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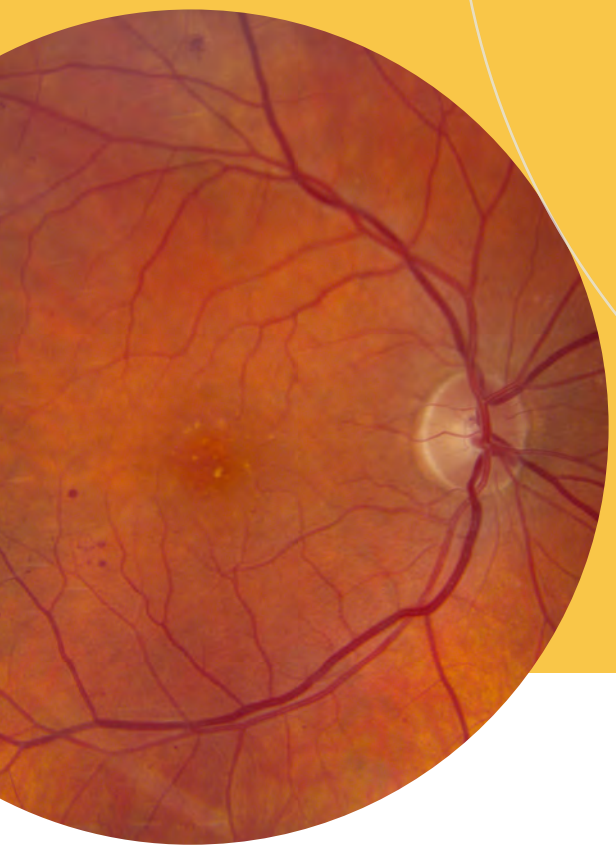

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TRUST THE POWER OF

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

EYLEA Offers Dosing Flexibility in Wet AMD[1]

3 FDA-Approved Dosing Regimens in Wet AMD[1]

Q4

Q8
following 3 initial monthly doses

After one year of effective therapy
Q12

The recommended dose for EYLEA is 2 mg (0.05 mL) administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months).[1]

AMD = Age-related Macular Degeneration; Q4 = every 4 weeks; Q8 = every 8 weeks; Q12 = every 12 weeks.

IMPORTANT SAFETY INFORMATION AND INDICATIONS

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.

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Schmidt-Erfurth U, Kaiser PK, Korobelnik JF, et al. Intravitreal aflibercept injection for neovascular age-related macular degeneration: ninety-six-week results of the VIEW studies. *Ophthalmology*. 2014;121(1):193-201. **3.** Khurana RN, Rahimy E, Joseph WA, et al. Extended (every 12 weeks or longer) dosing interval with intravitreal aflibercept and ranibizumab in neovascular age-related macular degeneration: post hoc analysis of VIEW trials. *Am J Ophthalmol*. 2019;200:161-168.

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

Q12 DOSING REGIMEN IN WET AMD[1-3]

As Demonstrated in Phase 3 Clinical Trials[1-3]

Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every-4-week (monthly) dosing after the first 12 weeks (3 months).

Although not as effective as the recommended every-8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly.

Visit HCP.EYLEA.US to see the data.

WARNINGS AND PRECAUTIONS (cont'd)

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

ADVERSE REACTIONS

- Serious adverse reactions related to the injection procedure have occurred in <0.1% of intravitreal injections with EYLEA including endophthalmitis and retinal detachment.
- The most common adverse reactions (≥5%) reported in patients receiving EYLEA were conjunctival hemorrhage, eye pain, cataract, vitreous detachment, vitreous floaters, and intraocular pressure increased.

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).

REGENERON

777 Old Saw Mill River Road, Tarrytown, NY 10591

04/2020
EYL.20.04.0009

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:

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 CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following 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.

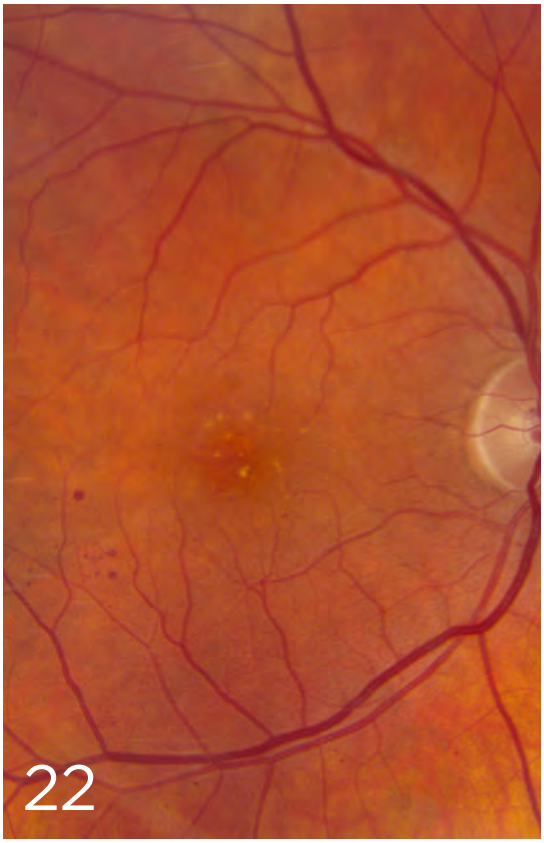
REGENERON

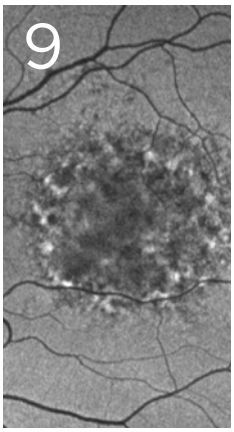
Manufactured by:
Regeneron Pharmaceuticals, Inc.
777 Old Saw Mill River Road
Tarrytown, NY 10591

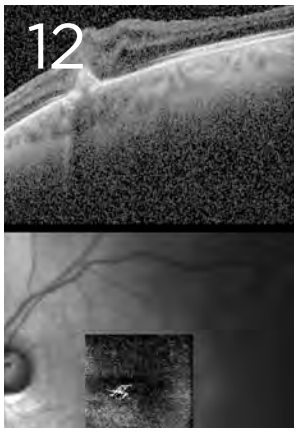
Issue Date: 08/2019
Initial U.S. Approval: 2011

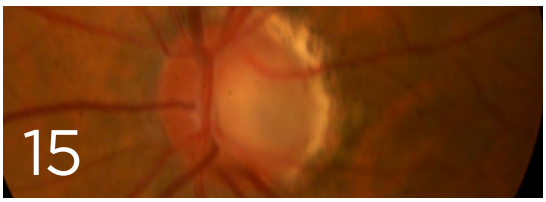
Based on the August 2019
EYLEA® (aflibercept) Injection full
Prescribing Information.

EYL.19.07.0306









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REPRINTS FOR
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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.

Vitreoretinal Surgery for COVID–19 Positive Patients

During this pandemic, we are continuing to do our best to safely provide optimal care for vision-threatening conditions, regardless of a patient's COVID-19 status, said Durga Borkar, MD, at Duke University School of Medicine in Durham, North Carolina.

But what if the patient is infected with SARS-CoV-2 and you need to perform vitreoretinal surgery? How does this change your practices?

"You want to delay as long as possible to avoid operating on someone who could be actively shedding the virus, but not so long as to produce negative visual consequences," said Benjamin Reiss, MD, at the Retina Institute of Washington in Renton.

Both Drs. Borkar and Reiss recently performed retina procedures on patients who tested positive for SARS-CoV-2. Together with Gary N. Holland, MD —who is one of three ophthalmologists curating clinical content for the Academy's aao.org/coronavirus web pages—they share their insights on how to balance the surgical needs of the patient with the safety of all concerned.

