular imaging is also invaluable as a supplementary tool. Preoperative and/or

(Continued on page 27)

New Insights in Imaging

The potential of mitochondrial FPF imaging in practice

Flavoprotein fluorescence imaging is a novel modality that can detect subtle functional alterations that may precede structural changes in the retina.

By Daiana R. Pur, MESc

Simrat Kaur Sodhi, MSc

Netan Choudhry, MD, FRCSC

By Daiana R. Pur, MESc, Simrat Kaur Sodhi, MSc, and Netan Choudhry, MD, FRCSC

Take-home points

- Mitochondria play an essential role in maintaining cellular energy homeostasis, particularly at the photoreceptor level.
- Mitochondrial flavoprotein fluorescence (FPF) imaging provides information about subtle functional alternations that may precede structural changes.
- FPF has the potential to act as a predictive marker of disease activity in age-related macular degeneration disease activity and to monitor the effects of treatment.
- Larger studies are needed before FPF can be widely used in the clinic.

BIOS

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DISCLOSURES: Ms. Pur and **Ms. Sodhi** have no relevant disclosures.

Dr. Choudhry disclosed relationships with Alcon, AbbVie, Apellis, Bayer, Carl Zeiss Meditec, Hoffman La Roche, Johnson & Johnson and Novartis.

The retina consists of highly metabolically active tissue, and consequently it's susceptible to mitochondria-related damage.[1] Mitochondria play an essential role in maintaining cellular energy homeostasis, particularly at the level of the photoreceptors.[2] Numerous studies have demonstrated that mitochondrial dysfunction is a key factor in the pathogenesis and progression of retinal diseases, such as diabetic retinopathy,[3] central serous retinopathy,[4] age-related macular degeneration,[5,6] glaucoma,[7,8] retinal dystrophies[9] and optic nerve pathologies.[10]

Mitochondrial metabolic dysfunction renders the neural retina and retinal pigment epithelium vulnerable to oxidative stress, which can be measured using mitochondrial flavoprotein fluorescence (FPF), also called fluorescence lifetime imaging. This novel, noninvasive imaging modality functions as a marker of oxidative stress and mitochondrial dysfunction by quantifying the ratio of oxidized flavoproteins to reduced flavoproteins in mitochondria.[11]

Compared to spectral domain optical coherence tomography, the gold standard for diagnosis and monitoring of retinal diseases, which offers visualization of structural alternations, FPF provides information about subtle functional alternations that may precede structural changes.

Clinical utility of FPF imaging

Emerging studies highlight that FPF may be an indicator of retinal disease activity.[12] Specifically, it may serve as a tool for early detection, classification and prognostication of retinal diseases, as well as evaluate a patient's response to therapy. FPF was shown to detect and classify disease stages of AMD into early AMD, intermediate AMD, advanced geographic atrophy and advanced neovascular AMD based on mean differences in flavoprotein fluorescence heterogeneity.[5,6] FPF has the potential to act as predictive marker of AMD disease activity, a promising idea given that little is known about a patient's individual-level risk of AMD progression.

Moreover, FPF has been shown to positively correlate with the degree of DR[3,12,13] and provide information regarding the therapeutic response to anti-VEGF that OCT may not capture.[14] A pilot study of eight patients with DR and diabetic macular edema, in whom FPF was measured in the same eyes before and after anti-VEGF treatment, showed a significant negative correlation between improvement in best-corrected visual acuity and average FPF intensity values.[14]

Interestingly, the authors remarked that improvements in BCVA and increased FPF values (i.e., signaling improved mitochondrial function), but not OCT central macular thickness (CMT), occurred in anti-VEGF-treated patients with good vision and lower degrees of CMT.[14] This suggests that FPF may evolve as a dynamic, early marker of treatment response, correlating with BCVA changes that precede those in OCT CMT.[14]

Potential in central serous retinopathy

Similar uses were reported in central serous retinopathy, specifically in a pilot study of three patients with CSR that reported detecting increased FPF average values as early as one week after symptom onset, compared with conventional FAF that detects changes several weeks after diseases onset.[4]

Furthermore, in a large cohort of 157 patients with inherited retinal dystrophies, mean FPF heterogeneity was found to correlate with FAF lesions, suggesting its relevance as a clinically relevant imaging marker.[9]

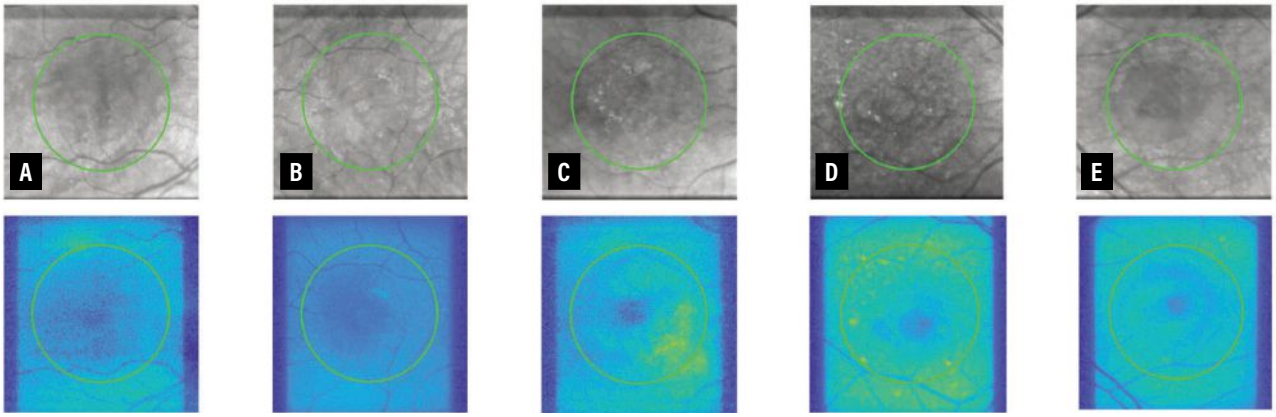
Other uses for FPF include disease detection and monitoring in optic nerve pathologies, open-angle glaucoma[7] and expanding knowledge on neurodegenerative conditions such as Parkinson's disease, Alzheimer's and other forms of dementia.[15,16]

Advantages and disadvantages of FPF

FPF offers several benefits, such as noninvasively providing objective, functional information of early alternations in mitochondrial metabolism, which have been suggested to precede structural changes captured by OCT. However, the promise of this evolving technique must be considered in the context of several limitations.

