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Retina 2022

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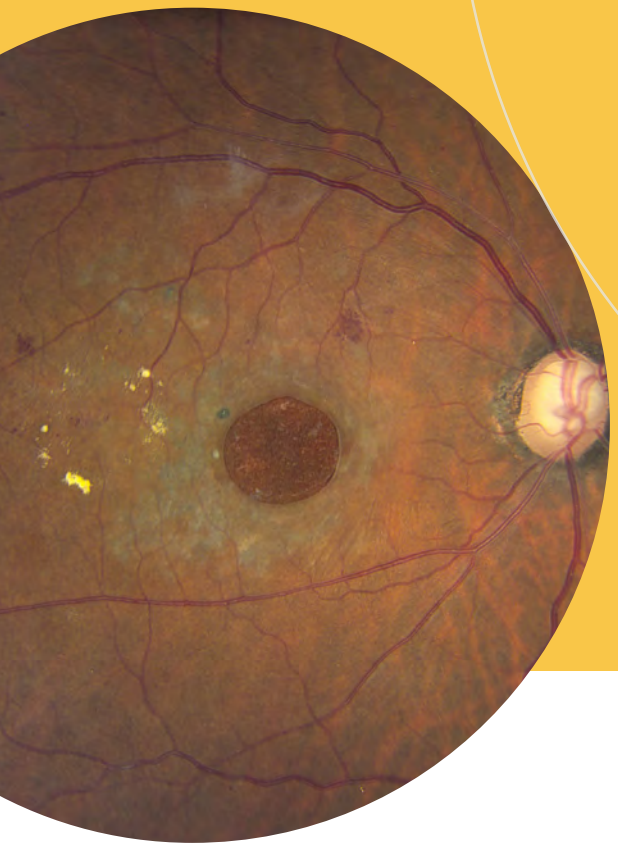


Protecting Sight. Empowering Lives.®

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

Inspired by a real patient with DME.

375 MATH TESTS

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.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

EYLEA ACHIEVED RAPID, SUSTAINED OUTCOMES IN DME

Demonstrated efficacy outcomes in VISTA and VIVID, phase 3 anti-VEGF trials in DME (N=862)[1]

Mean change in BCVA (ETDRS letters) at Year 1 from baseline[1-5,*]

	Initial Gains (Month 5)		Primary Endpoint (Year 1)		Prespecified Exploratory Endpoint (Year 3)	
	VISTA	VIVID	VISTA	VIVID	VISTA	VIVID
EYLEA Q4	+10.3 (n=154)	+9.3 (n=136)	+12.5 (n=154)	+10.5 (n=136)	+10.4 (n=154)	+10.3 (n=136)
EYLEA Q8†	+9.9 (n=151)	+9.3 (n=135)	+10.7 (n=151)	+10.7 (n=135)	+10.5 (n=151)	+11.7 (n=135)
Control	+1.8 (n=154)	+1.8 (n=132)	+0.2 (n=154)	+1.2 (n=132)	+1.4 (n=154)	+1.6 (n=132)

P<0.01 vs control at Year 1.

The analyses of these exploratory endpoints were not multiplicity protected and are descriptive only.

Year 2 data was consistent with results seen in Year 1.[5]

VISTA and VIVID study designs: Two randomized, multicenter, double-masked, controlled clinical studies in which patients with DME (N=862; age range: 23-87 years, with a mean of 63 years) were randomized and received: 1) EYLEA 2 mg Q8 following 5 initial monthly doses; 2) EYLEA 2 mg Q4; or 3) macular laser photocoagulation (control) at baseline and then as needed. From Week 100, laser control patients who had not received EYLEA rescue treatment received EYLEA as needed per re-treatment criteria. Protocol-specified visits occurred every 28 (±7) days.[1]

In both clinical studies, the primary efficacy endpoint was the mean change from baseline in BCVA at Week 52, as measured by ETDRS letter score.[1]

*Last observation carried forward; full analysis set.
†Following 5 initial monthly doses.

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH DME AT HCP.EYLEA.US

anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

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).

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Korobelnik JF, Do DV, Schmidt-Erfurth U, et al. Intravitreal aflibercept for diabetic macular edema. *Ophthalmology.* 2014;121(11):2247-2254. doi:10.1016/j.ophtha.2014.05.006 **3.** Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmoogy.* 2015;122(10):2044-2052. doi:10.1016/j.ophtha.2015.06.017 **4.** Data on file. Regeneron Pharmaceuticals, Inc. **5.** Heier JS, Korobelnik JF, Brown DM, et al. Intravitreal aflibercept for diabetic macular edema: 148-week results from the VISTA and VIVID studies. *Ophthalmology.* 2016;123(11):2376-2385. doi:10.1016/j.ophtha.2016.07.032

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

04/2021
EYL.21.03.0211

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.

5.3 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 (5.3)*]

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 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).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

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 humans 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 humans 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 in pediatric patients have not been established.

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.

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.

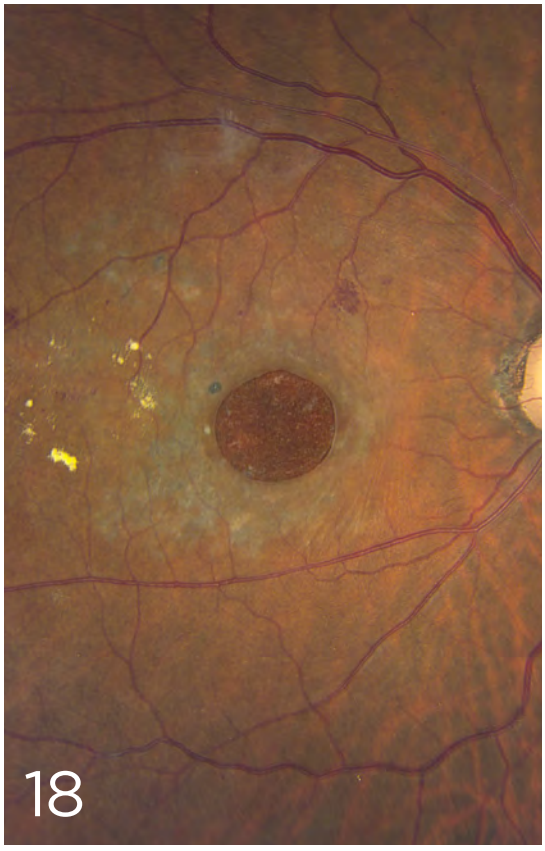
REGENERON

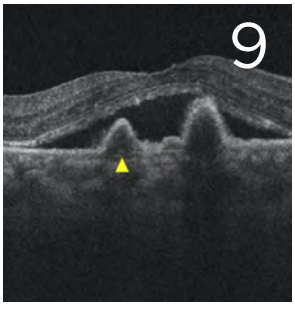
Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

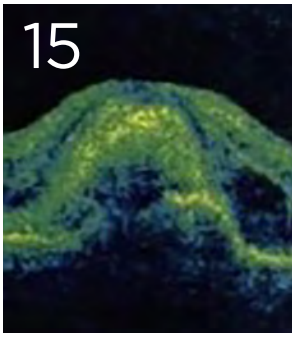
Issue Date: 08/2019
Initial U.S. Approval: 2011

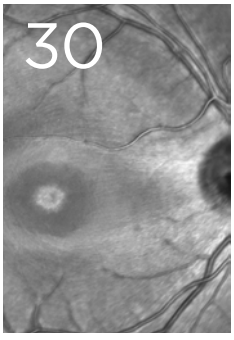
Based on the August 2019 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.20.09.0052









EyeNet Selections
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REPRINTS FOR
RETINA SUBSPECIALTY DAY
AT AAO 2022

COVER PHOTOGRAPHY
Jason S. Calhoun, COA

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Protecting Sight. Empowering Lives.

DISCLOSURE KEY. Financial interests are indicated by the following abbreviations: C = Consultant/Advisor; E = Employee; L = Speakers bureau; O = Equity owner; P = Patents/Royalty; S = Grant support. For definitions of each category, see aao.org/eyenet/disclosures.

Polypoidal Choroidal Vasculopathy, Part 1: Diagnosis

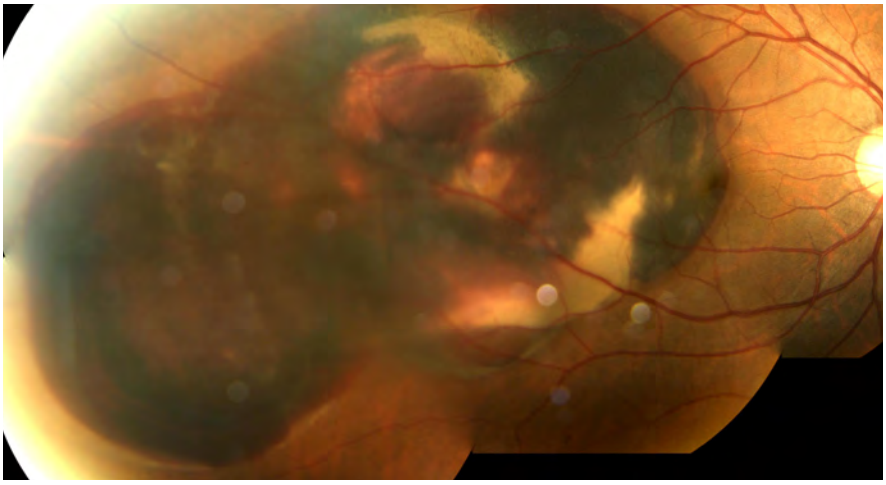
Is polypoidal choroidal vasculopathy (PCV) on your radar these days? If not, it should be. Recent studies have revealed a concerning picture of underdiagnosis of PCV, especially among ethnic groups previously thought to be relatively unaffected.[1]

Accelerated risk of blindness. "We've learned a lot about PCV over the past 10 years," said Gregg T. Kokame, MD, MMM, at the University of Hawaii in Honolulu.

Retinal specialists now know that PCV is a subtype of neovascular age-related macular degeneration (AMD)—and that, if left untreated, it can rapidly progress to blindness or hemorrhage. "Just a bit of gradual leakage in the macula with some recurrent episodes of bleeding can cause visual problems, and breakthrough hemorrhage and hemorrhagic retinal detachment" have been reported with the condition, said Timothy Y.Y. Lai, MD, FRCOphth, at the Chinese University of Hong Kong.

Role in anti-VEGF resistance. Research into the condition's prevalence has also shed light on its role in anti-VEGF resistance. "In all ethnic groups, [researchers have found that] PCV predicts anti-VEGF resistance, so it's critical to make the diagnosis," Dr. Kokame said.