Factors to Consider Before Deciding on Surgery

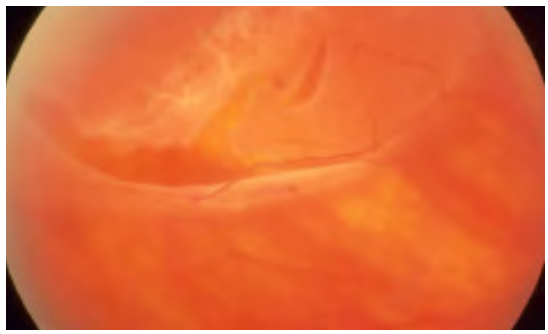
Deciding whether or not to operate on a COVID–19 positive patient involves a multifaceted calculus: It considers not only the patient's specific condition but also professional guidelines, institutional policies, risks to surgeon and staff, and the office workflow.

Professional guidelines. Both the Academy and the American Society of Retina Specialists (ASRS) provide general guidelines for ophthalmologists considering surgery, said Dr. Holland, at the Stein Eye Institute, University of California, in Los Angeles.

These guidelines cover everything from personal protective equipment (PPE) recommendations and risk assessments to specific protocols regarding patient care.[1,2] They leave room for discretion, said both Drs. Holland and Reiss. "That's partly because doctors must consider many specific details, such as whether or not a patient is functionally monocular," said Dr. Reiss.

Discretion is also called for because each region and institution varies in risk level and access to PPE, equipment, beds, and staff. "Not all places can adhere to the ideal," said Dr. Holland. "Also, there's a lot we still don't know, for example, whether or not procedures such as retina surgery are aerosol generating. Recommendations may need to change as we gather more information."

Institutional policies. Because of regional and institutional differences, hospitals have developed their own additional policies for handling COVID-19 positive patients, which surgeons need to follow, said Dr. Borkar. This requires a conversation with the hospital and OR staff to determine whether a team, room, and supplies are available, said Dr. Reiss.



RETINAL DETACHMENT. *Urgent and nonelective surgeries for conditions such as retinal detachment require extreme care in patients who are positive for COVID-19.*

The patient's condition. "Many conditions we treat in our retina subspecialty are urgent and nonelective," said Dr. Reiss. This includes conditions such as retained lens fragments, endophthalmitis, retinal detachment, acute vitreous hemorrhage of unknown etiology, and flashes and floaters.

Dr. Borkar said that three factors help influence her decision in an urgent case: 1) The patient is systemically well enough to safely undergo surgery. 2) The patient has good visual potential. 3) It's likely that taking the patient to the OR will provide a superior standard of care over an in-office procedure. Of course, she added, this deci-

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BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **DURGA BORKAR, MD, GARY N. HOLLAND, MD,** AND **BENJAMIN REISS, MD.**

sion is easier for physicians affiliated with an institution that has an adequate setup for taking care of a patient infected with SARS-CoV-2.

Infection risks to surgeons and staff. "We need to balance patients' needs against the safety of health care providers," said Dr. Holland. "As parts of the country open up and more physicians return to work," he cautioned, "we shouldn't be lulled into a false sense of security. Whether in the operating room or clinic, consider all patients as being potentially infected."

Office workflow. Surgeons need to consider not only the availability of an OR but also the scheduling of exams before and after surgery in the clinic setting, Dr. Holland said. "We need to maintain social distancing and rigorous disinfection procedures between cases, so we can't have waiting rooms full of post-op patients."

When it's a "no go." Because of PPE shortages, surgeons have been delaying cases, even when the patient tests negative, said Dr. Reiss. However, the longer you wait for most retinal procedures, the worse the outcome, he said. "Epiretinal membranes and macular holes may not be emergencies, but if you wait long enough, they will likely get worse."

Before Surgery: Planning and Precautions

With the advent of the pandemic, presurgical planning has become pivotal and more involved.

COVID-19 testing. The hospitals that Drs. Reiss and Borkar are affiliated with have initiated routine reverse transcription polymerase chain reaction testing for anyone going to the OR, whether symptomatic or not. "For urgent cases, we use point-of-care testing and can have results in less than 30 minutes," said Dr. Borkar.

If a case is urgent enough to be scheduled for surgery, testing for COVID-19 is a helpful tool, said Dr. Reiss. "For example, the surgeon and anesthesiologist can take extra steps to protect themselves." Where abundant testing is not available, said Dr. Holland, we have to balance the ideal with the practical. "Assume that asymptomatic patients may be infected and use universal precautions with all cases," he said. "Even as testing becomes more widespread, we need to remember that false-negative results can occur."

Presurgical clinic visit. "Our clinic has stringent protocols for all patients," said Dr. Reiss. In addition to minimizing contact between patients, cleaning exam rooms, and having patients wear masks, he said, the clinicians dilate or check pressures only if absolutely necessary. In some cases, telemedicine is used to minimize exposure.

Conversations about anesthesia. Because intubation and extubation are aerosol-generating procedures, said Dr. Holland, it's critical to talk with the anesthesiologist about the use of local versus general anesthesia.

"In ophthalmology, we do a lot of cases under monitored anesthesia care, although some cases, such as urgent trauma cases where the patient is in severe pain, may require general anesthesia," said Dr. Borkar. Making the appropriate decision preoperatively is imperative because switching midstream isn't easy with a patient who's positive for COVID-19, she said. "Intubation requires a coordinated effort on the part of the anesthesia team. If you're even considering general anesthesia, the anesthesiologist may recommend going ahead with it from the outset to allow doing it in the most controlled fashion."

If the case doesn't warrant general anesthesia, however, avoid it to minimize the risk to the anesthesiologist, said Dr. Reiss. "For the ophthalmologist, the highest risk would then be during the preprocedure block."

OR. Each institution has its own unique setup, said Dr. Borkar. "But at Duke, surgeons operate on COVID-19 patients in a dedicated operating room. In this setting, she said, "be sure to familiarize yourself with the available vitrectomy and visualization systems because they may be different than what you are used to."

If you're using an OR where eye surgeries are not normally performed, you'll need to make a clear list before surgery of all the equipment you'll need, said Dr. Reiss. At his hospital, everything has been removed from the OR. Only the exact supplies needed for each surgery are placed in the OR. That's because everything in the OR is thrown away after surgery, as it is considered contaminated.

Transport and pre-op holding area. "We don't normally have to think about logistics such as transporting the patient, but now we do," said Dr. Borkar. "Know your institution's special protocol for getting patients safely to the OR and where they will wait beforehand. We can't hold them in a general pre-op area where only curtains typically separate them from other patients." At Dr. Reiss's institution, an OR floor and negative-pressure pre-op bay have been specifically designated for COVID-19 positive patients.

Pre-op patient prep. "Upon arrival, my patient was wearing a mask and went straight to the negative-pressure pre-op bay," said Dr. Reiss. "Only the nurse and the anesthesiologist went into the room to prep the patient for the case. Since I had already spoken with the patient over the phone, I saved preoperative marking for the OR so I wouldn't have to gown up and use additional PPE to enter the preoperative bay."

Intubation, if needed. "To avoid risk of infection from aerosolization," said Dr. Borkar, "everyone except the anesthesia team stays outside the room during intubation [and extubation], and they wait 15 minutes before going in."[3]

During Surgery: Minimizing Risks

Minimalism. Have the minimum number of people in the room that's needed to provide the best level of care, said Dr. Holland. He added that it's now inadvisable to change out members of the surgical team while the surgery is in progress.

Dr. Borkar is at a teaching institution, and the pandemic has introduced additional challenges for fellows. "Although there's not a 'right' or 'wrong' approach," she said, "try to find a balance between training and expediting the case as quickly as possible."