First, no universal standards exist in the type of devices used, image processing parameters and healthy FPF reference values. For example, some authors have reported on FPF signal intensity while others reported on FPF signal heterogeneity. Furthermore, the choice of image processing parameters isn't generally justified, rendering the methodology and device features a "black box."

Our understanding is also evolving that patient factors such as age, gender, the presence of a cataract,[13] corneal pathology[17] and ocular or systemic comorbidities increase



A side-by-side comparison of intraretinal imaging (top row) and mitochondrial flavoprotein fluorescence (FPF, bottom row) for various disease states: A) healthy control; B) early age-related macular degeneration; C) intermediate AMD; D) advanced geographic atrophy; and E) advanced neovascular AMD.

the variability in FPF signal and consequently decrease the reliability and generalization of reported findings.

We need larger studies that include well-defined populations, that clearly outline methodology and adjust for confounding factors following a standard protocol before we can widely use these devices in the clinic.

Future of FPF

FPF is emerging as a powerful yet little-known tool for the detection and classification of retinal disease, and for monitoring the therapeutic effects of treatment of retinal diseases. It adds a complementary way of interrogating and visualizing function of retinal processes.

Perhaps one of the most exciting avenues for FPF is its potential use in conjunction with therapeutics that target mitochondrial dysfunction in ocular diseases.[18] Other future directions include its use along with artificial intelligence-based analyses of ocular biofluids and OCT imaging to provide care tailored to individual patients.[19] RS

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Pearls for biopsying vitreoretinal lymphoma

(Continued from page 24)

intraoperative OCT, a key portion of our surgical management, aids our decision to perform direct aspirate through a lesion vs. a dissection.[1] We favor subretinal aspirate (*Figure 1C, page 22*) when the pathology is confined to the subretinal and sub-RPE space, whereas we opt for a full-thickness retinal and RPE biopsy in cases with full-thickness retinal involvement without subretinal involvement (*Figures 2B, C, page 23*).

In terms of the biopsies themselves, we prefer complete vitrectomies in place of limited core vitrectomies to reduce the likelihood of false-negative results. This is because inflammatory and lymphoma cells, believed to be predominantly in the cortical vitreous, have a diminished chance to be sampled with only a core biopsy.[5] Necrotic cells may predominate the center of a lesion. Lesion margins are more likely to harbor the pathologic process.[5] We prefer to avoid oral or periocular steroids for at least two weeks preprocedure to limit risk of cellular necrosis before the biopsy Finally, we can't emphasize this enough: Proper coordination with cytopathology is a must.[6]

Bottom line

Retina specialists have several biopsy options for the diagnosis of atypical uveitis. Biopsy methods may differ depending on provider preference and experience. Consider RSRB during initial surgery for highly suspicious cases to expedite the diagnosis and treatment.[9] In the future, PCR or metagenomic sampling of aqueous or vitreous fluid may also play a key role in the diagnosis of vitreoretinal lymphoma.[10,11] RS

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New Insights in Imaging

Using OCT to identify biomarkers of early DR

Exploring the potential of optical coherence tomography to evaluate photoreceptor health before signs and symptoms of diabetic retinopathy manifest.

By Jennifer I. Lim, MD

By Jennifer I. Lim, MD

Take-home points

- A number of structural changes, including the loss of photoreceptor cells that manifests as thinning of the inner retinal layers and retinal nerve fiber layer, occur in diabetic retinas.
- Optical coherence tomography can be used to compare subclinical structural and reflectivity changes in eyes of patients with diabetes.
- A number of studies have demonstrated the ability of OCT to detect retinal thickness changes in eyes of patients with diabetes but without diabetic retinopathy.
- More recent studies have indicated that the location of neurogenerative changes in patients with diabetes but with minimal DR may be a marker of DR status.

Diabetes mellitus is known to induce neurovascular changes that result in structural abnormalities and functional losses before the onset of clinically visible diabetic retinopathy. Optical coherence tomography and OCT angiography reveal subclinical changes. Psychophysical testing uncovers functional losses in DM eyes without DR eyes. DM eyes with early DR demonstrate more neurovascular changes and corresponding functional abnormalities than DM eyes without DR.

This article will discuss the structural OCT changes in the early stages of DR, in eyes of DM patients without DR and those with mild nonproliferative DR.

Experimental diabetic animal models as well as human histopathology specimens reveal that neuroglial degeneration with resultant reactive gliosis and neural-cell apoptosis occur in DR.[1-3] In diabetic retinas, retinal ganglion cells and amacrine cells undergo diabetes-induced apoptosis early in the disease process. Photoreceptors are also affected early on. The loss of these cells manifests as retinal thinning of the inner retinal layers and the retinal nerve fiber layer.

OCT imaging scans contain not only structural but also reflectivity information about the health of the retinal layers. The OCT images can be used to compare subclinical structural and reflectivity changes of eyes in patients with diabetes with non-diabetes normal controls. In some DM eyes, retinal thickening, due to ischemia and vascular endothelial growth factor output, can also result even before visibly detectable edema.

Studies of retinal thickness changes

Several OCT studies have examined the retinal thickness of patients with type 1 and type 2 DM. An OCT study in 2004 compared the retinal and RNFL thickness measurements of 32 adult patients with type 2 DM without DR to 48 retinal controls and

BIO

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DISCLOSURES: Dr. Lim disclosed financial relationships with Genentech/Roche, Regeneron Pharmaceuticals, Opthea, Cognition, Viridian, Santen, Quark, Luxa, Aura, Alimera, Unity, Eyenuk, Aldeyra, NGM, Adverum, Regenexbio, Janssen, Spring Vision, Iveric Bio and EyePoint Pharmaceuticals.

to 34 RNFL controls in the temporal, superior, nasal and inferior retinal quadrants. This was one of the first studies to show that retinal thickness was significantly increased (p=0.03) and RNFL thickness was significantly decreased (p=0.02) in the superior retinal areas of DM without DR compared with controls.[4] Subsequently, many other studies also looked at the structural retinal thickness changes.

Studies found changes also occurred in children with DM. An OCT study compared scans of 60 children with type 1 DM but without DR to 60 normal age-matched controls without DM to evaluate the ganglion cell-inner plexiform layer (GC-IPL) and RNFL thicknesses. This study revealed thinning of the GC-IPL thickness in all quadrants except the superior-nasal quadrant (p < 0.05) and no difference in the RNFL thickness in all quadrants between the groups (p<0.05).[5]

Another study compared adolescents with type 1 and type 2 DM without DR, finding that the RNFL was disproportionately affected compared with the total retinal thinning for both groups. This study also found type 2 DM patients were more affected than type 1 DM patients with regard to the thickness of the retinal layers as well as reflectivity of the retinal layers seen on OCT.