Originally published in January 2022



BLEEDING RISK. *PCV can cause subretinal hemorrhage, as seen here in this fundus photo of a 52-year-old man.*

Diagnostic Challenge

"Diagnosis of PCV has always posed a challenge because indocyanine green angiography [ICGA] has been the gold standard for diagnosis," said Chiu M. Gemmy Cheung, MBBS, FRCOphth, at Duke-NUS Medical School in Singapore. "But ICGA is invasive and expensive, and it requires special equipment."

Initial studies of PCV "were done using fundus camera ICG, which is much less sensitive than the scanning laser ophthalmoscope [SLO] we now use with ICGA, so evaluations of prevalence were very low," said Dr. Kokame.

Rethinking ethnicity. Until relatively recently, the presumption was that PCV primarily affects those of Asian ancestry. But in a study among patients with wet AMD, Dr. Kokame found PCV in 51.6% of Asians, 28.6% of Pacific Islanders, and 31.9% of Caucasians—a rate much higher for Whites than previously thought.[2] This finding is bolstered by other research, Dr. Kokame said: "A number of papers from Canada and Europe show that PCV is underdiagnosed in Caucasians—and that 20% to 30% of Caucasian patients initially diagnosed with exudative AMD actually have PCV."

The condition is not as underdiagnosed in Black patients, he said, "because they often present with larger abnormal vessels and significant bleeding, visible on a fundus exam."

Coming to a Consensus

The problem of underdiagnosis spurred the Asia Pacific Ocular Imaging Society (APOIS) workgroup on PCV to tackle

BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING **CHIU M. GEMMY CHEUNG, MBBS, FRCOPHTH, GREGG T. KOKAME, MD, MMM,** AND **TIMOTHY Y.Y. LAI, MD, FRCOPHTH.**

two challenges: Defining diagnostic criteria[3] and comparing the diagnostic sensitivity and specificity of less-expensive OCT to ICGA.[4]

Their goal? A more accessible, affordable PCV diagnosis worldwide.

Defining terms. The APOIS recommended the following consensus terminology:

The polypoidal lesion. It may be tempting to shorten polypoidal lesion to polyp, said Dr. Cheung, "but since we can see a lumen and see dye filling it, we recommend the term polypoidal lesion since it appears to be more of a vascular lumen than a solid lump."

The branching neovascular network. The vascular network has been rebranded as neovascular. "The depth of the lesion is generally agreed to have breached Bruch membrane—exactly where we would find a type 1 neovascular membrane—and its exudation often responds to anti-VEGF, so we recommend the term branching neovascular network," said Dr. Cheung.

With PCV, said Dr. Kokame, "The blood vessels develop a bulge at the end of the vessels in the branching neovascular network—or, sometimes, within them. You see this beautiful network and then several of these aneurysmal dilations or polypoidal lesions."

Identifying key diagnostic criteria. "We initially evaluated the performance of nine signs for differentiating PCV from neovascular AMD," said Dr. Cheung. "It's now down to three primary criteria that can be detected without needing ICGA, and we can differentiate PCV from typical neovascular AMD with about 90% accuracy."

The APOIS proposed the following signs to differentiate PCV from typical neovascular AMD.

Using OCT. The three primary signs seen on OCT are:

- a sharp-peaked pigment epithelial detachment (PED), which appears as an inverted U or thumb-like protrusion;
- a ring-like lesion under the retinal pigment epithelium (RPE), possibly with a hyperreflective center; and
- a complex-shaped RPE elevation, with a hyperreflective branching neovascular network.

The first two signs can be seen on OCT-B scans; the third can be visualized with en face OCT.

Additional signs that can be observed on OCT are:

- a complex or multilobular PED;
- a double-layer sign (the split between the RPE and Bruch membrane, often where the branching neovascular network component lies);
- thick choroid with dilated Haller layer vessels; and
- fluid compartment with predominant subretinal fluid.

Using color fundus photography. Clinicians should look for an orange nodule appearing as a subretinal round elevation.

With regard to this sign, Dr. Cheung said, "If patients still have persistent fluid after three loading doses of anti-VEGF, we again look for the sharp-peaked PED and the sub-RPE ring—but now the third sign is an orange nodule, which may be due to the resolution of subretinal fluid and hemorrhage after initial treatment.

In addition, extensive subretinal hemorrhage may be seen.

Validating the role of OCT. In the second report, Dr. Lai noted, "We used only OCT to determine the PCV spot size—and by looking at the OCT findings alone, we could treat 100% of the polypoidal lesions and about 90% of the branching neovascular network."

The significance of the orange nodule was identified in this report, particularly in anti-VEGF nonresponders.[4] The nodules "can often be seen more clearly once fluid and blood decrease after initial anti-VEGF treatment," the authors wrote.

Other studies have validated the APOIS findings; a 2021 study in Singapore used OCT and fundus photography to identify asymptomatic PCV in a cohort of 961 ethnic Chinese without using ICGA.[5]

PCV Features in Asians and Caucasians

Corvi et al. compared potential PCV features in 128 Asians and 122 Caucasians using multimodal imaging (color fundus photography, spectral-domain OCT, fluorescein angiography, and ICGA). All were treatment-naive.

FEATURE	ASIAN	CAUCASIAN
Subretinal hemorrhage	53.9%	24.6%
Pachyvessels	84.4%	28.7%
Choroidal vascular hyperpermeability	70.3%	17.2%
Widespread polypoidal lesions	19.5%	8.2%
Drusen	49.2%	79.5%
BCVA	0.7 logMAR	0.4 logMAR
Size of hemorrhage	7.5 ± 15.2 mm^2	1.3 ± 3.3 mm^2

BCVA = best-corrected visual acuity
SOURCE: Corvi F et al. *Am J Ophthalmol.* Published online Aug. 23, 2021.

Additional OCT Nuances

OCT B-scans. In his research, Dr. Kokame found that OCT B-scans could be successfully used to diagnose PCV. The presence of characteristic inverted U-shaped elevations in the RPE were visible on the B-scans and helped differentiate PCV from typical wet AMD, he said. (See "OCT B-Scans Pin Down Dx of PCV," News in Review, in the August 2021 issue of *EyeNet*.)

"PCV is actually a type 1 choroidal neovascularization growing between

Bruch membrane and the RPE, but with aneurysmal dilations that cause the inverted U-shaped elevation," said Dr. Kokame.

The condition "often presents just like typical exudative macular degeneration, with leaking and bleeding in the macula and significant vision loss. However, the characteristic finding of an inverted U-shaped lesion with heterogeneous reflectivity is seen in up to 57% of cases of PCV and not in typical exudative AMD," he added.

It's critical to review OCT B-scans before treatment, he noted. "After anti-VEGF, the ability to identify those lesions with OCT-B scan goes down to 27%."

Are there other tips to differentiate PCV from typical exudative AMD? Other distinguishing features include greater height of subretinal fluid, more serous retinal detachment, more frequent RPE detachment, and more frequent subretinal hemorrhage, Dr. Kokame noted.

OCTA. With OCT angiography (OCTA), "you can look at the flow inside these lesions without using dye and see some of the branching neovascular network very well," said Dr. Lai. "But sometimes the polypoidal lesions don't show up well because of turbulent or slow flow inside them."

Currently, swept-source and wide-field OCTA, which give better resolution and depth-of-field analysis, are available primarily at research centers, said Dr. Lai. "But the price is going down; they'll likely be commercially launched in the next few years."

En face OCT. With regard to using en face OCT, "We found that the RPE-RPE fit slab is the most accurate in identifying PCV," said Dr. Kokame. "The ORCC slab, from the outer retina to the choriocapillaris, is also useful. You can simply go back to an old OCT to select both of those."

Sight-Saving Patient Education

How can clinicians educate patients about PCV? "Traditionally, we ask patients to look for scotoma, distortion, or waviness," said Dr. Cheung. In addition, the condition may not be picked up if only one eye is unaffected, she said. "One trick is to advise patients to check their eyes individually: Cover one eye at a time and look at a straight-edged object like a window or door-frame."

Dr. Cheung noted that phone-based apps are being developed, with the goal of furthering early detection.

But at this point, multimodal imaging and color fundus photography have a key role to play in making the diagnosis, particularly in those settings where ICGA is either unavailable or not routinely used.

The bottom line: While PCV presents similarly to wet AMD, an early differential diagnosis can save vision. With PCV, "there's leaking under the retina, macular edema, intraretinal edema, subretinal hemorrhage, and detachment, so it looks like typical exudative AMD until you do more specific testing," said Dr. Kokame.

1 Kokame GT et al. *Ophthalmol Retina.* 2021; 5(10):954-961.
2 Kokame GT et al. *Ophthalmol Retina.* 2019; 3(9):744-752.
3 Cheung CMG et al. *Ophthalmology.* 2021; 128(3):443-452.
4 Teo KYC et al. *Ophthalmol Retina.* 2021; 5(10):945-953.
5 Fenner BJ et al. *Ophthalmol Retina.* Published online Sept. 21, 2021.

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Dr. Kokame is chief of ophthalmology and clinical professor at the University of Hawaii School of Medicine and founding partner, senior consultant, and CEO of Retina Consultants of Hawaii, both in Honolulu. *Relevant financial disclosures: Bausch + Lomb: C,L; Carl Zeiss: L; Genentech: S; Novartis: S; Regeneron: S; RegenxBio: S.*
Dr. Lai is a clinical professor (honorary) of ophthalmology and visual sciences at the Chinese University of Hong Kong. *Relevant financial disclosures: Allergan: C,L,S; Bayer: C,L,S; Boeringher Ingelheim: C,L,S; Novartis: C,L,S; Roche: C,L,S.*
See the disclosure key, page 5. **For full disclosures,** see this article at aao.org/eyenet.

PAGE 9: Part 2: treatment.

Polypoidal Choroidal Vasculopathy, Part 2: Treatment

Greater awareness of the need to diagnose polypoidal choroidal vasculopathy (PCV) begs the question of best practices for treatment. Do therapies used for other forms of age-related macular degeneration (AMD) work?

Moreover, do therapies work for both components of PCV—its characteristic polypoidal lesions and its branching neovascular networks—to dry out the eye and occlude the lesion itself?

Traditionally, clinicians have been able to visualize the polypoidal lesion much better than the branching neovascular network when using indocyanine green angiography (ICGA), said Chiu M. Gemmy Cheung, MBBS, FRCOphth, at Duke-NUS Medical School in Singapore. This has led to the use of an occlusive method to target the lesion with focal laser or photodynamic therapy (PDT), she said.

But now, "with the advent of anti-VEGF therapy for typical neovascularization, anti-VEGF is being used in PCV," Dr. Cheung said. "Using OCT as an assessment tool, we have observed that anti-VEGF can reduce exudation effectively, although the rate of occluding the polypoidal lesions may be lower than therapies that include laser," she explained.