Don, doff, and dispose of PPE. Generally, your institution will have clear,

posted instructions about handling PPE, said Dr. Borkar. Some institutions may sterilize and reuse masks, which is a practice at Dr. Reiss's hospital.

Initial steps in the OR. "As soon as my COVID–19 positive patient was in the OR," said Dr. Reiss, "we used an oxygen mask to cover the [patient's] nose and mouth, instead of a nasal canula. We quickly scrubbed the eye, put the drape on, and gave propofol sedation and a retrobulbar block through the drape in case the patient coughed while sedated." Completely covering the airway—with only the eye exposed—helped protect the team during the highest-risk part of the procedure, he said.

Face protection. Know ahead of time what your institution's face-protection protocol is for operating on COVID-19 patients, advised Dr. Borkar. "We wear an N95 mask and an overlying face shield. Standard face shields don't work for ophthalmic surgery because you can't get your face close enough to the microscope." A couple of alternatives are surgical masks with a partial face shield attached or swim or chemistry goggles, she said.

Although he'd worn an N95 in the past, Dr. Reiss was test fitted again before operating on his patient. "In addition to a low-profile eye shield, I wore a surgical mask over the N95 in the OR, but I don't do this on a routine basis unless there's a known high-risk exposure."

Although the ASRS has recommended N95 masks for retina surgeons, if available, the need to use an N95 mask for all types of surgery has not been proven, said Dr. Holland, and there may not be an adequate supply for every case at every institution. "Wearing a surgical mask over the N95 mask helps keep it clean so the N95 can be reused," he said.

Gowns and gloves. Although gowning and gloving guidelines are also specific to each institution, it's common to wear a thicker gown than usual and to double glove, not normally done for eye surgery unless there's a higher infection risk from a needle stick, said Dr. Borkar. "Double gloving also allows you to remove the top pair at the end without touching anything and have a clean pair underneath to remove other PPE," she said.

Feet coverings. "Many of us take our shoes off to put our feet on the microscope and vitrectomy pedals when we're operating, but that's probably not the best idea around COVID–19 positive patients," said Dr. Borkar. "Either consider wearing foot covers over your socks, or wear really thin-soled shoes."

Longer-acting gas. For a superior retinal break, Dr. Reiss would normally use a shorter-acting gas. Instead, he and his colleagues recommend using C3F8 gas. This decreases the risk of an undetectable detachment while the patient quarantines for 14 days—not returning for the post-op visit until the end of week 2.

After Surgery: Continued Caution

Again, each institution will have its own processes, but these are a few things to consider.

Post-op recovery. "It is good to get a social worker involved, if that resource is available," said Dr. Borkar. That's because an urgent retinal condition is now complicated by infection with SARS-CoV-2. These are some of the biggest questions you might need help answering: Where will the patient go after surgery? Does the patient live alone? Will the patient need to be admitted? What are the quarantine restrictions once the patient is discharged, and how will the patient return for follow-up?

Post-op visit. At Dr. Reiss's facility, the hospital arranged for the patient to return the following morning to the negative-pressure bay for the post-op visit for an eye pressure check and a quick exam. "Otherwise, the patient would have come back to our clinic where we really don't have the best setup to protect our staff or other patients from being exposed."

In some cases, however, you can't avoid seeing the patient postoperatively in the office, said Dr. Borkar. She advises considering steps like these to lower risks and reduce the use of PPE:

- Have the attending surgeon do the whole post-op check from start to finish, without the participation of staff and trainees.
- Have affected patients call you when they arrive in the parking lot. Meet and walk them through a side entrance, if possible, where they can go directly into an area that is more sequestered.
- See the patient at the very end of the day, which allows environmental services to thoroughly clean afterward before any other patients are seen in the area.

Telehealth. What if patients can't get back to the office for appointments? They might have low acuity in both eyes and not be able to drive. And if they are being asked to quarantine from their family members, they can't get a ride. "This may be where telehealth can come in, especially for uncomplicated retinal detachment follow-up in the early postoperative period," said Dr. Borkar. "Whether the patient is COVID-19 positive or negative, we still want to minimize how much they are coming in for office visits during this pandemic."

A Positive Mindset

In closing, Dr. Reiss advises not treating COVID–19 positive patients differently overall. "If you take appropriate precautions, you can still take care of them," he said, adding that he felt completely safe during his procedure. "Don't shy away from treating these patients."

1 aao.org/headline/special-considerations-ophthalmic-surgery-during-c. Accessed on May 30, 2020.
2 asrs.org/advocacy/updates. Then scroll to "ASRS Issues Best Practices Update for PPE During Vitreoretinal Surgery." (Log in required.)
3 Chandra A et al. *Eye* (Lond). Published online May 12, 2020.

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Pentosan Polysulfate Maculopathy: An Elusive Masquerader

At first blush, pentosan polysulfate maculopathy may look like a pattern dystrophy or age-related macular degeneration (AMD). Dig deeper, however, and something unique emerges.

"The discovery of pentosan toxicity was a very astute observation by one of our former fellows, Nieraj Jain," said Mark E. Pennesi, MD, PhD, at the Casey Eye Institute in Portland, Oregon. "Dr. Jain noticed a cluster of patients with a curious pattern dystrophy who also happened be on pentosan polysulfate." Dr. Jain investigated other patients who had been on the drug and found more cases,[1] and he reached out to a number of colleagues who found similar cases.

Then began the process of working to confirm causality, as well as the presentation, scope, and mechanism of action of this specific condition.

Piecing Together the Puzzle

Used to prevent irritation of the bladder wall, pentosan polysulfate sodium (PPS; Elmiron) is the only FDA-approved oral prescription medication for interstitial cystitis. The drug has been on the market for more than 20 years, and doctors have prescribed it for hundreds of thousands of patients, said Nieraj Jain, MD, at Emory Eye Center in Atlanta.

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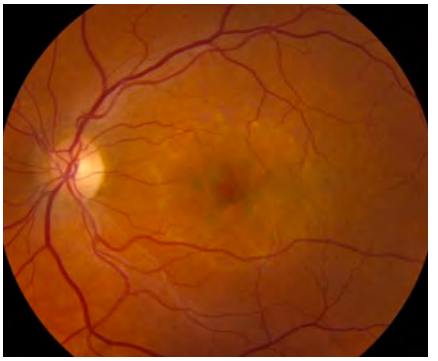
Typical presentation. Patients with PPS maculopathy can have fairly normal visual acuity—even 20/20, said Dr. Jain. "But patients tend to suffer from significant subjective visual problems, such as trouble reading or adjusting to dim lighting, glare, and blind spots. In advanced stages, the condition can lead to profound disability, with some patients meeting the criteria for legal blindness."

On imaging, you see an expanding maculopathy that involves the optic disc as well as the entire posterior pole, said Stephen T. Armenti, MD, PhD, at the Kellogg Eye Center in Ann Arbor, Michigan. As the condition advances, added Dr. Pennesi, you start seeing severe loss of the retinal pigment epithelium (RPE) with photoreceptor loss. "It can be widespread, extending beyond the macula to the far periphery," he said.

Risk factors. "Long-term exposure seems to have the strongest correlation so far," said Dr. Pennesi. "This makes sense since most toxicities are related to dosage or duration." Interestingly, a recent retrospective study of medical claims data found no significant association between PPS use and a diagnosis of macular disease at five years.[2] Although this appears to contradict earlier reports, it is still consistent, said Dr. Jain. He noted that very few patients in this cohort used the drug for as long as five years; in fact, the mean duration of use was less than one year.



Courtesy of Nieraj Jain, MD

COLOR FUNDUS PHOTOGRAPHY. *Paracentral pigment clumps amid a background of yellow subretinal deposits.*

By contrast, in another recent study of claims data, Dr. Jain and colleagues identified a significant association between PPS use and macular disease at seven years.[3]

Dr. Jain and his team have looked at average daily dose by body mass and ideal body weight; and they have explored other possible risk factors, including race, a history of smoking or other medications, and problems with the kidney, liver, or spleen—due to the way the drug is metabolized. Yet, they have not identified an association.