Further evidence of structural changes

A more recent OCT study compared 30 patients with DM but without DR and 44 with NPDR with controls. The researchers found a significant increase of inner plexiform layer and inner nuclear layer (INL) thicknesses in DR eyes (p<0.001) and a significant decrease (p<0.01) of RNFL layers as well as specific sites of retinal GCL layer (p=0.02) in the macula. They found no differences in the peripapillary area between DM patients and controls.[7]

Another study of 102 patients compared 46 DM patients without DR and 28 with mild NPDR with 28 controls. Quantitative analysis showed that the mean GCL and mean RNFL layers were thinner in the DM patients without DR than in controls. The mild NPDR eyes demonstrated significant retinal thinning compared to controls (p=0.032) and thinner RNFL and GCL.[8]

The *en face* OCT maps can show these differences between controls and DM without DR patients. RNFL thinning and thickening of the outer nuclear layer (ONL) occur in eyes of patients with DM but without DR. These studies are similar to previous studies that found peripheral RNFL thinning in DM with no or minimal DR.

Locational changes

More recent studies have focused on the location of the neurodegenerative changes in patients with minimal DR. Quantitative analysis revealed the pericentral area of the macula shows thinning in the RNFL, GCL and IPL in patients with minimal DR vs. controls (respective difference = 1.9 µm, 95% confidence interval [CI] 0.3-3.5 µm; 5.2 µm, 95% CI 1.0-9.3 µm; and 4.5 µm, 95% CI 2.2-6.7 µm respectively).

In the peripheral macula, the RNFL and IPL layers were also thinner in patients with minimal DR vs. controls (respective difference 3.2 µm, 95% CI 0.1-6.4 µm; 3.3 µm, 95% CI 1.2-5.4 µm). Multiple linear regression analysis showed DR status to be the only significant explanatory variable

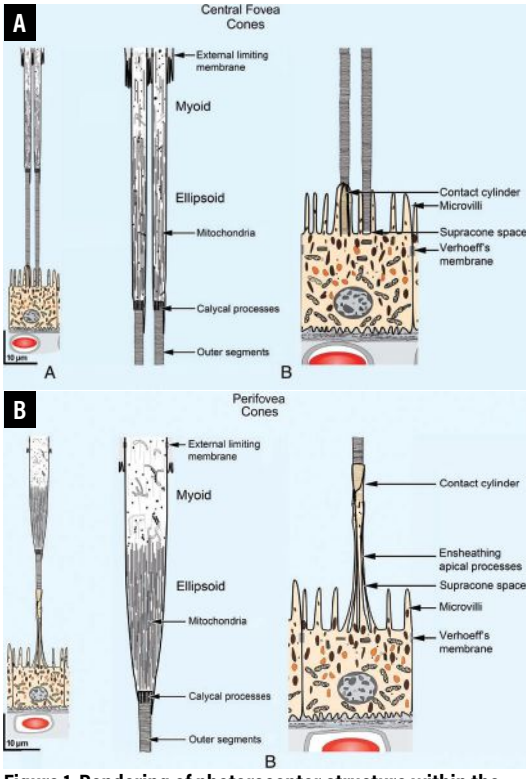

Figure 1. Rendering of photoreceptor structure within the retina highlights the location of the mitochondria in the inner-segment ellipsoid of the photoreceptors. Scale drawings are of the outer retina at central foveal (A) and perifoveal (B) regions. Images on the left are low-magnification illustrations. Images in the center are high-magnification illustrations in two parts of the anatomically correct model. *(From Yao X, Son T, Kim TH, Le D. Interpretation of anatomic correlates of outer retinal bands in optical coherence tomography. Exp Biol Med (Maywood). 2021;246:2140-2150. Modified with permission from Spaide RF, Curcio CA. Anatomical correlates to the bands seen in the outer retina by optical coherence tomography: literature review and model. Retina 2011;31:1609–1619. Used with permission)*

(r=0.31, p = 0.03) for this retinal thinning. [9]

Longitudinal studies have documented that the neuroretinal thickness loss (RNFL, GCL, IPL) in DM without DR or with minimal DR is about 0.54 µm per year (loss of 0.25 µm/yr in the NFL and loss of 0.29 µm/yr in the GCL). This translates to a significant loss of 5.4 µm over 10 years, similar to that in severe glaucoma, although perhaps more diffuse than the scotomas found in glaucoma.[2] Research on streptozotocin-induced type 1 DM mice has documented that neurodegenerative changes precede microvascular changes, implicating a primary neuronal degenerative process in DR.[2]

OCT retinal reflectively

The OCT scan can also be analyzed by the intensity of hyperreflective and hyporeflective bands. Typically, hyperreflective bands occur at interface junctions and hyporeflective bands at nuclear layers. The retina can be split into the inner retina, ranging from the ILM to the INL, and the outer retina, extending from the OPL/ONL to the RPE.

The ILM is the first hyperreflective line on OCT and depicts the vitreous-retinal interface border. The RNFL is the hyperreflective band at the temporal edge of the optic disc and extends toward the fovea, sitting above the hyporeflective ganglion cell layer (GCL). Below the GCL is the IPL, which, with the outer plexiform layers, form the other hyperreflective lines of the inner retina. The INL is the hyporeflective band sandwiched between these two hyperreflective lines.