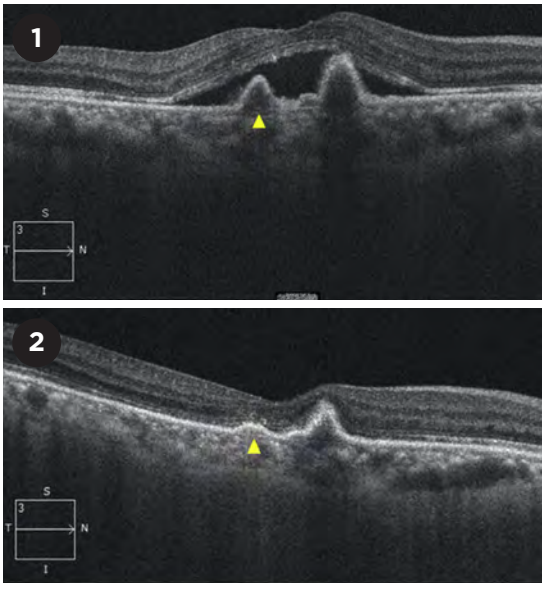
Originally published in February 2022

A Growing Role for Anti-VEGF

Last year, the Asia Pacific Ocular Imaging Society (APOIS) clarified its latest thinking on how the pathophysiology of PCV differs from typical AMD.[1]

"Our newest understanding is that the neovascularization is the backbone of the PCV complex," said Dr. Cheung. "We treat the exudation with anti-VEGF, whereas the polypoidal lesions behave like a complication of the network that can come and go."

"With this type of choroidal neovascularization, the blood vessels develop a bulge at the end of the vessels, or within the vascular complex, so the polypoidal lesions are actually part of the abnormal subretinal vessels themselves," added Gregg T. Kokame, MD, MMM, at the University of Hawaii in Honolulu.



ANTI-VEGF IMPACT. *OCT B-scan images (1) before and (2) after anti-VEGF treatment. Arrowhead = a U-shaped elevation of the retinal pigment epithelium that is typical of polypoidal lesions.*

The big three. Bevacizumab, ranibizumab, and aflibercept are all used to treat PCV. "I would be happy to use any of the three commonly available anti-VEGF agents," said Dr. Cheung. She added, "I start off with three monthly loading injections and, after achieving a dry retina, continue with a treat-and-extend protocol. If there is persistent fluid after the three initial doses, I might add three further monthly injections until month 6."

"We've been using ranibizumab and bevacizumab over the past 15 years to treat PCV, and aflibercept in the 10 years it's been available," said Timothy Y.Y. Lai, MD, FRCOphth, at the Chinese University of Hong Kong.

"Ranibizumab works well as a monotherapy: It can maintain or improve vision, and even reduce some polypoidal lesions, but frequent injections are required," Dr. Lai said. "Some data show that aflibercept might be slightly better compared with ranibizumab, but there is no real head-to-head trial."

BY REBECCA TAYLOR, CONTRIBUTING WRITER, INTERVIEWING **CHIU M. GEMMY CHEUNG, MBBS, FRCOPHTH, GREGG T. KOKAME, MD, MMM,** AND **TIMOTHY Y.Y. LAI, MD, FRCOPHTH.**

Kokame GT et al. *Ophthalmol Retina.* 2021;5(10):954-961.

What about brolucizumab? The newest anti-VEGF drug, brolucizumab (Beovu), was approved in 2019 but is not yet available worldwide.

In the HAWK and HARRIER trials, researchers compared brolucizumab to aflibercept. While the trials were designed for neovascular AMD, a later subset analysis of data from HAWK involving outcomes in patients with PCV showed comparable gains in vision with the two drugs and better resolution of intraretinal and subretinal fluid with brolucizumab than with aflibercept.[2] Results of this analysis showed that brolucizumab is "the best agent to decrease subretinal fluid, but patients can develop severe vitritis and vasculitis with vision loss, so it's only used when other agents have not had an adequate response, and patients are well informed of the risks of vision-threatening inflammation," said Dr. Kokame.

The evidence evolves. The EVEREST II study compared ranibizumab monotherapy to ranibizumab plus PDT for treatment of PCV.[3] And the PLANET study of PCV patients compared aflibercept monotherapy to aflibercept plus PDT—but PDT was only given as rescue therapy after 12 weeks.[4]

In PLANET, only 18% of patients met the criteria for rescue PDT, and most of these patients only received one PDT treatment. "Because of this design, the study really compares a group where 100% of patients were treated only with aflibercept to a group where 82% of patients were treated only with aflibercept, so the assessment of the effect of PDT was limited," said Dr. Kokame.

"The PLANET data suggest we can be quite confident of using aflibercept monotherapy in about 80% of cases," said Dr. Cheung. As for closing the polypoidal lesions, "the EVEREST II study with ranibizumab monotherapy achieved closure in about one in three lesions—and in the PLANET study, aflibercept monotherapy was similar, at 30% to 40%," she said.

Ad hoc studies. Given the lack of large PCV trials, some retina specialists are doing their own research. "We did a number of studies on our own showing that patients receiving ranibizumab didn't do as well as patients with aflibercept; they had more lesions and persistent leakage," said Dr. Kokame. "When we switched to aflibercept, the lesions and leakage lessened. Bevacizumab also doesn't work as well, anatomically, as aflibercept."

And Dr. Cheung said, "In one of our latest trials in Singapore, we used aflibercept monotherapy to achieve polypoidal lesion closure by extending the loading phase to up to six doses in the first 24 weeks, and we achieved closure in 55% of the eyes."[5]

A note on treatment response. The key with using anti-VEGF for PCV is to assess treatment response at month 3, looking at pigment epithelial detachments (PEDs) as well as vision and fluid, said Dr. Cheung.

"We have learned from the latest data that instead of the strict protocol to achieve a completely dry retina, we may be able to tolerate a little subretinal fluid if there are no other signs of disease," said Dr. Cheung. However, "an aggressive polypoidal lesion may manifest as high PEDs with sub–retinal pigment epithelium rings, and these eyes may develop a sudden-onset hemorrhage and devastating reduction in vision." Given this, she said, "I may recommend combination therapy to achieve control of disease faster."

A note on insurance requirements. In the United States, the insurance companies play an outsized role in anti-VEGF protocols. As Dr. Kokame noted, "We often have to start with bevacizumab and are usually required to use at least three injections. Only then can we request alternative injections if there is anti-VEGF resistance."

High Index of Suspicion Needed

With PCV, the risks of delayed diagnosis or treatment are high, the experts emphasized. The condition can lead to "gradual leakage in the macula with recurrent episodes of bleeding that can cause fibrosis—or one big episode of bleeding," Dr. Lai said. "Breakthrough vitreous hemorrhage and hemorrhagic retinal detachment have also been reported, requiring vitrectomy to deal with these very complicated cases."

With neovascular AMD, Dr. Kokame said, "injections of anti-VEGF medications are our usual treatment, but we often have cases that don't respond—so it's important to make the PCV diagnosis" in these instances.

Quiescence isn't cure. PCV is now seen as a chronic disease requiring long-term follow-up, said Dr. Cheung. "We've come to realize it's not just about giving three or six injections," she said. "Many of these eyes will have recurrences after a period of quiescence lasting a few months, but it's dangerous to wait until patients present with another drop in vision, because sometimes you can't recover that vision again."

"If you treat patients properly with anti-VEGF or combination therapy, they usually get a vision improvement in the first year or two, but they are very prone to recurrences in the future," Dr. Lai said.

A Continuing Role for Combination Tx

A poor response to anti-VEGF injections is common with PCV, Drs. Cheung, Kokame, and Lai pointed out. As Dr. Kokame noted, "PCV predicts anti-VEGF resistance, which is why it's critical to make the diagnosis—and to look for PCV with OCT-B scan, en face OCT, and ICGA if available." (For more on diagnosis, see part 1 of this story in the January issue at aao.org/eyenet.) He added that a PCV diagnosis "can suggest alternative therapy, including combination therapy with PDT or laser photocoagulation for extrafoveal polypoidal lesions."

Use of PDT. Photodynamic therapy "is not performed enough in the United States, although PDT with anti-VEGF is a primary treatment we offer [PCV]

patients, resulting in fewer injections and better anatomic results," said Dr. Kokame. "In EVEREST II, it gave better vision with fewer injections."

Specifically, EVEREST II found that ranibizumab plus PDT brought higher gains in visual acuity and nearly twice the rate of lesion closure (69.3% vs. 34.7%) compared to ranibizumab alone.[3] These gains held at 24 months, and combination therapy required half the number of injections. Moreover, Dr. Lai noted, "In EVEREST II, 20% to 25% of patients after combination therapy required no additional treatment."

Challenge of cost and access. Given the EVEREST II results, why not start with PDT? As Dr. Cheung explained, PDT is expensive—and it isn't widely available. "Combination therapy requires additional setup, generally with ICGA, to target the lesion, a special laser, and the drug verteporfin," she said. "Currently, there's a global shortage of verteporfin."

Fortunately, new research suggests that OCT-B scans can successfully target the PDT treatment sites, bypassing the need for ICGA. As the APOIS review reported, OCT-guided treatment spots were able to cover 90% of the branching neovascular networks and 100% of polypoidal lesions targeted by ICGA.[1]

On the Horizon: Future Tx

Bispecific antibodies, in-dwelling drug delivery, and gene therapy are in the running as future PCV treatments. "Agents promising increased durability have shown potential in neovascular AMD," said Dr. Cheung. "We hope they will also benefit eyes with PCV."

Faricimab. This investigational anti-VEGF drug, developed by Roche, targets two pathways. "Faricimab is a bispecific antibody that binds to angiopoietin-2 as well as VEGF," said Dr. Lai. "It showed better durability in treatment effect in the TENAYA and LUCERNE studies on neovascular AMD, and, compared to brolucizumab, it was very well tolerated with few cases of intraocular inflammation." PCV patients were recruited to both studies.

Reservoir drugs. With Susvimo (formerly known as the Port Delivery System), "you put a reservoir of ranibizumab inside the eye in the pars plana that lasts six to nine months, with the ability to refill the reservoir with an office procedure," said Dr. Kokame.

In-dwelling drug delivery addresses the goal of treatment durability. Susvimo (Roche) is now FDA approved for treatment of neovascular AMD. "Some PCV patients require such frequent injections—and with this device, you might be able to keep the macula at the quiescent stage," said Dr. Lai.

Gene therapy. Gene therapy targets the *ARMS2* and *HTRA1* genes associated with AMD. Studies involve injecting a virus vector inside the eye, which induces the eye to produce its own anti-VEGF treatment, Dr. Kokame said.

As for delivery, "Gene therapy is being developed with subretinal, intravitreal, and suprachoroidal delivery methods," he said.