Other factors at play? There is variability in patients' responses to the drug. "In a fairly small cohort of 35 patients,[4] we saw a patient who had been on a relatively low cumulative dose in the past who subsequently had a phenotype of maculopathy after being off the medication for several years," said Dr. Armenti. Other patients have taken a higher dose for a longer time but have relatively mild disease, he said. "It is

BY ANNIE STUART, CONTRIBUTING WRITER, INTERVIEWING **STEPHEN T. ARMENTI, MD, PHD, NIERAJ JAIN, MD,** AND **MARK E. PENNESI, MD, PHD.**

likely other factors are playing a role that we're not yet aware of."

Progression after cessation. In an unpublished retrospective study of 12 patients followed for a median of one year after drug cessation, Dr. Jain and colleagues did not see any reversal of the disease. "In fact, the majority of patients reported that their visual symptoms continued to worsen." Dr. Pennesi offers two possible explanations for this: The drug may get sequestered in the RPE or may bind to something, creating a reservoir effect. Alternatively, irreversible cell damage may begin, but it may take a long time to fully materialize.

Mechanism of action. Several groups, including Dr. Jain's, are conducting animal studies to determine the underlying mechanism of action. "We know this drug is a macromolecule similar to glycosaminoglycans," said Dr. Jain. "It is a highly negatively-charged compound, which causes it to bind to positively-charged molecules, and this could play a role. From the clinical imaging studies we've done, we think the primary site of damage is at the level of the RPE or possibly at the interphotoreceptor matrix."

Regardless, the condition fills in a missing piece of the pattern dystrophy puzzle, said Dr. Pennesi. "For the many patients with inconclusive genetic test results, we have long suspected that there were either more genes that we hadn't yet discovered or there was some other acquired cause."

What You Will—and Won't—See

This condition can easily be missed, not only because visual acuity is often fairly good but also because fundus findings tend to be subtle, said Dr. Jain.

Fundus photography. "With fundus photography, you can see some very subtle pale-yellow or even orangish deposits deep in the macula," said Dr. Jain. "Hyperpigmented spots may be present around the fovea, but they don't stand out as being very prominent."

Optical coherence tomography (OCT). "In combination with fundus autofluorescence, macula OCT is helpful in finding the outer retinal and RPE changes that you see with this disease and in differentiating from the typical findings seen in macular degeneration," said Dr. Armenti.

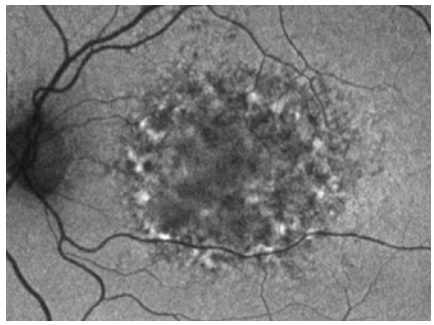
Near-infrared fundus reflectance (NIR). With NIR, you can see a pattern of hypo- and hyperreflective abnormalities in the posterior pole, said Dr. Jain. "However, this imaging modality often reveals nonspecific changes that may make it difficult to distinguish between different conditions."

Fundus autofluorescence (AF). With fundus AF, said Dr. Armenti, PPS maculopathy produces a pattern of hypo- and hyperautofluorescent spots throughout the macula, which extends throughout the posterior pole and can expand over time—a sign of RPE dysfunction.

Fundus AF imaging best captures the subtle manifestation of this condition and the extent of the diseased tissue, added Dr. Jain, describing a "wow" effect from viewing fundus AF images after observing relatively subtle findings in the clinic. "In cases where the disease involves the peripapillary retina," he said, "we identified a unique, fairly consistent feature—a hypoautofluorescent ring around the optic disc. This helps distinguish the condition from common hereditary maculopathies."

Multimodal imaging. Dr. Jain noted that integrating information from multiple imaging modalities may be necessary, especially since PPS maculopathy can mimic both hereditary maculopathies and AMD. It can be particularly hard to distinguish it from AMD, he said, because the two conditions share similar demographics—usually middle-aged or older white women.

Multimodal imaging is very helpful, agreed Dr. Pennesi. "Near-infrared reflectance is useful for seeing the characteristic bright deposits. Short wavelength autofluorescence is useful for seeing a pattern of changes in deposits and RPE dropout. Combined with a history of medication use, these two modalities can allow you to make a fairly confident diagnosis."



FUNDUS AUTOFLUORESCENCE IMAGING. *A dense pattern of hyper- and hypoautofluorescent spots that involves the fovea.*

Courtesy of Niraj Jain, MD

Watch for PPS Maculopathy

Here are some tips for spotting pentosan toxicity.

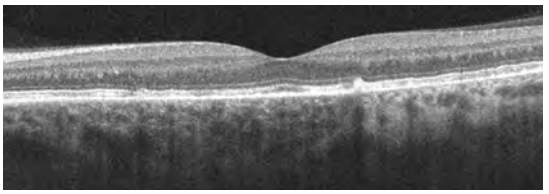
Scan medication lists. Look for PPS and add it to your list of the drugs you ask about whenever a patient has macular pathology, said Dr. Pennesi.

Beware the mimics. "If a patient has an atypical form of AMD or a pattern dystrophy, or if the 'AMD patient' is young, put this condition on your differential," said Dr. Jain.

Cast a broad net. Consider asking all patients with atypical maculopathy whether they are on this drug, said Dr. Armenti. "Otherwise, the topic may not come up unless the patient has a history of interstitial cystitis, the drug appears on a medication list, or specific signs show up on a fundus exam or retinal imaging."

Know that effects can continue after the drug is stopped. Dr. Armenti pointed to an example of a patient with concerning features on the fundus exam and OCT. "I had to dig way back in the history to help her remember that she was on this medication for a short time more than 15 years ago."

Consider referring PPS suspects to retina experts. They may have greater access to the advanced fundus imaging technology needed to confirm a diagnosis, said Dr. Jain.



OPTICAL COHERENCE TOMOGRAPHY. *Irregularity to the outer retinal bands with a focal thickening of the retinal pigment epithelium temporal to the fovea.*

Courtesy of Niraj Jain, MD

Minimizing the Risks

Hydroxychloroquine maculopathy has robust screening guidelines promoted by the Academy, said Dr. Jain. Although there isn't yet enough data to formalize similar PPS screening guidelines, he does offer some recommendations.

Informal screening guidelines. "We recommend that all patients initiated on a long-term treatment course undergo a baseline screening exam, which includes a dilated fundus exam, color fundus photography, fundus AF imaging, and OCT imaging of the macula," said Dr. Jain.

In addition, patients with underlying macular disease should use caution in starting on this drug, he said. Patients who do proceed with a long-term course should have repeat screening with the same fundus imaging within five years of being on the drug, and annually thereafter. He added that these guidelines are likely to evolve as we learn more about the condition.

Case-by-case assessments. "Given that data regarding risk are continuing to emerge, it's hard to make a specific recommendation about screening and stopping the drug," said Dr. Armenti. He manages patients on a case-by-case basis, in part, by assessing how the patient weighs the risk of worsening cystitis against the possible risk of maculopathy.

"Without more information, I can't yet really make a clear recommendation for those taking the drug that have no signs of toxicity," said Dr. Pennesi. It's also not possible to tell patients that stopping the drug will prevent pentosan toxicity, added Dr. Armenti.