The outer retina extends from the ONL to the retinal pigment epithelium. The outer retina has four hyperreflective lines, traditionally thought of as the external limiting membrane, ellipsoid zone, interdigitation and the RPE band. The ELM is the hyperreflective line formed by junctional complexes between Müller cells and photoreceptor inner segments. The second outer band corresponds to the inner-segment ellipsoid and the third band to the interdigitation zone, according to the 2014 International OCT Nomenclature Meeting.[10]

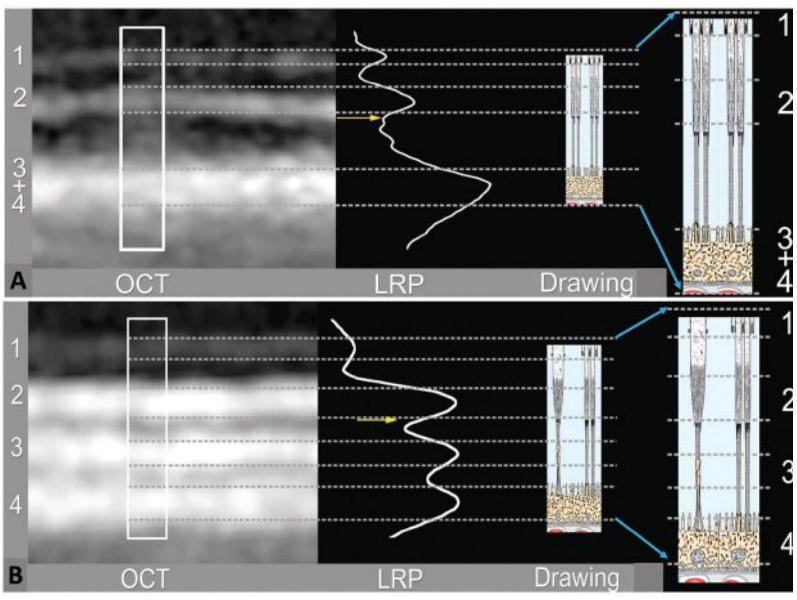

Figure 2. Optical coherence tomography reflectance profiles aligned with the retinal structures show comparative alignment of clinical OCT bands with the anatomically correct model at the central foveal (A) and perifoveal (B) regions. *(From Yao X, Son T, Kim TH, Le D. Interpretation of anatomic correlates of outer retinal bands in optical coherence tomography. Exp Biol Med (Maywood). 2021;246:2140-2150. Modified with permission from Spaide RF, Curcio CA. Anatomical correlates to the bands seen in the outer retina by optical coherence tomography: literature review and model. Retina 2011;31:1609–1619. Used with permission.)*

Hyperreflective RPE band

The RPE band may appear as two distinct hyperreflective bands, especially when pathology is present and Bruch's membrane (2-to-4-µm thick acellular matrix) is separated from the RPE. More recently, Xincheng Yao, PhD, and colleagues at the University of Illinois at Chicago redefined the second ORL hyperreflective band as inner-segment ellipsoid and inner-segment/outer-segment junction and connecting cilium and the third band as an amalgam of outer segment, outer-segment tip and RPE apical processes (*Figure 1, page 29*).[11]

DR stage has been shown to affect the intensity of the retinal hyperreflective lines. INL intensity (p<0.04) has been shown to be higher in all macular subfields in NPDR eyes compared with controls (p<0.04).[13] Thus, reflectance, along with depth and

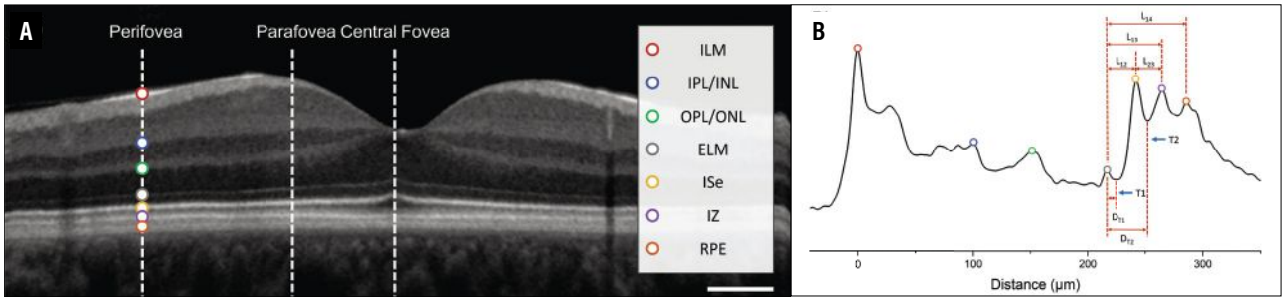

Figure 3. Diagrams of the reflectance intensity of the outer retinal bands and the location of the distance measurements between the reflectance bands. A) A representative optical coherence tomography B-scan of a healthy control subject. The dashed white lines represent eccentricities for A-line analysis. The colored markers represent retinal locations, with the corresponding band location summarized in the legend. B) Representative averaged A-line profile of the perifovea to illustrate individual retinal locations and outer retina thickness measurements. Key: D12,distance from the external limiting membrane to inner-segment ellipsoid; D13, distance from the ELM to interdigitation zone; D23, distance from the inner-segment ellipsoid to the interdigitation zone; D14, distance from the ELM to the retinal pigment epithelium; D1T1, distance from the ELM to T1; and D1T2, distance from the ELM to T2. The scale bar represents 0.5 mm. *(From Le D, Son T, Lim JI, Yao X. Quantitative optical coherence tomography reveals rod photoreceptor degeneration in early diabetic retinopathy. Retina 2022;42:1442-1449. Used with permission.)*

spatially resolved measurements of retinal thickness, is a potential biomarker for monitoring DR development, progression and response.[12] Reflectance from these layers and the distances between the reflective outer bands can be used as a surrogate for the photoreceptor lengths.[13]

Mitochondria-rich inner segment

Retinal photoreceptors harbor 75 percent of the retinal mitochondria, which is mainly located in the inner-segment ellipsoid zone. The photoreceptor layer is the most metabolically active retinal component and accounts for 75 percent of the retinal oxygen consumption.[14-16] This inner-segment ellipsoid is rich in mitochondria and mitochondria scatter light. In retinal diseases, the inner-segment myoid decreases in length and mitochondria move inward. Diseased mitochondria undergo fission resulting in smaller mitochondria and more scattering of light and reduced reflectivity.[17] Thus, the reflectivity of the OCT outer retinal bands contain information about photoreceptor health.

Disease states have been reported to result in qualitative changes.[11] The ELM, because it's formed by junctional complexes between Müller cells and photoreceptor inner segments, has traditionally been considered a biomarker of photoreceptor integrity.

Researchers have shown that inner-segment ellipsoid reflectivity (absolute and relative) is lower in mild NPDR eyes compared with controls (p<0.001), while the reflectivity of the RPE and ELM didn't differ (p = 0.126; p=0.053).[18] Indeed, in DM-without-DR eyes, the GCL and INL reflectivity changes occurred and correlated with the severity of the retinal layer thickness changes more so than with control eyes.