1 Teo KYC et al. *Ophthalmol Retina.* 2021;5(10): 945-953.
2 Ogura Y et al. *Br J Ophthalmol.* Published online July 22, 2021.
3 Lim TH et al. *JAMA Ophthalmol.* 2020;138(9): 935-942.
4 Chaikitmongkol V et al. *Asia Pac J Ophthalmol.* 2020;9:260-268.
5 Teo KYC et al. *Br J Ophthalmol.* Published online Feb. 11, 2021.

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See the disclosure key, page 5. **For full disclosures,** see this article at aao.org/eyenet.

WHAT COULD SHE SEE THIS YEAR?

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

304 BINGO CARDS

Inspired by a real patient with Wet AMD.

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.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

PROVEN VISUAL OUTCOMES AT YEAR 1 IN THE VIEW STUDIES

Fewer injections with EYLEA Q8 vs ranibizumab Q4

Demonstrated in the largest phase 3 anti-VEGF trials completed to date in Wet AMD (N=2412)[1-3]

Proportion of patients who maintained vision (<15 ETDRS letters lost of BCVA) at Year 1 from baseline[1-3,*]

	Primary Endpoint (Year 1)	
	VIEW 1	VIEW 2
EYLEA Q4	**95%** (12.5 injections†)	**95%** (12.6 injections†)
EYLEA Q8‡	**94%** (7.5 injections†)	**95%** (7.7 injections†)
ranibizumab Q4	**94%** (12.1 injections†)	**95%** (12.7 injections†)

*Last observation carried forward; full analysis set.
†Safety analysis set.
‡Following 3 initial monthly doses.

Vision was maintained at Year 1 with ≈5 fewer injections with EYLEA Q8 vs ranibizumab Q4

EYLEA was clinically equivalent to ranibizumab.

VIEW 1 and VIEW 2 study 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 Q8 following 3 initial monthly doses; 2) EYLEA 2 mg Q4; 3) EYLEA 0.5 mg Q4; or 4) ranibizumab 0.5 mg Q4. Protocol-specified visits occurred every 28 (±3) days.[1] 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]

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH WET AMD AT HCP.EYLEA.US

anti-VEGF, anti–vascular endothelial growth factor; BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks; Q8, every 8 weeks.

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).

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc. **3.** Heier JS, Brown DM, Chong V, et al; for the VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548. doi:10.1016/j.ophtha.2012.09.006

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

03/2021
EYL.21.02.0019

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.

5.3 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 (5.3)*]

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 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).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

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 humans 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 humans 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 in pediatric patients have not been established.

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.

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: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.20.09.0052

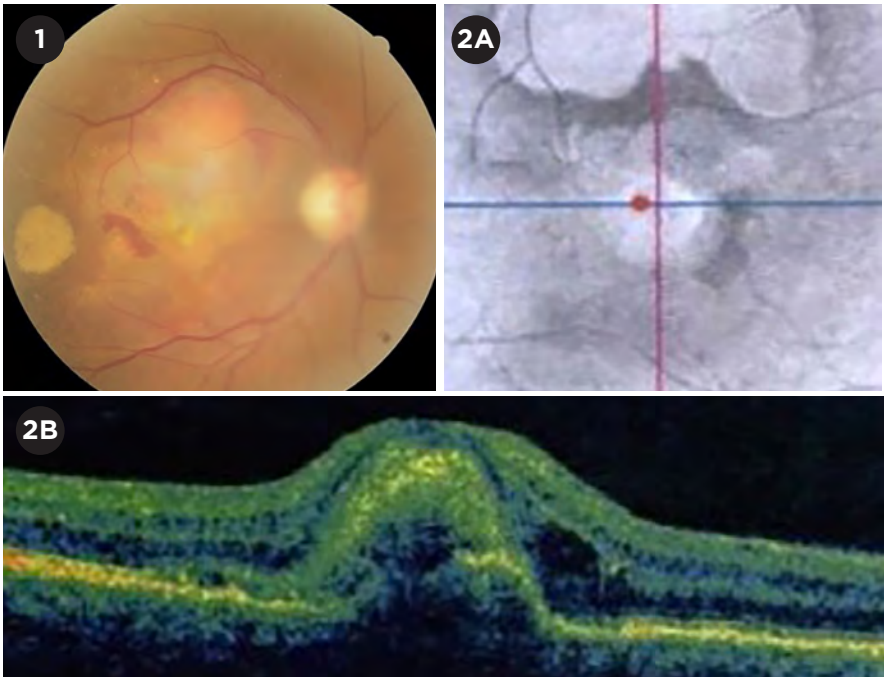
The Case of Deteriorating Vision and a Mysterious Yellow-Orange Lesion

Paula Pearl,* a 55-year-old Black woman, rescheduled her diabetic retinopathy fundus photo screening multiple times over a two-year period. At her appointment, she did not express concerns about her vision. Fundus photography of her right eye showed a yellow-orange subfoveal lesion that extended superiorly and a separate lesion of the right temporal macula. The left fundus was normal. We scheduled her for an appointment in the retina clinic for further evaluation.

At the Retina Clinic

Following an additional five-month delay, Ms. Pearl presented to the retina clinic and reported seeing a "worsening brown spot" in her right eye.

History. Ms. Pearl had a past medical history of hypertension, hyperlipidemia, and well-controlled type 2 diabetes without significant previous ocular history. During the previous two years, she had reported to the emergency department (ED) on three occasions after motor vehicle accidents. The ED notes documented all three collisions as "minor," and there was no evidence of ecchymosis, lacerations, or other head, eyes, ears, nose, and throat (HEENT) abnormalities. None of the accidents involved direct ocular trauma.



WHAT WE SAW AT THE RETINA CLINIC. *(1) A fundus photo shows a yellow-orange subfoveal lesion with nasal subretinal hemorrhage, a temporal subretinal hemorrhage with associated exudation, and retinal thickening superiorly. (2A) An OCT near infrared image shows variable reflectivity. (2B) An OCT B-scan section through the fovea demonstrates subretinal elevation centrally with distortion of foveal contour and adjacent intraretinal hyporeflectivity consistent with intraretinal fluid.*

Vision and anterior segment exam. Uncorrected visual acuity (VA) in the right eye had deteriorated from 20/80 at the earlier fundus photo screening to counting fingers (CF), but the left eye was stable at 20/50. Both eyes had normal IOP. Pupils were round and reactive without afferent pupillary defect, extraocular movements were full, and confrontation fields were full to counting fingers. Both eyes had a mild nuclear sclerotic cataract.

Funduscopic exam. Funduscopic exam of the right eye revealed a subfoveal yellow-orange retinal lesion that was 2 to 3 disc diameters in size. There was superior elevation, as well as superonasal and temporal subretinal hemorrhage (Fig. 1).

The left eye fundus examination was normal.

OCT. OCT near-infrared images

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BY **JAMES A. DAVID, MD,** AND **JARED M. VINCENT, MD.** EDITED BY AHMAD A. AREF, MD, MBA.

(Fig. 2A) of the right eye showed central and superior abnormalities. B-scan cross sections (Fig. 2B) showed a subretinal complex with intraretinal and subretinal fluid consistent with choroidal neovascularization. The subretinal complex at the fovea was surrounded by subretinal fluid nasally, temporally, and superiorly.

Other imaging. Fundus autofluorescence (FAF) imaging of the right eye taken at subsequent visits showed stippled central hyper- and hypoautofluorescence surrounded by a sharply demarcated ring of hyperautofluorescence (Fig. 3A). Fluorescein angiography (FA) of the right eye demonstrated early hypofluorescence centrally, consistent with blocking, followed by late hyperfluorescence consistent with staining and leakage (Figs. 3B-3D).

Initial Misdiagnosis

We made a diagnosis of choroidal neovascular membrane (CNVM) and presumed its origin to be idiopathic due to negative history of infections or inflammatory disorders, absence of intraocular inflammation, and lack of direct trauma.

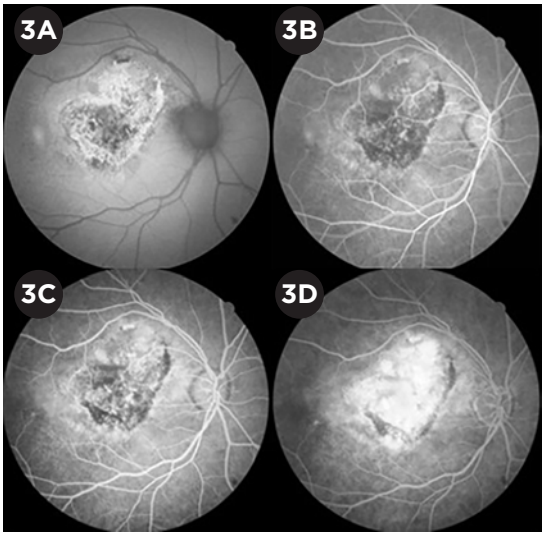
Ms. Pearl received an intravitreal injection of bevacizumab and was followed monthly. After six injections, the fluid continued to resolve, and her VA improved to 20/200. But she started to miss appointments, and VA in her right eye subsequently declined to CF. Change of therapy to aflibercept improved her vision to 20/100.

However, with poor follow-up and return of subretinal fluid, Ms. Pearl's vision subsequently regressed to CF despite multiple aflibercept and ranibizumab injections.

No Longer "Idiopathic"

Three years after the initial diagnosis of idiopathic CNVM, a different physician examined the patient and performed B-scan ultrasonography, which demonstrated that the lesion was hyperechogenic with a high A-spike and shadowing consistent with choroidal calcification (Fig. 4).

The diagnosis was changed to choroidal neovascularization secondary to choroidal osteoma.



FUNDUS AUTOFLUORESCENCE AND FLUORESCEIN ANGIOGRAM OF THE RIGHT EYE. *(3A) FAF shows stippled central hypoautofluorescence surrounded by a sharply demarcated ring of hyperautofluorescence. (3B) FA shows decreased central fluorescence consistent with blocking in arteriovenous phase, (3C) increased fluorescence consistent with staining versus early leakage during the venous phase, and (3D) significantly increased central hyperfluorescence with slightly indistinct margins most consistent with leakage in the recirculation phase.*

A Rare Finding

Choroidal osteomas are composed of ectopic mature bone tissue that grows in the choroid, most often in a peripapillary location. The first known case was presented at a meeting of the Verhoeff Society in 1975, and Gass et al. published the first case series of four patients in 1978.[1]

When we searched PubMed, we found that 135 cases were reported between 2010 and 2017. Shields et al. recorded 74 eyes of 61 patients with choroidal osteoma across 26 years, and Helsinki University Hospital estimated an incidence of 1 in 5 million.[2]

Roughly 80% of cases are unilateral. There is a female predominance with a female:male ratio of 2:1. The condition is usually detected in early adulthood, but pediatric cases have been documented in patients as young as 3 years old.[1]

Differential Diagnosis

The differential diagnosis for choroidal osteomas includes other types of ocular calcifications and tumors, such as sclerochoroidal calcification, choroidal hemangioma, choroidal melanoma, choroidal carcinoma, choroidal nevus, organoid nevus syndrome, posterior scleritis, and posterior scleral choristoma.