A placebo effect? Although some patients swear by the drug, there is some controversy about its efficacy. Based on a randomized controlled trial that found PPS no more effective than placebo,[5] the Royal College of Obstetricians and Gynaecologists no longer recommends its use. As Dr. Pennesi noted, a placebo effect often can be seen with the different therapies used to treat chronic conditions such as interstitial cystitis. While this is often harmless, "if something can cause toxicity, you have to rethink how you manage the disease," he said.

When signs of toxicity appear. "If a patient on this medication has any signs of toxicity, we disclose that the drug is a suspected cause of maculopathy," said Dr. Armenti. "We also encourage the patient to speak with the urologist about whether to continue or stop the medication, or whether to try a different treatment."

When Dr. Pennesi sees evidence of toxicity, he also asks patients whether the drug is making a difference and whether they really need to take it. "We also explain that the longer they stay on it, the worse things may get, so they really need to weigh the risks versus the benefits."

So far, there is no known treatment, said Dr. Jain.

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

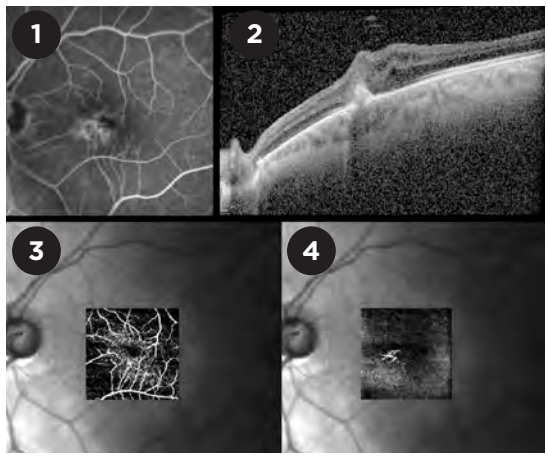
Myopic Choroidal Neovascularization

Myopia and pathologic myopia (PM) are among the leading causes of visual impairment in the world. One of the most feared complications of myopia or PM is the development of choroidal neovascularization (CNV). High myopia is defined as an axial length greater than 26.5 mm or refractive error greater than –6 D. Pathologic myopia is defined as the presence of structural changes due to axial elongation in eyes with high myopia. Other clinical findings associated with PM include posterior staphyloma, lacquer cracks, tessellated fundus, tilted optic disc, and straightened and attenuated vessels. It is now recognized that myopic CNV can occur in patients with any degree of myopia, even in the absence of characteristic degenerative retinal changes.[1]

Epidemiology

The reported prevalence of myopia and PM is highest in East Asian countries, with reported rates around 40%.[2] According to a comprehensive systematic literature review of English-language studies, PM is present in 3% of the global population.[2]

Myopic CNV has been reported in 5% to 11% of patients with PM. Notably, 62% of these patients developed CNV before the age of 50,[3] and a patient with a history of myopic CNV in one eye has an average risk of 34.8% for developing CNV in the fellow eye.[4] The relationship between the degree of myopia and CNV is not fully understood; in one study, 5.2% of eyes with axial length greater than 26.5 mm were found to have CNV.[3]



MYOPIC CNV. *(1) Early phase of FA shows hyperfluorescence due to leakage, suggestive of active type 2 (classic) CNV. (2) SD-OCT shows a highly reflective area above the RPE, corroborating type 2 CNV. (3, 4) OCTA with segmentation of the outer retinal layers shows an irregular, tangled CNV pattern.*

Genetics

Although some information is available regarding the genetics of PM, the genetic factors specifically associated with the development and presentation of myopic CNV are not yet fully understood. One study found a correlation between the *COL8A1* gene and the presence of myopic CNV. Interestingly, this gene encodes chains of collagen type VIII, one of the major components of Bruch membrane and choroidal stroma. Mutations in this gene might lead to the structural changes frequently observed in patients with PM. Alterations in *SERPINF1*, the gene that encodes pigment epithelium–derived factor, may also be related to CNV progression.[5]

Pathophysiology

In addition to genetic factors, structural and hemodynamic mechanisms have been postulated to contribute to the development of myopic CNV. Excessive elongation of the globe is presumed to cause mechanical stress, with retinal damage and imbalance of proangiogenic and antiangiogenic factors resulting in CNV. The axial elongation promotes alteration in collagen proteins that subsequently leads to degenerative changes in the retina, choroid, and sclera. A chain of molecular and inflammatory events may occur as a consequence of this mechanical and structural stress. The amacrine cells in the retina are thought to play a part in this process.[6]

Compared to unaffected individuals, patients with PM had significantly higher levels of inflammatory factors such as high-sensitivity C-reactive pro-

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tein and complement factors C3 and CH50; these findings strongly suggest that inflammation is involved in myopic CNV. Another hypothesis suggests that hemodynamic changes at the level of the choroid lead to choroidal thinning and hypoperfusion, predisposing to CNV development.[2]

Visual acuity (VA) can be impaired even in the absence of funduscopic changes typically associated with PM. This may be attributable to excessive stretching in the posterior pole, which alters the arrangement of photoreceptors. In high myopia, the cones in the nasal macula are aligned toward the optic nerve, while those in the temporal zone are aligned toward the center of the pupil. This displacement in directional sensitivity is known as the Stiles-Crawford effect of the first kind.[7] Specifically, light that enters the eye near the pupillary edge stimulates a lesser photoreceptor response compared with light of equal intensity that enters the eye near the center of the pupil.

Diagnosis

Clinical findings. A diagnosis of myopic CNV should be considered for a middle-aged myope who presents with sudden vision loss, metamorphopsia, and typical funduscopic changes. Establishing a diagnosis in an elderly patient is more challenging because other conditions that can lead to CNV, such as age-related macular degeneration (AMD), may be present. Nevertheless, some clinical findings can help distinguish among the conditions.

Staging. In 1998, Tokoro[8] outlined three stages of myopic CNV: active, scar, and atrophic, defined according to funduscopic and other clinical findings.

Active. In the active stage, patients usually have sudden visual loss associated with a central scotoma or metamorphopsia; fundus changes include a small, slightly elevated, grayish lesion in the subfoveolar zone, although CNV may also be seen in the juxtafoveal zone. The neovascular membranes of myopic CNV are typically less than 1,000 µm in diameter, and sub–retinal pigment epithelium (RPE) fluid or exudates are uncommon. In contrast, AMD-associated CNV lesions are typically larger, are often associated with hemorrhage and drusen, and may be accompanied by sub-RPE fluid.

Scar. In the scar phase, the CNV regresses, and a characteristic hyperpigmented area known as a Fuchs spot forms around the prior lesion. In this phase, the patient experiences a period of stabilization or transient improvement in VA. Patients with AMD, however, usually do not have VA improvement without treatment, and the pigmentary changes seen in the fundus are associated mainly with drusen.

Atrophic. Finally, in the atrophic phase, further visual decline occurs. Patchy and, over time, diffuse atrophy may be present in the macula.[2] In AMD, the areas of atrophy are more prominent and confluent; additional findings including drusen, pigment epithelial detachment, and generalized pigmentary changes will be present, helping to differentiate AMD from myopic CNV.

Differential diagnosis. Inflammatory conditions such as multifocal choroiditis, presumed ocular histoplasmosis syndrome, recent hemorrhage from lacquer crack formation, idiopathic CNV, and various hereditary disorders including Best disease, reticular dystrophy, and retinitis pigmentosa should be considered. Blunt ocular trauma with choroidal rupture can also lead to CNV. As noted above, AMD should always be ruled out in elderly patients.

Imaging. Imaging studies can aid in the differential diagnosis and help avoid unnecessary treatment.

Fluorescein angiography (FA). On FA, myopic CNV typically shows a "classic" pattern, with hyperfluorescence in the early phase. Less than 10% of the membranes will leak beyond the borders in the late phase, and the amount of leakage is minimal compared with that seen in AMD. Some inactive membranes will stain only in the late frames.