ORL band distances

Recently, our group compared outer retinal band reflectance and ORL band distances in DM-without-DR and DM-with-early DR eyes with non-DM control eyes.[13] Because the distances between the outer bands vary across macula—fovea to parafovea to perifovea—these areas were analyzed separately for comparisons of the DM eyes to control eyes. The study compared reflectivity of the ELM, inner-segment ellipsoid and interdigitation zone and RPE layers, and the distances between the ELM to inner-segment ellipsoid, inner-segment ellipsoid to interdigitation zone and interdigitation to RPE (*Figure 2*).

We noted differences in reflectivity and distance between the outer hyperreflective bands in the controls and the DM-without-DR and mild NPDR eyes (*Figure 3*).

(Continued on page 36)

Understanding the risk of GA in nAMD

A look at research that sheds new light into the progression of geographic atrophy in neovascular age-related macular degeneration.


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By Daniele Veritti, MD, Valentina Sarao, MD, Deborah Martinuzzi, MD, and Paolo Lanzetta, MD

Take-home points

- Neovascular age-related macular degeneration and geographic atrophy often coexist in the same eye, contributing to visual deterioration, especially in the long term.
- Contrary to previous hypotheses, no association seems to exist between vascular endothelial growth factor inhibition and the progression of GA in these patients.
- The demographic characteristics of the population, injection frequency and type of VEGF agent used in treatment don't appear to be linked to the rate of GA progression.
- The rate of GA progression is primarily linked to the type of macular neovascularization that underlies the nAMD.
- Identifying nAMD patients with the highest risk of GA progression is crucial because they could potentially benefit from a combination of anti-VEGF and anti-GA treatment in the near future.

BIOS

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DISCLOSURES:

Dr. Veritti is a consultant to Bayer, Novartis and Roche.

Dr. Sarao is a consultant to I-Care.

Dr. Lanzetta is a consultant to AbbVie, Aerie, Apellis Pharmaceuticals, Bausch + Lomb, Bayer, Biogen, Boehringer Ingelheim, Genentech, I-Care, Novartis, Ocular Therapeutix, Outlook Therapeutics and Roche.

Dr. Martinuzzi has no relevant financial disclosures.

As we all know, age-related macular degeneration is the primary cause of blindness worldwide.[1] It's a progressive condition that affects the macula, resulting in damage to the retina, retinal pigment epithelium and choriocapillaris, ultimately leading to central vision impairment.[1,2] This maculopathy affects a significant proportion of adults and it can cause severe and permanent visual impairment, and even legal blindness, presenting a considerable public health issue.[3–5]

AMD is categorized into early, intermediate and late stages.[2] The late stage encompasses two primary forms that aren't mutually exclusive: geographic atrophy and neovascular AMD.[1,6] GA is characterized by localized sharply demarcated atrophy of outer retinal tissue, RPE and choriocapillaris.[7] The neovascular form is associated with choroidal neovascularization, which leads to intraretinal or subretinal leakage, hemorrhage and RPE detachment.[1,6]

Is AMD categorization outdated?

As the current standard of care for treating neovascular AMD,[8,9] anti-VEGF agents have resulted in a significant improvement in nAMD prognosis.[5,10] The conventional approach to categorizing advanced AMD into treatable nAMD and untreatable GA may soon become outdated, thanks to the emergence of novel GA-targeting therapies. Pegcetacoplan (Syfovre, Apellis Pharmaceuticals) is one such treatment, having shown promising results in reducing GA progression during Phase III trials at the 24-month mark.[11]

However, it's worth noting that neovascular AMD and GA can coexist in the same eye, making it particularly important to understand the impact of GA progression on

patients receiving anti-VEGF treatment. The worsening of GA can severely affect a patients' quality of life and long-term visual prognosis.

Moreover, some evidence suggests that anti-VEGF therapy may contribute to the development of macular atrophy and GA.[8] The CATT study reported that 20 percent of patients receiving anti-VEGF therapy for nAMD developed GA after two years, doubling to 41 percent after five years.[12,13] One possible explanation may be that anti-VEGF treatment can lead to choroidal thinning, which is a known risk factor for macular atrophy.[8]

But the correlation between anti-VEGF treatment and the development of macular atrophy and GA is still controversial. For this reason, we've developed a multistep approach that aims to shed light on this issue. First, we plan to identify the incidence of GA in nAMD patients at different time points using a meta-analysis and meta-regression approach. Second, we aim to report on long-term data regarding GA progression and its correlation with baseline characteristics in patients with nAMD using high-quality multimodal imaging.

Incident GA in nAMD patients: A meta-analysis and meta-regression

The primary objective of our research was to synthesize available evidence on the incidence of new-onset GA during anti-VEGF treatment for nAMD, and to determine whether a possible correlation exists between the use of anti-VEGF agents and the development of GA.

The literature has reported several risk factors associated with AMD and its progression to GA, but no consensus exists about the possible link between the development of GA and treatment with anti-VEGFs. We aimed to identify and investigate the risk factors associated with GA progression, comparing pooled data with the natural history of AMD.