Sclerochoroidal calcification versus choroidal osteoma. Sclerochoroidal calcification occurs bilaterally in roughly half of cases and, compared with choroidal osteoma, targets an older demographic (mean age, 69 years old versus 28 years), is more likely to be multifocal, and appears along the vascular arcades as compared to a posterior or peripapillary location in osteomas.[3]

Pathogenesis

The exact origin of choroidal osteomas is unknown. Theories have included a metaplastic response to inflammation, trauma, or hormone levels, while some researchers have reported a genetic predisposition. However, the most recent hypothesis proposes that choroidal osteomas are congenital choristomas. Following years of ossification, the bone tissue eventually deossifies, which damages the outer retina, photoreceptors, and retinal pigment epithelium (RPE). A sight-threatening CNVM forms in 31% to 47% of cases.[3] This may be followed by accumulation of subretinal fluid or hemorrhage.

Imaging Characteristics

Choroidal osteomas can remain asymptomatic for years and usually are not diagnosed until visual impairment has developed. Although multiple imaging modalities have been used in the diagnosis and characterization of these tumors, funduscopy and B-scan ultrasonography are sufficient for diagnosis. The classic funduscopic appearance is a white-cream, yellow-gray, or orange lesion with well-defined, scalloped margins frequently located in the peripapillary region. The orange appearance may be more prevalent in areas with more

Kim Pecoraro

ossification.[4] Alternatively, a yellow hue may be due to RPE degeneration.[3] One series found basal diameter to range from 3 to 20 mm and thickness to range from roughly 0.75 to 3 mm.[5]

Ultrasound. Ultrasonographic characteristics include a highly reflective, elevated choroidal lesion with a high intensity A-spike and marked shadowing. The B-scan may measure the lesion to be larger than it seemed on funduscopic exam.[1]

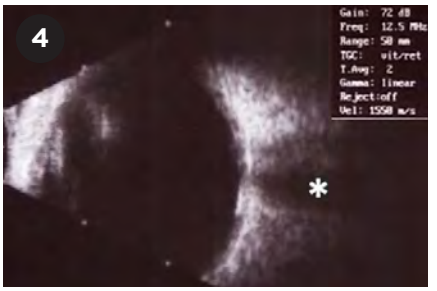
FAF. FAF can be used to document the extent of damage to the RPE. Deossified areas will initially be hyperautofluorescent, as the RPE is stressed and accumulates lipofuscin in the pigment epithelial cells. These areas will then become hypoautofluorescent as RPE atrophy takes place. Hypoautofluorescence in the fovea is associated with subnormal VA.[4]

FA. FA shows early patchy hyperfluorescence and late diffuse staining and is useful for detecting damage to the RPE and formation of a CNVM.

ICGA. Indocyanine green angiography (ICGA) shows early hypofluorescence and late diffuse multifocal fluorescence.[1]

OCT. On OCT, choroidal osteomas appear as a sponge- or lattice-like multilayered bony lamellar structure that is transparent to infrared light and thus has minimal optic shadowing. The tumor surface has been described as flat, dome-shaped, or undulating and can be hypo- or hyperreflective. Shields et al. have described findings such as horizontal lamellar lines and other findings on enhanced-depth imaging OCT that may correspond to bony structures such as Haversian canals, Volkmann canals, cement lines, and vascular channels.[4] A hyperreflective layer over the RPE on OCT should raise suspicion for development of a CNVM.[1] Subretinal fluid may be indicative of RPE dysfunction or CNVM. OCT angiography may allow better visualization of CNVM than FA or ICGA due to blocking from the tumor. OCT angiography can also be helpful in demonstrating regression of CNVM.[4]

Radiologic imaging such as computed tomography demonstrates a white bone-like lesion in the outer



ULTRASOUND B-SCAN OF THE RIGHT EYE. *B-scan ultrasound of the central macula shows hyperreflectivity at the level of the choroid with posterior acoustic shadowing (asterisk).*

border of the globe. T1-weighted gadolinium-enhanced magnetic resonance imaging demonstrates a high-intensity signal, while T2 weighting shows low intensity.[1]

Treatment Options

The treatment goal for choroidal osteomas is early detection and treatment of associated CNVM to preserve the patient's vision. Asymptomatic and peripheral cases should be monitored. Spontaneous resolution of subretinal fluid is possible.

Intravitreal anti-VEGF therapy as a standalone therapy can be used for subfoveal lesions with CNVM and exudation, while a combination of intravitreal anti-VEGF and photodynamic therapy should be considered for extrafoveal lesions. In areas of well-demarcated pigment epithelial leaks on FA, some authors have described success using light treatment with focal argon laser. However, laser therapy must be used with caution, as it may induce the harmful deossification process as well as the atrophy of outer retinal layers, including photoreceptors.[6] There are no proven surgical treatments.

Ultimately, the prognosis for visual acuity depends on the lesion's proximity to the fovea and degree of deossification. Deossified osteomas, particularly those that are subfoveal, have worse visual outcomes.[4] The overall likelihood of 20/200 vision or worse has been reported to be as high as 58%.[3]

Our Patient

We met with Ms. Pearl to discuss the etiology of her CNVM formation. We explained the new diagnosis of choroidal osteoma, along with her poor prognosis. The decision was made to extend the time between appointments and change the treatment schedule to treat as needed.

*Patient name is fictitious.

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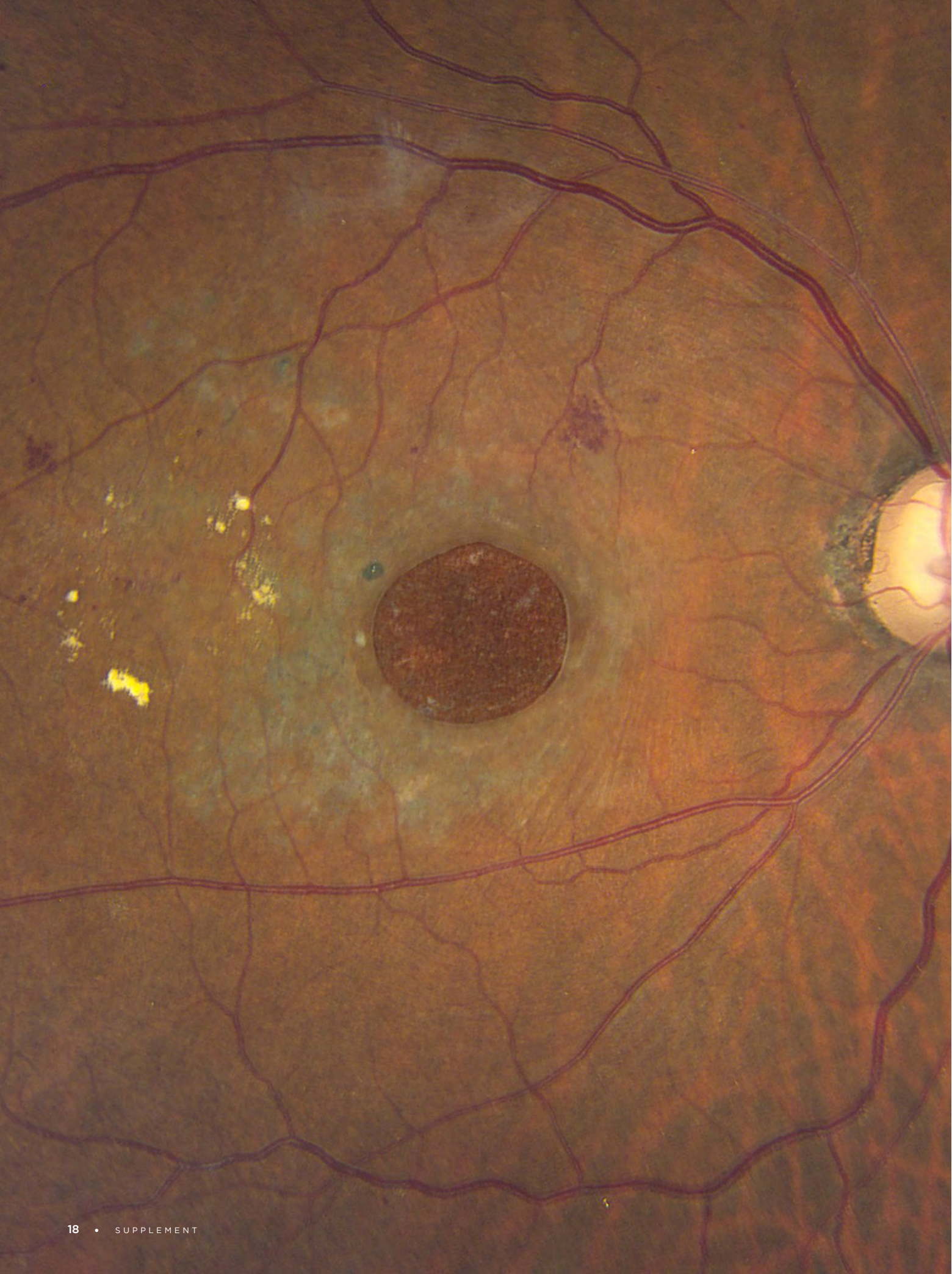

Repairing Challenging Macular Holes

The latest tissue scaffolding techniques offer both anatomic and visual acuity gains, even for the most difficult cases.

By Rebecca Taylor, Contributing Writer

THE INTERNAL LIMITING MEMBRANE (ILM) peel has been the gold standard to treat small, full-thickness macular holes since it was introduced in 1997.[1] But what happens when primary surgery fails? Do the latest surgical techniques, building on the initial success of the ILM peel, have a role to play in repairing challenging macular holes?

Tackling Complex Cases

"With macular holes in general, we have a 95% to 96% success rate, but these are smaller holes, the patient's first surgeries," said Peter K. Kaiser, MD, at the Cleveland Clinic's Cole Eye Institute. "The harder-to-fix holes are re-operations, very myopic or post-trauma holes, or longstanding holes."

High myopia. When a macular hole occurs in patients with high myopia, these affected eyes "sometimes have a posterior staphyloma, which makes it harder for the retina to stretch and close the hole," said John T. Thompson, MD, who practices in Baltimore. "Some have myopic macular schisis, a splitting of the retina around the hole," which also makes it difficult to close.