However, because other conditions may present with similar staining on FA, other modalities such as indocyanine green angiography (ICGA), spectral-domain optical coherence tomography (SD-OCT), and OCT angiography (OCTA) may be useful.

ICGA. In patients with extensive hemorrhages, ICGA can provide better information than can FA about the choroidal circulation, particularly about the presence and status of lacquer cracks, and ICGA can help distinguish myopic CNV from AMD. In myopic CNV, ICGA generally shows an early small, hyperfluorescent area, surrounded by a hypopigmented halo, sometimes associated with lacquer cracks.

OCT. SD-OCT can delineate the retinal structure in different stages of myopic CNV and helps to differentiate it from conditions such as posterior staphyloma, retinoschisis, thinned choroid, posterior vitreous detachment, macular atrophy, macular hemorrhage, vitreomacular traction, or macular hole formation. It can also be helpful in identifying some inflammatory conditions such as multifocal choroiditis and panuveitis.

- *Choroid.* Myopes are known to have a significantly thinned choroid. This essential finding is usually associated with sporadic large choroidal vessels with defects at Bruch membrane.
- *CNV.* In the acute phase of myopic CNV, a highly reflective area above the RPE (CNV type 2) can typically be seen, without or with minimal subretinal fluid (SRF). However, the use of OCT alone may not be adequate in distinguishing subretinal hemorrhage caused by recent lacquer crack formation from that caused by myopic CNV, which could result in unnecessary treatment. Recent evidence shows that leakage and exudative changes associated with myopic CNV were identified on FA in up to 82% of cases, compared with 48.6% with use of SD-OCT alone. Thus, FA may be more reliable in confirming the diagnosis of acute CNV.[9]

OCTA. A study by Querques et al. analyzed the utility of OCTA in detecting CNV and its morphological patterns in eyes with PM. They found a sensitivity of 90.48% and specificity of 93.75% for detection of CNV in this group of patients. They also reported that the OCTA findings suggestive of myopic CNV disease activity were predominantly in a vascular network pattern described as "tangled" or "interlacing."[10]

Another study compared the effectiveness of OCTA to that of other imaging methods for detecting CNV in patients with suspected AMD, chronic central serous retinopathy, or PM. It found that OCTA had an overall sensitivity of 71% and specificity of 81% compared with FA and was particularly sensitive in detecting type 2 CNV in AMD.[11]

Both studies noted that although OCTA was an excellent aid in situations of diagnostic uncertainty by FA or SD-OCT, it has limitations, including inability to show leakage, and should be considered an adjunct to those tests.[10,11]

Management

Anti-VEGF therapy is considered the first-line treatment for myopic CNV. Ranibizumab (Lucentis) is the only FDA-approved anti-VEGF agent for this indication, although bevacizumab (Avastin) and aflibercept (Eylea) are often used off label. Verteporfin photodynamic therapy (vPDT) may be considered for cases in which anti-VEGF is contraindicated.

Ranibizumab. Several studies propose a treatment regimen of a single 0.5-mg ranibizumab injection followed by additional injections as needed (1+PRN).[12] Other studies suggest starting with three monthly doses, followed by as-needed treatment (3+PRN).[13] However, the majority of clinical studies with 0.5 mg of ranibizumab showed consistent gains in best-corrected VA (BCVA), regardless of the anti-VEGF treatment regimen.[2]

The phase 2 REPAIR study (1+PRN)[12] showed that 86% of patients had improved BCVA, with 37% achieving a gain of more than 15 letters. Moreover, a marked decrease in central macular thickness (CMT) was seen at the 12-month follow-up.

Another pivotal study was the phase 3 RADIANCE trial, which compared the efficacy of ranibizumab (group 1: injection on day 1 and month 1+PRN; group 2: day 1+PRN) versus vPDT (PDT day 1+PDT or ranibizumab at investigator's discretion starting at month 3). Ranibizumab was superior in mean change in BCVA from baseline during 12 months of follow-up. In addition, between 63% and 65% of patients showed resolution of leakage from the CNV.[14]

Aflibercept. The phase 3 MYRROR study evaluated the safety and efficacy of 2.0 mg aflibercept for the treatment of myopic CNV. The dosing regimen in the treatment group was 1+PRN. After 24 weeks, 39% of the treated patients experienced a gain of more than 15 letters in BCVA and demonstrated a decrease in CMT. These changes were maintained for 48 weeks. The sham injection group received aflibercept for the first time at week 24; after that injection they had a modest gain in VA, substantially less than that in the treatment group. These results support early initiation of treatment to achieve optimal visual outcomes.[15]

Bevacizumab. Several studies have demonstrated the effectiveness of bevacizumab in treating myopic CNV. Although there is no standardized dosage, the use of 1.25 mg of bevacizumab has been reported to be safe in a 1+PRN or 3+PRN regimen, with no marked difference in efficacy between the two treatment regimens.[2]

A recent retrospective comparative study examined the efficacy of bevacizumab versus aflibercept. Both agents were administered on a 1+PRN basis. No significant differences were found in VA outcomes; however, significantly fewer injections were administered in the aflibercept group, suggesting that it has a more prolonged effect.[16]

Verteporfin photodynamic therapy (vPDT). The VIP study examined the effect of vPDT compared with placebo in maintaining or improving vision.[17] Although VIP yielded better visual outcomes for vPDT at 12 months, later studies suggest worsening after the second year; at five years, chorioretinal atrophy was seen in 83% of patients.[18] Currently, this treatment should be considered only if anti-VEGF therapy is contraindicated.[2]

Follow-up and Prognosis

In a 1+PRN regimen (the preferred approach in our clinic), the patient is monitored every month for the next three to six months with VA evaluation and ancillary tests such as FA, SD-OCT, or OCTA.[1] The criteria for retreatment are based on signs and symptoms of CNV activity, including visual loss and metamorphopsia, evidence of new leakage on FA, and persistent or increased intraretinal fluid on OCT. If there are no signs of active CNV, follow-up can be extended to every three months during the first year. Patients with myopic CNV usually respond rapidly to treatment, and recurrence is much less frequent than in other neovascular disorders such as AMD.

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

Diagnosis and Management of Optic Disc Pits

First described in the late 19th century by Wiethe, optic disc pits (ODPs) are anomalous cavitations of the optic nerve.[1] ODPs are rare, and they can be congenital or acquired. Although cases of bilateral ODPs have been reported, ODPs typically present unilaterally. ODPs tend to be solitary, but two or three pits occurring together have also been described.[1] The main complication of ODPs is optic disc pit maculopathy (ODP-M), which can lead to severely decreased visual acuity (VA). The pathogenesis of ODPs is not fully understood, and there is no consensus regarding their treatment.[2]

Epidemiology

The prevalence of ODP is approximately 1:11,000.[2] The majority of cases are thought to be congenital (CODPs); however, acquired ODPs (AODPs) may occur secondary to glaucoma or myopia.[3] AODPs occur twice as frequently in women and tend to be inferior in location, whereas CODPs typically involve the temporal region of the optic disc.[4] Although ODPs are most often unilateral, they are bilateral in approximately 15% of cases overall; however, 21% to 48% of AOPD cases are bilateral.[1]

ODP-M occurs in approximately 25% to 75% of ODP patients.[5] This complication manifests as serous retinal detachment, cystic changes, or degenerative pigment changes of the macula.