We conducted a meta-analysis at different

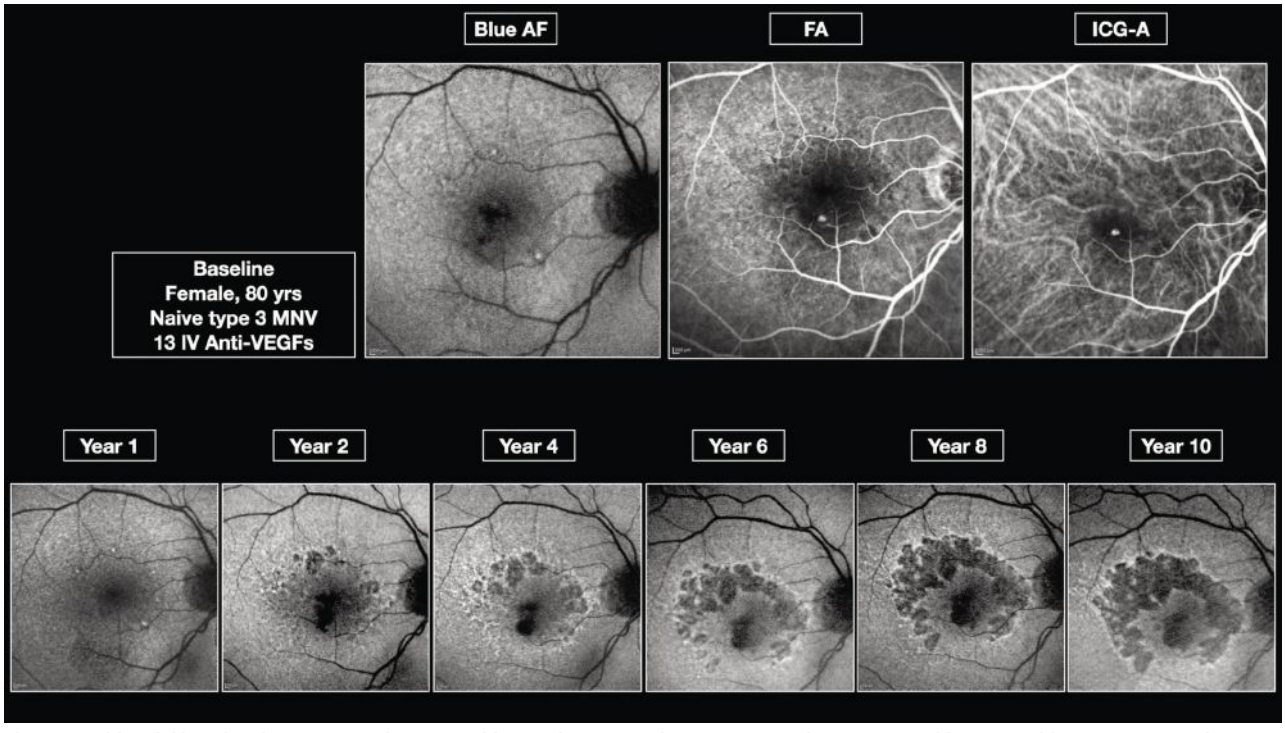

Figure 1: Multimodal imaging demonstrates the geographic atrophy progression over 10 years in an 80-year-old woman with type 3 neovascular membrane.

time points using data from large published studies on incident GA in eyes affected by wet AMD treated with anti-VEGFs, and then compared the incidence rate with that of intermediate AMD that didn't require anti-VEGF treatment.

Our findings revealed that the incidence of GA in patients with wet AMD treated with anti-VEGFs follows a linear progression, with approximately 17 percent incidence in the first year of treatment, 26 percent in the second year, 34 percent between the third and sixth year and 48 percent in 10 years. The angular coefficient that characterizes the incidence of GA in treated neovascular AMD populations (0.05) and untreated intermediate AMD populations (0.057) is very similar, indicating that there doesn't seem to be any influence of VEGF inhibition in the development of GA.

Our model also showed that the incidence rate of subfoveal GA was significantly associated with the time interval since the start of treatment, but not with the mean age of patients at the start of anti-VEGF therapy or the number of injections.

However, our study has limitations due to the variability of the selected populations and the differences in the type and regimen of drug administration in each study. In addition, demographic characteristics and ethnicity may have introduced biases in the population considered. Undoubtedly, refined studies using advanced imaging techniques are necessary to comprehensively describe the progression of GA, and to accurately categorize patients based on various subtypes of neovascular membrane.

Our findings support the notion that GA is a component of nAMD and that intravitreal injections of anti-VEGF drugs don't influence the incidence or progression of GA.

Long-term progression of GA in nAMD: A retrospective analysis with high-quality multimodal imaging

To assess the long-term progression rate of GA in eyes with nAMD treated with anti-VEGF agents, we designed a retrospective study. We included eyes that were followed up for five to 10 years and had high-quality multimodal imaging available, including infrared reflectance, optical coherence tomography and fundus autofluorescence. The aim of the study was to report the long-term GA progression rate and to identify risk factors associated with GA progression, specifically focusing on differences between neovascular membrane subtypes.

We included a total of 100 eyes, with a mean follow-up of 8.1 (±2) years. Patients received an average of 22.1 (±11.5) intravitreal anti-VEGF treatments. The study population was evenly distributed between the genders, with an average age of 71.9 (±8.3) years. We found that the overall GA

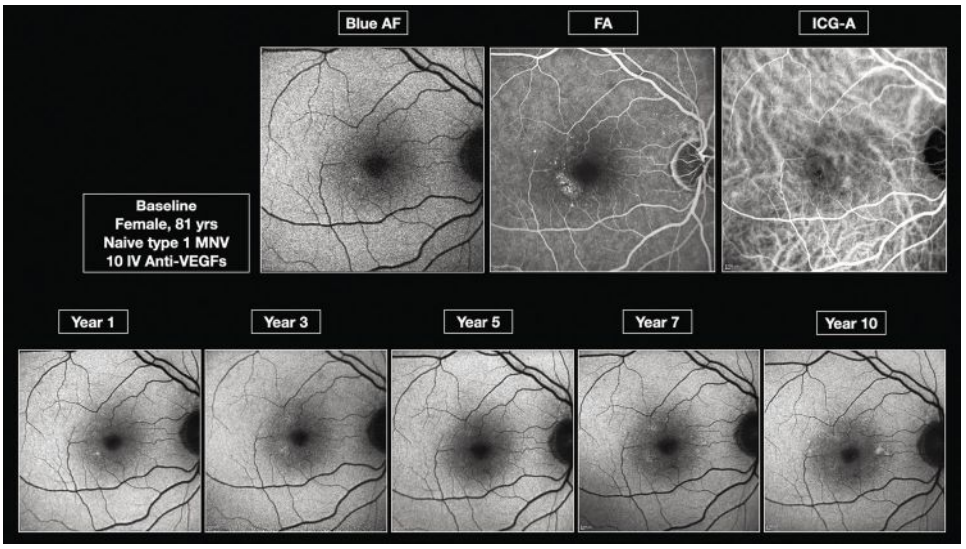

Figure 2. Type 1 choroidal neovascularization without geographic atrophy development over a 10-year period.