Chronic or refractory. Chronic holes (those older than a year) and refractory holes (those with one or more failed surgeries) typically have lower success rates. For instance, with a chronic hole, you may have more traction, such as additional epiretinal membrane, said Tamer H. Mahmoud, MD, PhD, at the William Beaumont School of Medicine in Royal Oak, Michigan. "You may be able to close that hole by releasing the tractional forces, but functional improvement may be limited because of underlying retinal pigment epithelium [RPE] atrophy."

Post-trauma. As for macular holes related to trauma, these can be very large with extensive RPE loss, Dr. Mahmoud said. In cases with a taut retina, tissue loss, and tangential traction, functional outcomes are reduced, and hole closure is limited, he added.

Other surgical challenges. Macular holes that present in patients with Alport syndrome or macular telangiectasia also can be problematic, as they limit the use of the ILM in repair, Dr. Mahmoud said. Another challenging scenario, said Chi-Chun Lai, MD, at the Chang Gung University College of Medicine in Taiwan, involves the macular hole with retinal detachment. And even accurate pre-op measurement of macular holes can be tricky (see "Shooting for Success," page 23).

Novel solutions. Faced with these difficulties, retina surgeons have developed a series of novel surgical strategies. ILM flaps, autologous retinal transplants (ARTs), and amniotic membrane transplants (AMTs) have garnered the most attention. Other techniques, including lens capsule transplants and subretinal blebs, also are used (see "Four Additional Options," page 22).

"The common thread for the most popular, successful techniques is to provide a scaffold of tissue beneath, within, or on the surface of the macular hole," said Dr. Thompson.

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Jason S. Calhoun, COA

ILM Flaps

In 2010, Polish surgeon Zofia Michalewska reported that her inverted ILM flap technique improved both hole closure and vision outcomes for macular holes larger than 400 µm.[1] Since then, a variety of ILM flap techniques employ the peeled ILM to serve as a scaffold to repair challenging macular holes.

Theme and variations. A number of ILM flap variations exist. Retina surgeons have more than 10 years of data on the ILM variants, said Dr. Lai. "They are very dependable and sustainable techniques to treat challenging macular holes."

"The ILM flap technique is simple yet brilliant because you're using tissue you were going to remove anyway, and it works very well for most complicated macular holes," said Dr. Thompson. Results of histologic studies indicate that with a successfully closed macular hole, "a glial plug seals the hole and pulls its edges together so that the foveal photoreceptors are where they belong."

With the flap techniques, the ILM becomes the tissue scaffold, whether it's an inverted flap, a "retracting door" flap, or even what's known as a "Texas taco" flap. (In the latter approach, the nasal ILM is peeled beyond the temporal edges of the hole, and the ILM flap is draped over the hole.[1])

Inverted ILM flap. "For any of the atypical holes, we may seriously consider doing an ILM flap initially and not an ILM peel," said Dr. Mahmoud. "We start by peeling the ILM, which disrupts the tangential traction, and use that ILM flap to cover the hole and help the retina bridge the gap."

"You can do an ILM flap from any direction, but if you do it temporally, it's by far the easiest. That's because the vector forces, when you go to air, allow that flap to cover the hole without additional manipulation," Dr. Kaiser said. "If you make it nasally, you have to use something to brush the flap over the hole."

A global meta-analysis of the ILM peel and the inverted flap technique in 1,403 eyes with macular holes found the flap technique better at closing holes of all sizes, including those with retinal detachment.[2] The inverted flap technique also resulted in greater BCVA improvement.

"Retracting door" ILM flap. For myopic patients, Dr. Mahmoud said, this technique is often his initial choice.[3]

"We start from the nasal side of the hole close to the optic disc, peel the ILM across the hole to the temporal side, then re-drape the ILM over the hole so it's a hinged flap," he said. "Because of the tangential traction from myopia, we're removing all tractional forces around the hole, and the ILM retracts and covers the hole."

He added, "We know from OCT angiography that the retina moves from temporal to nasal after gas tamponade, and since the flap moves from nasal to temporal where the base of the flap is, it closes the hole."

SPOT technique. To boost the success of ILM flaps, Dr. Lai employs an approach that combines sub-perfluorocarbon liquid (PFCL) and an ophthalmic viscoelastic device (OVD). The OVD acts as a "glue" to hold the flap in place. This approach is known as SPOT (sub-PFCL OVD injection). In one study, the technique reduced the risk of foveal gliosis and resulted in 74% of flaps still being present at six months postoperatively.[4]

Retina surgeons use SPOT to ensure that the ILM flap isn't dislodged during the procedure, said Dr. Lai. He also noted that he uses it to secure retinal transplants.

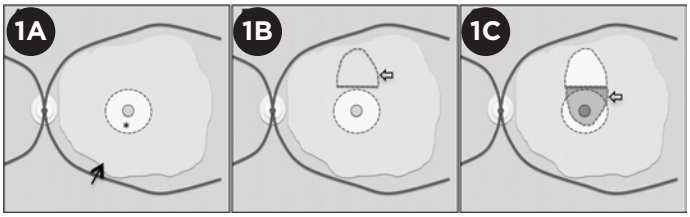
SWIFT technique. Another novel ILM flap technique is known as SWIFT (superior wide-base internal limiting membrane flap transposition). In a study of SWIFT in 17 eyes, it resulted in closure of myopic and chronic holes in 94% of eyes.[5] Follow-up VA was at least 20/70 in 48% of eyes and 20/80 to 20/200 in 53% of eyes.

Autologous Retinal Transplants

The ART procedure uses peripheral retina to close the macular hole.[6]

Using ART, "now we can close almost 100% of holes, and the beauty is not the procedure; it's the biology, the plasticity of the retina," said Dr. Mahmoud. On OCT, "initially, you see vertical lines between the graft and host, and the peripheral retina is thin. Over a few weeks, it starts thickening, and you see the alignment of the nuclear layer and plexiform layers. Eventually, you don't even see the margins," he said.

"Retina grows well with retina, so it integrates within the hole," said Dr. Thompson. "Everything outside the macula is 20/200 vision or worse, so most patients don't notice

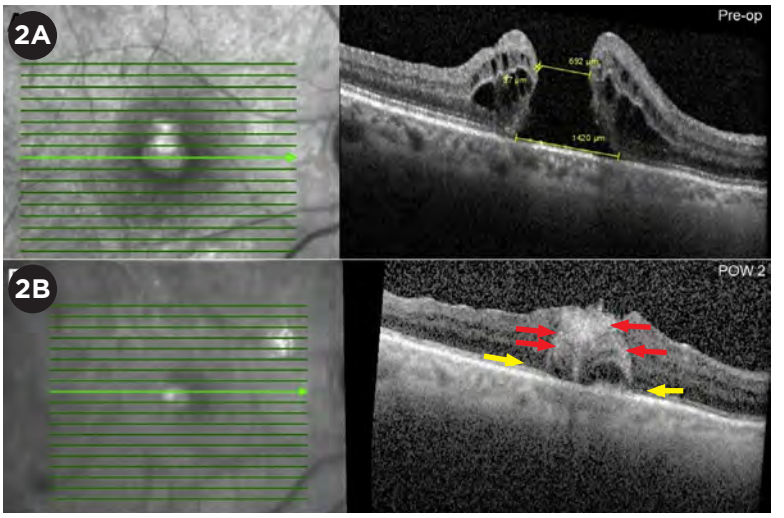


FLAP VARIATION. *For the SWIFT technique, following ILM peel (1A), a strip of residual ILM forms the base of the flap (1B). The flap is then positioned over the hole (1C), covering the hole and the neurosensory retina. (* = central macular region; black arrow = residual stained ILM; lighter arrows = ILM flap and macular hole).*

the blind spot created by the graft site." He agreed that ART can close even difficult holes but cautioned that "we don't know yet how well vision recovers."

In a 2019 study of 41 eyes with refractory macular holes undergoing ART, 87.8% had complete anatomic closure. Mean corrected VA improved in 36.6% of eyes, stabilized in 41.5%, and worsened in 21.9%.[7]

In a global study in 2020, 33 surgeons pooled data from 130 macular holes repaired with ART. While case type varied—from large primary holes to refractory holes and holes with retinal detachments—outcomes appeared consistent. Overall, the closure rate was 89% (78.5% complete and 10% small eccentric defect), and 43% of patients gained 3 lines of vision, 29% gained 5 lines or more, and 12% achieved 20/50 vision or better.[8]



ART. *(2A) Pre-op images show a macular hole with minimum diameter of 692 µm and maximum diameter of 1,420 µm. (2B) At post-op week 2 after ART, early integration of the transplant and partial reconstitution of the external limiting membrane and ellipsoid zone band (yellow arrows) are evident. (Red arrows = hyperreflective foci within the graft.)*

Cautionary notes. ART requires more skill and technical expertise than ILM flap techniques, said Dr. Lai. "Some publications say the graft should be 30% larger than the macular hole, which makes it difficult to measure." In addition, he said, schisis of the graft has been observed.

Overall, Dr. Lai concluded, more long-term data are needed.

Amniotic Membrane Transplants

Human amniotic tissue provides more than mechanical scaffolding: It's believed to spur the secretion of growth factors and RPE cell proliferation.[1] In AMT, Dr. Thompson said, "you create a tiny punch of the amniotic membrane, fold it, and plug the hole." He added, "Stan Rizzo in Italy deserves credit for this idea."

In a 2020 study, 36 patients with failed macular hole surgeries underwent AMT. At three months, 35 holes were still closed, and all but three patients experienced improved BCVA by at least 1 Snellen line.[9] Post-op imaging found gains in macular

Anatomy Versus Vision: A Tale of Two Timelines

After macular hole surgery, anatomic repair takes place before vision improves. "Hole closure is definitely the shorter of the two timelines, and you generally know, by two months out, if the hole is closed," said Dr. Thompson.

Although the ILM flap, ART, and AMT procedures can result in improved vision, patients may not achieve their best VA until six to 12 months after surgery, he added. "There's a reorganization process that gradually allows the patient to regain vision." (See "The Role of Retinal Plasticity," next page.)

Setting expectations. "A lot of these challenging holes have a loss of photoreceptors," Dr. Kaiser said. Thus, even though the blind spot will be smaller, and most patients will experience a slight improvement in vision postoperatively, "we warn them before surgery that because there's been damage to the outer retina, we won't get as much of a vision improvement" over the long-term.

During recovery, Dr. Thompson said he encourages patients to "use the eye, so the brain learns how to interpret the slightly distorted image from the eye with the macular hole." With regard to final visual outcomes, he said, "We're happy if they end up with 20/63 to 20/125 vision with these more challenging macular holes; that would be a win."

Even so, a patient's post-op mood may be positive. As Dr. Lai noted, if patients are concerned about the presence of a macular hole, "even if they don't get better vision after you repair the hole, they feel better psychologically."

sensitivity and photoreceptors around the plug edges.