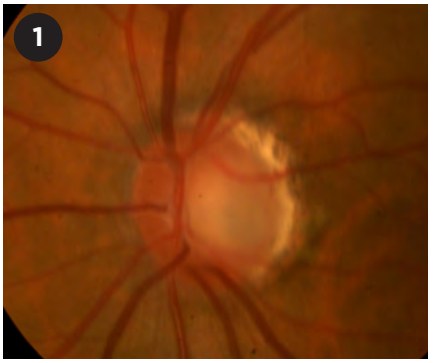
Etiology and Risk Factors

There is no consensus on the embryologic origins of CODPs. Classically, ODPs were thought to represent a more benign variant of optic disc coloboma. ODPs are thought to develop from anomalies in the neuroectodermal folds of the primitive papillae, leading to an abnormal communication between the pit and the subarachnoid space.[1] However, later studies have posited that ODPs are not true colobomas because they are almost exclusively unilateral, sporadic, and rarely inferonasal in location. Moreover, they are typically not associated with iris or retinochoroidal colobomas and usually are not located near the optic fissure.[2]

Certain rare diseases are associated with an increased risk of ODP and other malformations of the optic disc. They include basal encephalocele, Aicardi syndrome, Alagille syndrome, bilateral renal hypoplasia, and midline neurodevelopmental defects.[1]

Pathophysiology

Histologically, an ODP appears as a herniation of dysplastic retinal tissue through a defect in the lamina cribrosa, extending posteriorly to the subarachnoid space. This defect may lead to intraretinal and subretinal fluid in the macula,[4] although the source of fluid and the mechanism of fluid migration are not fully understood.[2]



FUNDUS PHOTO. *A temporally located gray ODP is seen in a 56-year-old man with primary open-angle glaucoma.*

Two commonly accepted fluid sources are vitreous humor and cerebrospinal fluid (CSF). A less likely source is leakage from vessels at the optic pit base.[2] Hypothesized mechanisms of fluid migration in ODP-M include vitreous traction and movement of fluid down pressure gradients due to an ODP.[2] Progressive vitreous liquefaction usually occurs in the third or fourth decade of life, which coincides with typical presentation of ODP-M.

Additionally, pars plana vitrectomy (PPV) has been demonstrated to be a viable therapy for some cases of ODP-M. This suggests that reduction of vitreous traction may play a role in the treatment of some manifestations of ODP-M. However, several optical coherence tomography (OCT) studies have failed to demonstrate an association between vitreous traction and ODPs, and macular detachment may

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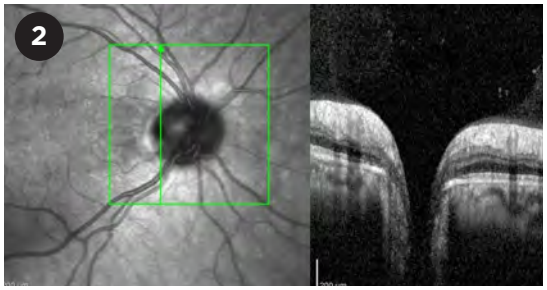

OCT VIEWS. *Horizontal and vertical OCT scans show ODP in the right eye of a 38-year-old man.*

recur after PPV; both of these observations suggest that vitreous traction is not the sole pathologic factor leading to macular detachment in ODP-M.[2]

A normal eye is a closed system with little difference in pressure between its compartments. However, an ODP forms a conduit that may transmit intracranial pressure (ICP) to the eye from the CSF and vice versa. OCT studies have shown glial tissue and vitreous strands projecting into ODPs, which implies that when ICP is low, vitreous and other tissue may be drawn posteriorly into the pit following the pressure gradient.[4]

Clinical Presentation

ODPs are most often asymptomatic and diagnosed incidentally on fundus examination, although they may sometimes cause visual field defects (most commonly arcuate scotomata).[2] Generally, ODPs cause symptoms only if they are complicated by ODP-M, which classically presents in the third or fourth decades of life as rapid, progressive visual deterioration due to lesions such as cystic degeneration of the macula and serous macular detachment. However, ODP-M can manifest at any age.[2]

VA is generally reduced to 20/200 or worse in ODP-M. Spontaneous resolution of macular edema and detachment with recovery of VA is thought to occur in only 25% of cases.[1]

Diagnostic Approach

Diagnosis of ODP is mainly based on direct fundus examination and OCT.

Fundus findings. On fundus exam, an OPD is visible as a round depression in the optic disc that appears gray, white, yellow, or black and occupies $^1/_8$ to $^1/_4$ of the disc (Fig. 1).[1,5] Most ODPs are located in the inferotemporal segment of the optic disc, 20% are located centrally, and 10% are located in other regions. ODPs do not obscure the optic disc margin or the physiological optic cup, which differentiates them from optic disc colobomas.[1]

CODPs and AODPs are morphologically similar, thus difficult to distinguish on ophthalmoscopic exam. However, CODPs tend to be temporal, whereas AODPs tend to be inferior in location.

OCT. OCT imaging of an ODP will show a defect in the lamina cribrosa with herniation of nerve tissue into the pit (Fig. 2). If ODP-M is present, OCT will demonstrate both intraretinal and subretinal fluid collections. The pattern specific to ODP-M is the dual morphology of serous retinal detachment with a schisis cavity and a coexisting detachment of the outer layer of the retinal pigment epithelium.[2]

Fundus autofluorescence (FAF). FAF will reveal hyperfluorescence in a granular pattern, as well as subretinal precipitates. Also, areas of serous retinal detachment and inner retinal schisis appear hypofluorescent, but they will become bright after successful vitrectomy and retinal reattachment.[2]

Visual field defects. In patients with ODPs, visual field defects are variable and usually do not correspond with the location of the pit; paracentral arcuate scotomata are the most common type.[6]

Differential diagnosis. Other conditions to consider in the differential include the following:

- Optic nerve hypoplasia, which is an abnormally small optic nerve head.
- Megalopapilla, which presents as an enlarged optic nerve head with an increased cup-to-disc ratio and a horizontally elongated cup.
- Morning glory syndrome, which appears as a funnel-shaped excavation, an enlarged optic nerve head, and an increased number of disc vessels.
- Optic nerve coloboma, which is characterized by an inferior excavation and is often associated with iris and choroidal colobomas.

In contrast to these entities, ODPs present as round depressions in the disc with a normal or large optic nerve size and may be associated with maculopathy.[1]

Management

Macular edema and detachment secondary to ODP-M were originally treated conservatively. However, because observation alone is often associated with poor visual outcomes, a more aggressive surgical approach is appropriate in some cases.

PPV and adjunctive therapies. PPV is the most widely accepted treatment for serous macular detachment associated with ODP-M. Induction of complete posterior vitreous detachment is likely important because it potentially relieves unidentified tractional forces.[2] Adjuncts to PPV include internal limiting membrane peeling, laser, and gas or silicone tamponade.[7]

Although laser photocoagulation is sometimes used as monotherapy to treat serous macular detachment in ODP-M, laser alone has been shown to have worse outcomes compared with vitrectomy. It is now more commonly used as an adjunct to vitrectomy and/or gas tamponade.[7]

Intravitreal gas injection with perfluoroethane, sulfur hexafluoride, or perfluoropropane is performed to attempt reattachment of the macula in cases of ODP-related detachment. This technique is often used in conjunction with PPV and laser.[6]

Macular buckling. This surgery involves fixation of a sponge implant to the posterior segment of the globe to produce a buckling effect under the macula. Although it is associated with good outcomes in the management of ODP-related macular detachment, it is a technically difficult surgery with a steep learning curve. Thus, it is not utilized as often as vitrectomy.[2]

Other techniques. Other approaches have produced promising results.

- Autologous platelet injection over the ODP after PPV has been successful in treating a patient with persistent ODP-related macular detachment.[8]
- Vitrectomy with radial inner retinal partial-thickness fenestration is a newer surgical technique that has been shown

to completely resolve subfoveal fluid in 94% of eyes.[9]

- Sealing of ODPs with autologous scleral flaps has been reported to be effective in inducing retinal reattachment and improving VA.[2]
- PPV and temporal-side single radial optic neurotomy is thought to create a barrier to fluid passage by creating scar tissue and is associated with fluid resolution in 86% of eyes.[10]

Conclusion

ODPs may be asymptomatic or may be complicated by ODP-M, leading to significant visual loss. Diagnosis of an ODP is achieved by fundus examination, OCT of the optic nerve, and FAF. ODP-M is managed surgically with PPV, macular buckling, and other techniques. Surgical management of ODP-M often leads to good visual outcomes. Although OPDs are rare, it is important for ophthalmologists to be aware of this condition and to monitor ODP patients for signs of developing ODP-M.