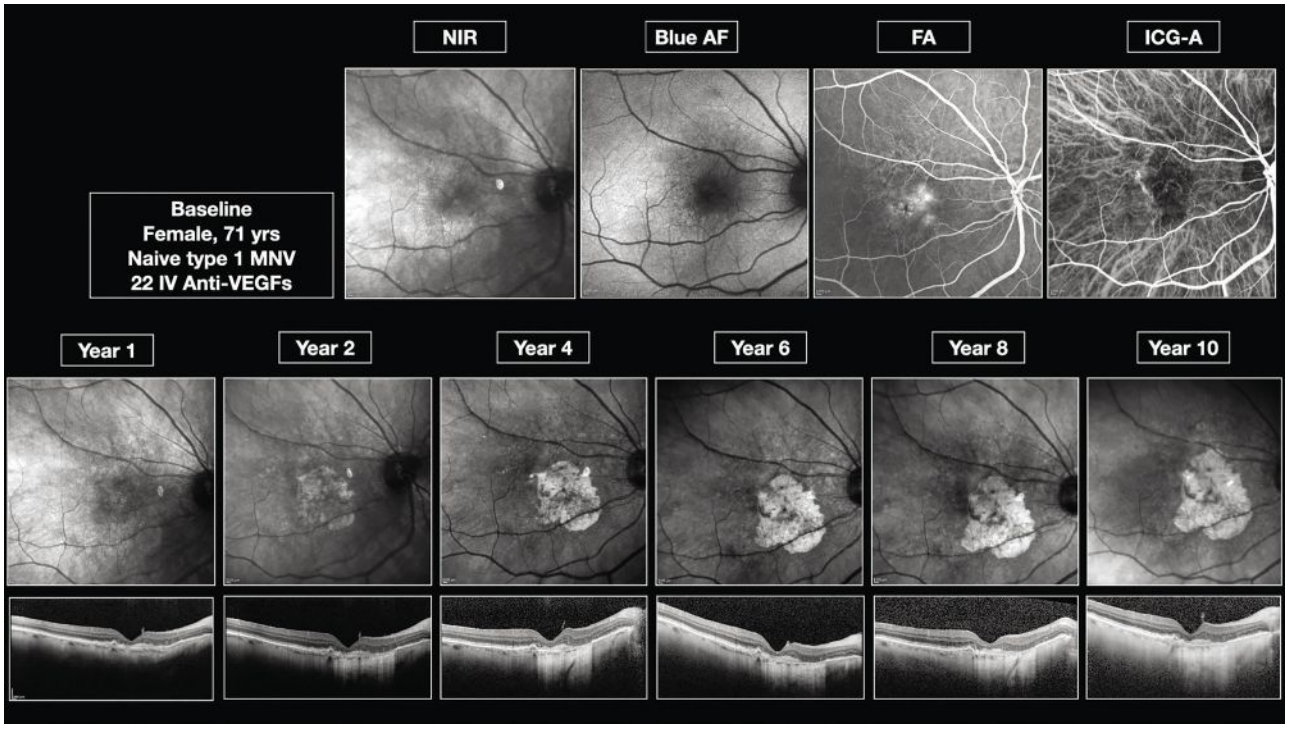

Figure 3. Type 1 choroidal neovascularization with geographic atrophy development over a 10-year period.

progression rate was 2.1 (±1.9) mm^2/year, which is consistent with previous literature reporting a range of 0.53 to mm^2/year and a median of 1.78 mm^2/year.[7]

However, the GA progression rate differed significantly depending on the neovascular membrane subtype. We found:

- Type 3 had the fastest growth rate, 3.2 ± 0.70 mm^2/year (*Figure 1, page 33*).
- Type 1 had the second-fastest growth rate, 2.4 ±1.12 mm^2/year (*Figures 2, 3*).
- Mixed type followed, 2.2 ±0.69 mm^2/year.
- Polypoidal choroidal vasculopathy was next, 2 ±0.53 mm^2/year.
- Type 2 had the slowest growth rate, 1.9 ± 0.52 mm^2/year.

Our analysis found that demographic characteristics didn't significantly affect GA progression rate, although intrinsic population characteristics, such as genetics and lifestyle habits, have been shown previously to influence the prevalence of AMD.[2]

Additionally, we found that the frequency of injections and the type of anti-VEGF agent used for nAMD treatment weren't associated with GA progression, which seems to be primarily related to the type of neovascular membrane underlying the nAMD.

Bottom line

Our findings support the notion that GA is a component of nAMD and that intravitreal injections of anti-VEGF drugs don't influence the incidence or progression of GA. We observed that the incidence rate of GA in nAMD has a linear increment with an angular coefficient that's very similar to that observed in populations with intermediate AMD who aren't treated with anti-VEGFs.

Furthermore, we identified that the incidence and rate of progression of GA in nAMD vary depending on the type of neovascular membrane underlying the maculopathy. Demographic characteristics, which are known to be risk factors for the incidence of AMD in general, didn't show any correlation with the incidence or rate of progression of GA in our analysis.

GA progression has a devastating impact

on the quality of life of patients already undergoing intravitreal treatments for wet AMD, significantly affecting their long-term visual prognosis. It's crucial that we identify patients at the highest risk of progression, who may benefit from concurrent treatment for both choroidal neovascularization and the loss of RPE and photoreceptor cells in the near future. RS

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OCT biomarkers in early DR

(Continued from page 31)

Inner-segment ellipsoid reflectivity decreased progressively while RPE reflectivity increased progressively with disease progression from controls to DM-without-DR and to mild NPDR.

A ratio of normalized inner-segment ellipsoid/RPE intensity showed a significant decreasing trend in the perifoveal zone, but no detectable difference in the central fovea. This suggests a rod-predominant photoreceptor abnormality in early DR.

We also found differences in the distance between the inner-segment ellipsoid and interdigitation zone for controls and mild DR in the central (p<0.005), parafovea (p=0.044) and perifoveal zones (p=0.036). This distance was significantly different between DM-without-DR and mild NPDR eyes for the perifoveal zone (p=0.039). The inner-segment ellipsoid-to-interdigitation zone distance correlated with outer photoreceptor length, suggesting photoreceptor abnormalities in early DR.

Functional abnormalities, including electroretinogram[20-22] and contrast sensitivity[23] findings, accompany these anatomic abnormalities. Thus, neurovascular dysfunction occurs early in DM without DR and in minimal to mild DR eyes before other abnormal OCT findings develop.

Bottom line

OCT imaging contains information about photoreceptor health and can detect abnormalities in eyes with DM but without DR as well as early DR. OCT can be helpful in detecting the earliest manifestations of neurovascular dysfunction in these eyes. As preventive therapeutics become available, OCT imaging will enable us to target eyes at higher risk of progression to clinically evident DR. RS

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Don't be a Dr. Octopus

Take charge of your social media use so it doesn't overtake your thoughts like the villain in Spider-Man 2.

By Jayanth Sridhar, MD

Dated cultural reference incoming. In Sam Raimi's 2004 blockbuster film, *Spider-Man 2*, Dr. Otto Octavius (played to perfection by Alfred Molina) uses an amazing technology in the form of robotic arms that make him more productive and efficient.