Cautionary notes. "The stem cells and trophic factors may hypothetically help with hole closure and be neuroprotective," said Dr. Kaiser, "but AMT is not a magic cure-all."

Moreover, as with any new technique, there may be unforeseen downsides to the procedure. "The amniotic membrane persists in the subretinal space," said Dr. Mahmoud. Thus, over the long term, "it may prevent the diffusion of nutrients from the choroid and the RPE to the neurosensory retina."

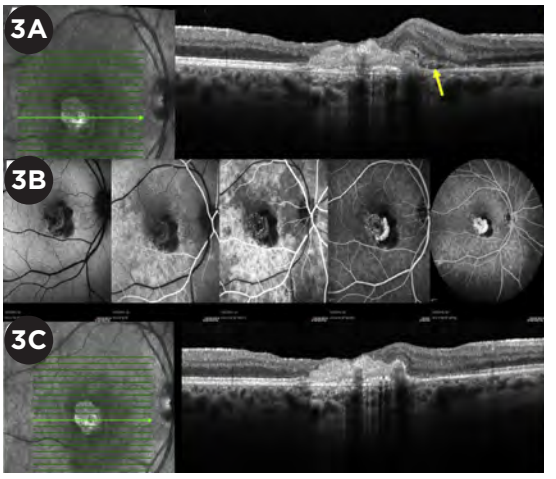
In addition, he noted, "Because of the mechanical adhesion and manipulation, you're destroying the RPE and photoreceptors at the edges of the hole, and those cells are critical for functional recovery [seen on] microperimetry and multifocal electroretinography."

Four Additional Options

Though the following techniques are less commonly used, they are potentially useful and worth considering, the experts said.

Lens capsule transplant. In this approach, the lens capsule serves as a scaffold, with a piece of the capsule used as a free flap. The creation of the capsular flap depends on the patient's lens status: In pseudophakic patients, the surgeon removes the posterior capsule, Dr. Kaiser said. "For phakic patients, you can use the anterior capsule, which is considerably easier" from a technical standpoint.

In one study of 50 eyes with large macular holes, lens capsule transplants showed a 96% closure rate with vision improvement. However, 31 eyes in this study also received autologous platelet concentrate to reduce capsule dislocation.[1]



AMT. *Late post-op images from AMT in a persistent macular hole. (3A) VA was counting fingers, and a retinal hemorrhage could be seen on exam (arrow). (3B) Images from fluorescein angiography show an area of blockage in the nasal fovea from the hemorrhage and leakage from a choroidal neovascular membrane. (3C) Following a series of anti-VEGF injections, VA improved to 20/150.*

Autologous platelet concentrate (APC). "If a patient doesn't have an ILM and you don't have access to other options, you might try this," said Dr. Kaiser. Autologous platelets contain growth factors and promote healing. However, Dr. Kaiser said, the use of APC is an older technique that is being replaced, "because if you use too much concentrate, it can 'gel' together and plug the hole, preventing closure."

The Role of Retinal Plasticity

These novel macular hole surgeries have revealed insights into how retina tissue heals.

In the meta-analysis by Marques et al.,[1] the researchers found that significant vision improvement is more likely to occur if the neurosensory layer is aligned, said Dr. Mahmoud. "Retina is like brain tissue; it takes time for the retina to connect. When we have a macular hole or retinal detachment, there is a disruption in the synapses between cells, although now we understand retinal plasticity from retinal transplants." He added, "That's why [flap] positioning and oversizing are important for closing the hole completely to allow more alignment for a better functional outcome." (For more, see "Shooting for Success," next page.) And while the surgeon can never predict how much a patient's vision might improve following macular hole surgery, "at least if we're successful at closing the hole, especially for high myopes, we can prevent a retinal detachment."

The precise mechanisms behind retinal plasticity are still unknown. "One hypothesis is that stem cells produced by the peripheral Müller cells have a role," said Dr. Mahmoud. Ectopic synaptogenesis also contributes to the process, he said: "When we put that retina in the center of the macula, it starts connecting with the adjacent macula and sends back more signals to the brain." Connections at the level of the nerve fiber layer may be involved, he added.

1 Marques RE et al. *Ophthalmic Surg Lasers Imaging Retina.* 2020;51(3):187-195.

In a randomized study of injection of APC after vitrectomy for macular holes, those who received APC (n = 53) experienced a 98% closure rate compared to 82% for those who didn't get injections of the concentrate (n = 57).[1] APC has also shown anatomic and functional benefits when combined with ILM peels.[1]

Subretinal blebs. Subretinal injection of balanced salt solution (BSS) hypothetically releases adhesions between photoreceptors and the RPE.[1]

Oftentimes, chronic holes and those that have undergone multiple prior procedures are held open by scar tissue, Dr. Kaiser noted. The subretinal bleb technique "comes from doing translocation procedures in macular degeneration. It produces a localized retinal detachment around the hole, freeing up scar tissue and allowing the hole to close."

Three small studies showed this technique achieved closure for persistent macular holes at rates from 85.4% to 90%.[1] In contrast, a 24-month study comparing ILM flaps to subretinal blebs in the treatment of refractory holes showed 85.7% closure in the flaps versus 57.1% in the blebs, with better functional outcomes with the flaps.[10]

Retinal incisions. Another technique intended to resolve scar tissue involves cutting "relaxing" or "radial" incisions in the retina. In one small study, six eyes had incisions to repair large macular holes that had failed previous surgery. All told, five holes closed, and three patients saw vision improve.[1]

Shooting for Success

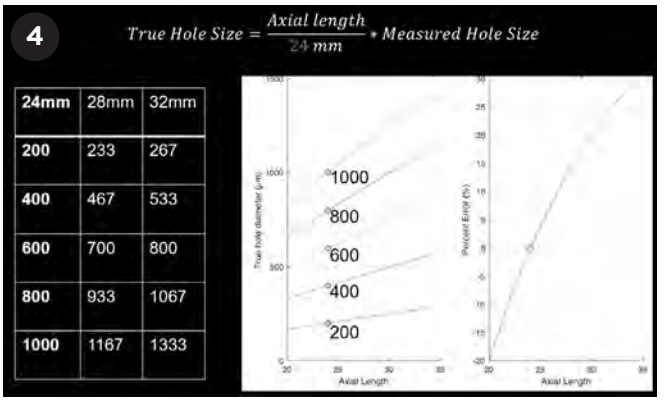
Pre-op planning. "For a patient with a hole smaller than 300 µm, we do an ILM peel," said Dr. Mahmoud. "If it's larger, we go for an ILM flap; and if it's larger than 650 to 700 µm, my personal choice is an ART."

"For the really big holes around 1,500 µm," said Dr. Kaiser, "the flap techniques or the subretinal blebs won't work, so you start to consider ART."

"Often the hole enlarges if the first surgery fails, so these [chronic] holes are 600 to 1,000 µm," said Dr. Thompson. "Because of the large gap in the macula, it's harder to get the edges to come together."

Measurement challenges. True measurement of the minimum linear diameter of macular holes poses its own challenges.[11]

"OCT is based on an eye-length of about 24 mm, but high myopes have longer eyes," said Dr. Mahmoud. "You have to multiply the OCT measurement by the true axial length and divide by 24 to know the true measurement: For example, a 400-µm hole in a 30-mm eye is actually 500 µm. This underestimated size of myopic holes may partially explain the historically low closure rate with just an ILM peel." Once adjusted to true size, he said, these holes can be matched to the best procedure for optimal outcomes.



POTENTIAL ERROR. *Transverse OCT measurements are subject to error in patients with long axial lengths. The graph at right shows the percentage of error for a hole that measured 400 µm on OCT with a 24-mm reference axial length. For the true measurement, multiply the OCT measurement by the true axial length and divide by 24, Dr. Mahmoud said.*

Intraoperative decision-making. "Unlike a typical hole where the technique is standardized, in these situations you get into surgery and decide how to repair it, based on the anatomy you find while operating," said Dr. Kaiser.

Dr. Thompson agreed. For instance, he said, the surgeon may have gone into surgery planning to do an ILM flap, but the flap breaks apart in an eye with a very thin ILM. "That's when we switch to a transplant; these are game-time decisions based on what the eye is giving us."

Post-op care. During follow-up, said Dr. Lai, it is important to watch for inflammation, infection, increase of IOP, a failed closure, or the patient's inability to keep a prone position—although, as he noted, "most of the patients are very stable."

With regard to prone positioning, Dr. Kaiser said, "I always get buy-in from patients: They need to be facedown for a week, for the majority of the day, period. This is the last dance; we need this surgery to work."

Looking Ahead: Research Needs

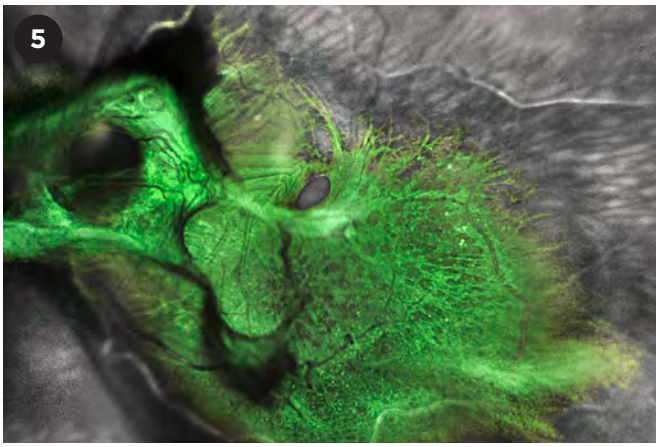
To date, no trials have compared these surgical techniques head-to-head, said Dr. Kaiser. "Right now, each surgeon has a pet technique they publish on." Moreover, he noted, "Currently, there are no imaging biomarkers or other features to help us predict which technique would work best with which hole."

Courtesy of Tamer H. Mahmoud, MD, PhD

Issues under investigation. Investigators at Dr. Lai's institution are developing a retinal "glue" to shorten the time patients need to spend in the prone position and doing basic research on the mechanism of wound healing, Dr. Lai said. "In the future we might introduce AI to predict [occurrence of] a macular hole, as patients are so worried about their fellow eye."

Other researchers are investigating a clear, permanent vitreous substitute that could be used after removing the vitreous gel, said Dr. Mahmoud, as well as "working on stem cell and RPE transplants in the form of a sheet, which might be combined with the retinal transplant for better functional improvement."

"A stem cell retinal patch would be a huge improvement in our field," Dr. Thompson said. Also on his wish list: "A gas bubble that stays large for a prescribed time and then rapidly disappears, so you'd have a good tamponade until it's no longer needed." This would eliminate a second surgery to remove the silicone oil currently used as tamponade for some transplants, he said.



CONCURRENT. *This 76-year-old patient presented with both a tractional retinal detachment and a macular hole.*

Bottom Line

Despite the work that remains to be done, radically improved outcomes for these surgeries mean that comprehensive ophthalmologists can now feel confident referring patients to repair older, challenging macular holes, said Dr. Kaiser. "In the past, the party line was that beyond two years, don't bother sending them to a retina specialist—but now, you may be pleasantly surprised."

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See disclosure key, page 5. **For full disclosures,** see this article online.

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WHAT COULD SHE SEE THIS YEAR?

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Inspired by a real patient with MEfRVO.

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.

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

CLINICALLY SIGNIFICANT VISION GAINS IN MEfRVO ACROSS 3 ROBUST CLINICAL TRIALS

Proportion of patients who gained ≥15 ETDRS letters (primary endpoint) and mean change in BCVA (ETDRS letters) (secondary endpoint) at Month 6 from baseline vs control[1-4,*]

VIBRANT (MEfBRVO)		COPERNICUS (MEfCRVO)		GALILEO (MEfCRVO)	
Gained ≥15 ETDRS letters	Mean change in ETDRS letters	Gained ≥15 ETDRS letters	Mean change in ETDRS letters	Gained ≥15 ETDRS letters	Mean change in ETDRS letters
EYLEA (n=91)	**EYLEA (n=91)**	**EYLEA (n=114)**	**EYLEA (n=114)**	**EYLEA (n=103)**	**EYLEA (n=103)**
53% vs 27% in the control group (n=90)	**+17.0** vs +6.9 in the control group (n=90)	**56%** vs 12% in the sham control group (n=73)	**+17.3** vs -4.0 in the sham control group (n=73)	**60%** vs 22% in the sham control group (n=68)	**+18.0** vs +3.3 in the sham control group (n=68)

P<0.01 vs control and sham control.

VIBRANT study design: Randomized, multicenter, double-masked, controlled study in which patients with MEfBRVO (N=181; age range: 42-94 years, with a mean of 65 years) were randomized to receive: 1) EYLEA 2 mg Q4 or 2) laser photocoagulation administered at baseline and subsequently as needed (control group). The primary efficacy endpoint was the proportion of patients who gained ≥15 letters in BCVA at Week 24 compared with baseline.[1]

COPERNICUS and GALILEO study designs: Randomized, multicenter, double-masked, sham-controlled studies in patients with MEfCRVO (N=358; age range: 22-89 years, with a mean of 64 years). Patients were assigned in a 3:2 ratio to either: 1) EYLEA 2 mg Q4 for the first 6 months or 2) sham injections (control) Q4 for a total of 6 injections. In both studies, the primary efficacy endpoint was the proportion of patients who gained ≥15 letters in BCVA at Week 24 compared with baseline.[1]

*Last observation carried forward; full analysis set.

SEE WHAT EYLEA COULD DO FOR YOUR PATIENTS WITH MEfRVO AT HCP.EYLEA.US

BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; Q4, every 4 weeks.

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).

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. *Ophthalmology*. 2015;122(3):538-544. doi:10.1016/j.ophtha.2014.08.031 **3.** Boyer D, Heier J, Brown DM, et al. Vascular endothelial growth factor Trap-Eye for macular edema secondary to central retinal vein occlusion: six-month results of the phase 3 COPERNICUS study. *Ophthalmology*. 2012;119(5):1024-1032. doi:10.1016/j.ophtha.2012.01.042 **4.** Holz FG, Roider J, Ogura Y, et al. VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol*. 2013;97(3):278-284. doi:10.1136/bjophthalmol-2012-301504

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

03/2021
EYL.21.02.0050

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.

5.3 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 (5.3)*]

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 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).

6.2 Immunogenicity
As with all therapeutic proteins, there is a potential for an immune response in patients treated with EYLEA. The immunogenicity of EYLEA was evaluated in serum samples. The immunogenicity data reflect the percentage of patients whose test results were considered positive for antibodies to EYLEA in immunoassays. The detection of an immune response is highly dependent on the sensitivity and specificity of the assays used, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to EYLEA with the incidence of antibodies to other products may be misleading.
In the wet AMD, RVO, and DME studies, the pre-treatment incidence of immunoreactivity to EYLEA was approximately 1% to 3% across treatment groups. After dosing with EYLEA for 24-100 weeks, antibodies to EYLEA were detected in a similar percentage range of patients. There were no differences in efficacy or safety between patients with or without immunoreactivity.

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 humans 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 humans 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 in pediatric patients have not been established.

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.

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: 08/2019
Initial U.S. Approval: 2011

Based on the August 2019 EYLEA® (aflibercept) Injection full Prescribing Information.

EYL.20.09.0052

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SATURDAY, OCT. 1

Patient Variability in Wet Age-Related Macular Degeneration (AMD)

Speaker: Yannek Leiderman, MD, PhD

Presented by Regeneron and designed for US retina specialists.

SUNDAY, OCT. 2

Making the Case: Expert Perspectives on Dry Eye

Speaker: Jay Mattheis, MD, MSPH, FACS—
Director, Peer Education, Novartis US Ophthalmics

Dr. Mattheis is an employee of Novartis. Dr. Mattheis no longer sees patients. Presented by Novartis Pharmaceuticals Corporation and designed for US eye care specialists.

MONDAY, OCT. 3

Explore a Different Path to Treating Dry Eye Disease

Speaker: Francis S. Mah, MD

Presented by Oyster Point Pharma, Inc., and designed for US eye care specialists.

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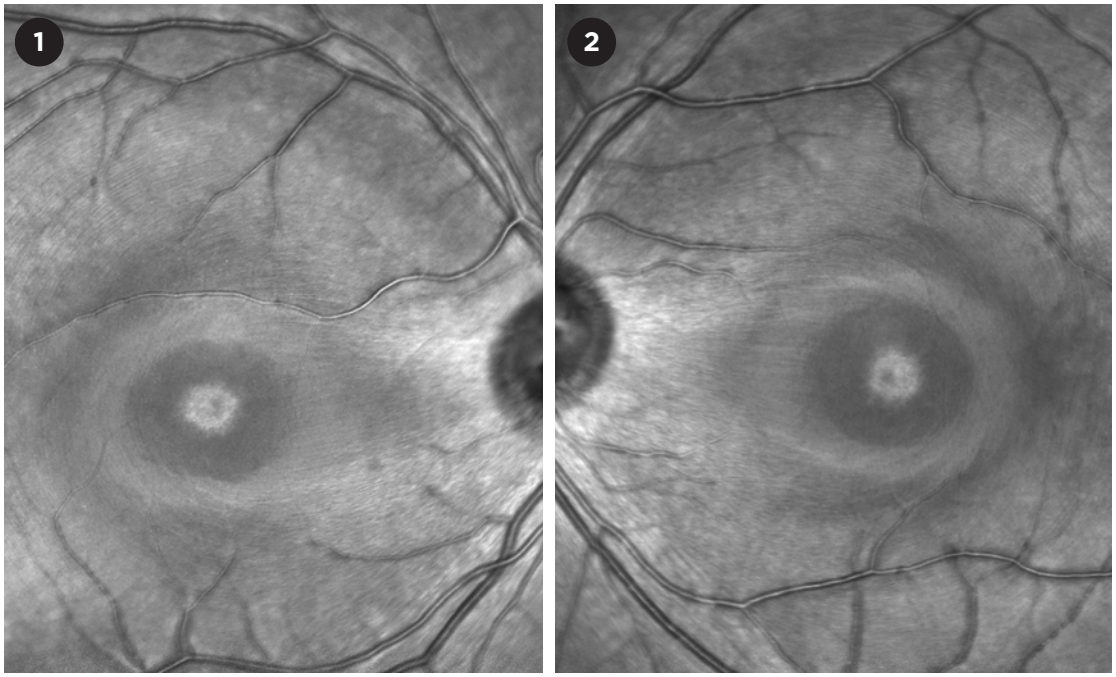
MYSTERY IMAGE

BLINK



Becky Weeks, John Moran Eye Center, Salt Lake City.

WHAT IS THIS MONTH'S MYSTERY CONDITION? *Visit aao.org/eyenet to make your diagnosis in the comments.*

LAST MONTH'S BLINK

Sialidosis Type 1

An asymptomatic 14-year-old boy was referred for a second opinion of cherry-red spots in his maculae. The best-corrected visual acuity was 20/20 in both eyes. The slit-lamp exam revealed snowflake cataracts, and the fundus exam found perifoveal graying with a cherry-red spot in both maculae. OCT showed deposits in the ganglion cell layer, and no leakage was found with fluorescein angiogram. Fundus autofluorescence (Figs. 1, 2) revealed a bull's-eye appearance to the maculae with hypoautofluorescence surrounding a hyperautofluorescent center.

Genetic testing through Invitae Comprehensive Lysosomal Storage Disorders Panel revealed a pathogenic variant in *NEU1* (neuraminidase 1) and a variant of unknown significance in *SMPD1* (sphingomyelin phosphodiesterase 1).

The patient was diagnosed with sialidosis type 1. This gene mutation causes a lysosomal storage disease that is inherited as an autosomal recessive trait.

The patient's family members came in for genetic testing and imaging. His 18-year-old brother also was diagnosed with sialidosis type 1; his father was diagnosed with MacTel (macular telangiectasia); and his mother and sister were not found to have any gene mutations.

WRITTEN AND PHOTOGRAPHED BY **BECKY WEEKS, BS, CRA, OCT-C,** MORAN EYE CENTER, SALT LAKE CITY.

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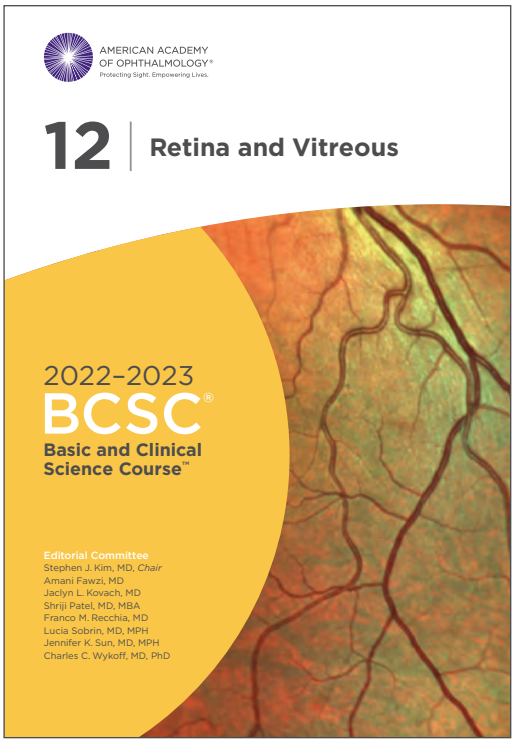

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