Unfortunately, the control chip for the arms sustains damage, and the technology takes charge, influencing Dr. Octavius' thoughts and corrupting his brain for nefarious design. Thus is born the villain, Dr. Octopus.

Similar to those robotic appendages, social media applications allow us to learn, communicate and disseminate information faster than ever before.

Still, as intelligent as humans are, we're ultimately animals with brain neurochemistry that dictates our mood and behaviors. The digital age has accelerated the dopamine boosts we gain from interacting with media and other people. Ultimately, our brains can be rewired to our detriment if we're not cautious and intentional with our social media usage.

Social media addiction: it's a thing

According to the Addiction Center, psychologists estimate that up to 10 percent of Americans today meet the criteria for social media addiction, defined as impairment in important life areas due to over-concern with social media, uncontrollable urges to check social media and excess time dedicated to social media usage.[1]

We're all vulnerable to it. More than once a day I find myself on Twitter or LinkedIn mindlessly scrolling and wondering how I got there. Excess digital engagement can make us irritable, alter our sleep patterns, and alienate our surrounding loved ones.

Should we run from the technology then? I believe the answer lies in embracing the technology but focusing on intentional and purposeful uses of social media.

It also depends on accepting our own limitations and accepting that this isn't simply a question of willpower, but a matter of avoiding scenarios where our curious human brain gets trapped in the digital information treasure troves.

In the movie, Dr. Octavius dramatically breaks free from the arms' influence, barking, "You listen to ME now!" and taking control of the robots to save New York City. Congruently, we need to take ownership of our social media usage to achieve our goals, whether they include practice building, learning a cool surgical trick or academic engagement.

'Digital detox'

Per the Addiction Center's advice, I take "digital detox" breaks in which I don't use any electronics in certain hours of the day. I also turn off phone notifications when I'm working on a project, exercising or spending time with loved ones. You can set notifications to still allow important people in your life to get through a "Do Not Disturb" barrier.

I've set a daily time limit for my social media apps and I track my usage each week to make sure I'm spending less time on them than the week before. Finally, at night I not only put up the "Do Not Disturb" setting, but I also physically keep my phone plugged in far enough away from me to avoid the temptation of checking it when I should be sleeping.

I'm not perfect. Never will be. But hopefully you can incorporate some of these tools to remain purposefully engaged and in control of your social media usage.

REFERENCE

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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.

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

Department Editor ***Richard Mark Kirkner***

Reviving dormant photoreceptors in LCA1

The gene therapy ATSN-101 has demonstrated safety and shown signals of efficacy in restoring vision in Leber congenital amaurosis.

With Paul Yang, MD

Paul Yang, MD

ATSN-101 (Atsena Therapeutics), a subretinal gene therapy that targets biallelic mutations in the *CUCY2D* gene in Leber congenital amaurosis, was the subject of a recent six-month readout of a Phase I/II clinical trial.[1] The trial so far has met its primary safety endpoint. It enrolled 15 patients, including three children. Three adult cohorts (n=3 each) received three ascending doses. Six additional patients received the highest dose of 1 x 10^{11} gene vectors/eye in the dose expansion-phase.

Here, Paul Yang, MD, an associate professor of ophthalmology at Oregon Health & Science University in Portland and a trial investigator, answers questions about ATSN-101.

Q How would you describe the treatment in your own words?

A This gene therapy uses an adeno-associated virus, which is the most common gene therapy strategy. AAV is a way of delivering a good copy of the gene to any tissue—in this case photoreceptors. The gene is encapsulated inside the AAV.

Q How is the vector delivered?

A A needle injects the vector into the potential space between the photoreceptor and the retinal pigment epithelium. The virus almost instantaneously transduces the tissues and delivers the gene into the cell. The gene product isn't integrated into the host genome. Instead, it resides in the nucleus as a DNA strand, where it's available for the host cell to use to transcribe and translate and hopefully start expressing the *GUCY2D* protein. Once it expresses those normal proteins, the photoreceptors start working more normally.

Q Why is LCA1 a suitable target for this approach?

A In LCA1, *GUCY2D* fails to encode a protein that helps to recycle cGMP, a crucial second messenger for the phototransduction cascade. Without cGMP, the photoreceptors can't recover after being stimulated by light. Optical coherence tomography studies have shown the photoreceptor layer appears to be relatively intact throughout life in most of these patients and they have stable, albeit severe, vision loss. For gene therapy to be successful, the tissue needs to be intact, the photoreceptors need to be intact. Thus, LCA1 is a good fit for gene therapy.

Q What more can you tell us about the design of the Phase I/II trial?

A The first three cohorts that received ascending doses included three adults each with 20/200 vision or worse. Cohort 4 included adults with 20/80 vision or worse, and cohort 5 enrolled three children ages 6 to 18 with 20/80 vision or worse, all of whom received the highest dose.

Q What's been learned so far?

A It's almost a year since the last patients were treated. The treatment is relatively well-tolerated and the study met the safety endpoint so far. The change in best-corrected visual acuity from baseline was variable. The highest-dose cohorts trended toward being able to read smaller letters, but it wasn't statistically significant.

In the high-dose cohorts, improvement in full-field stimulus (FST) test results were statistically significant starting at 28 days and sustained thereafter. And some patients showed improvement on a mobility test, although only four high-dose patients were tested.

BIO

Dr. Yang is an associate professor of ophthalmology at Oregon Health & Science University, Portland.

DISCLOSURE: OHSU receives support from Atsena for clinical trials, but Dr. Yang receives no direct honorarium from the company.

REFERENCE

1. Kay CN. Six-month safety and efficacy of ATSN-101 in patients with Leber congenital amaurosis caused by biallelic mutations in GUCY2D (LCA1). Paper presented at the Association for Research in Vision and Ophthalmology 2023; New Orleans, LA; April 24, 2023.

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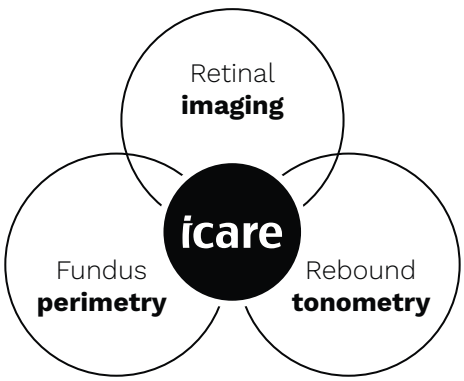

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