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IMPORTANT SAFETY INFORMATION AND INDICATIONS

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.

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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.

INDICATIONS

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

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

anti-VEGF = anti–vascular endothelial growth factor; AMD = Age-related Macular Degeneration; DME = Diabetic Macular Edema; MEfRVO = Macular Edema following Retinal Vein Occlusion.

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2.** Data on file. Regeneron Pharmaceuticals, Inc.

11/2019
EYL.19.10.0044

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:

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 CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following 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.19.07.0306

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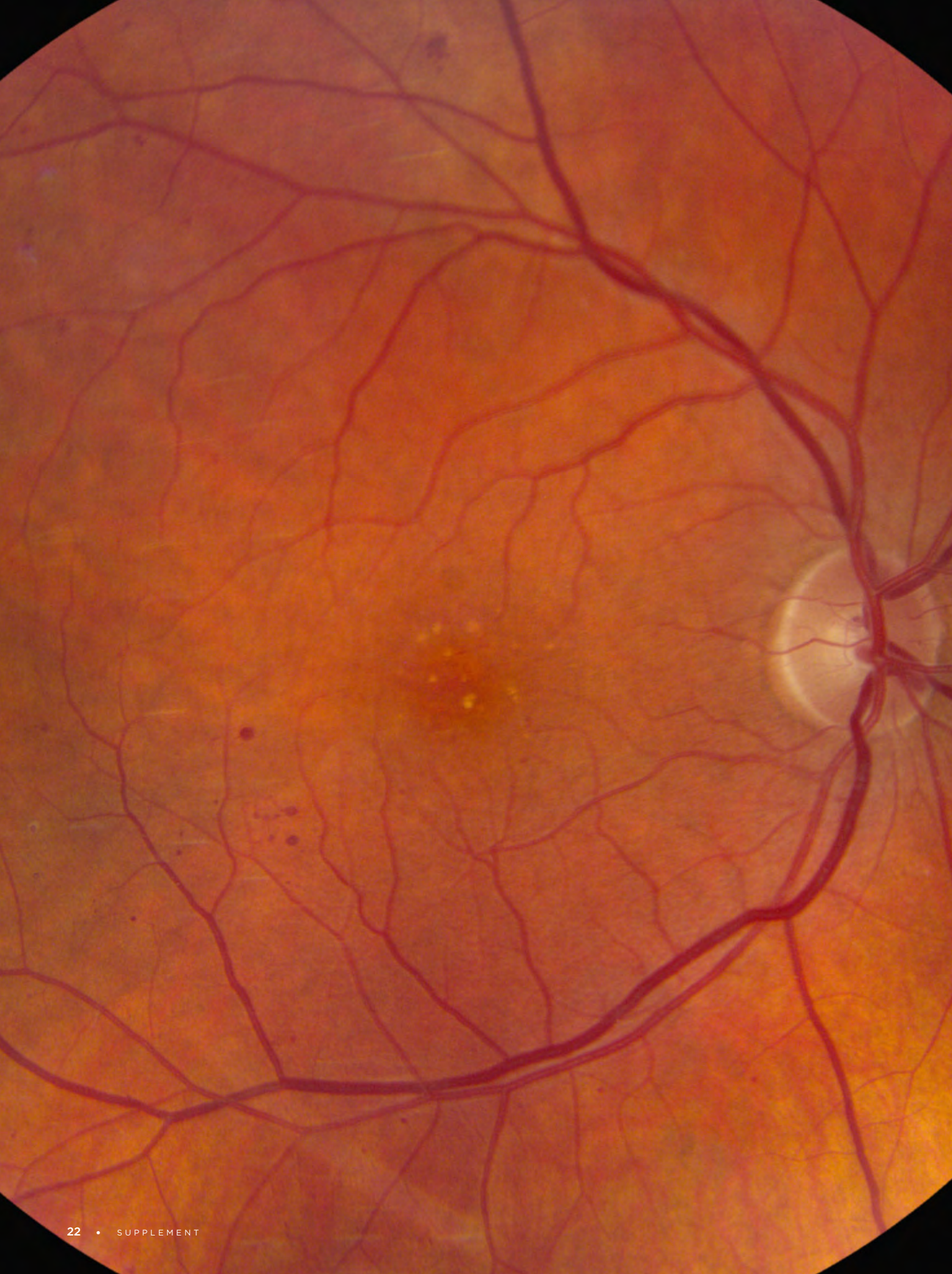


DME Treatment Evolves

A look at a decade of significant advances—and a preview of what's in the pipeline.

By Lori Baker-Schena, MBA, EdD, Contributing Writer

Treating patients with diabetic macular edema (DME) is a complex endeavor. But for the past 10 years, studies from the DRCR Retina Network have provided clinicians with valuable guidelines and insight into this leading cause of visual loss in working-age adults.

To begin with, the network's studies were instrumental in establishing anti-VEGF agents as first-line therapy for DME in visually impaired eyes. More recently, the network confirmed that anti-VEGF drugs could be used as rescue therapy following observation or laser for DME with good visual acuity (VA). Moreover, the studies have helped define treatment algorithms for these medications, and they've refined the role of optical coherence tomography (OCT) and other imaging devices in evaluating disease.[1]

"For example, the DRCR Retina Network reported that OCT results do not always reflect vision outcomes," said Neil M. Bressler, MD, at Johns Hopkins University in Baltimore. "OCT central subfield thickness tells us if there is worsening or stable or improving edema—but it doesn't necessarily tell us how the vision is doing. Consequently, we realized we should not use OCT as a surrogate of whether the patient is seeing well or not. Instead we need to focus on what the VA testing tells us about the patient's vision."

A Revolution Begins

In 2010, the network published primary outcome results from Protocol I, the first large randomized clinical trial demonstrating that intravitreal anti-VEGF was superior to focal/grid laser photocoagulation or intravitreal corticosteroids plus laser for the treatment of DME.[2] "This landmark study definitively showed the effectiveness and superiority of a new alternative to laser photocoagulation for DME," said Dr. Bressler, chair of the network from 2006 to 2012. "Focal/grid laser had been the mainstay of treatment since 1985, when its benefit was reported by the Early Treatment Diabetic Retinopathy Study (ETDRS) Group."

The revolution didn't end with Protocol I. Here's an overview of four subsequent studies—Protocols S, T, V, and U—plus an assessment of potential new treatments.

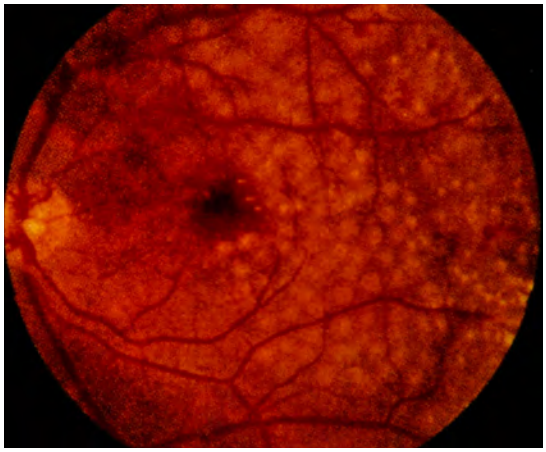
Protocol S: Anti-VEGF Versus PRP

Rationale. Protocol S[3] was designed to compare panretinal photocoagulation (PRP) with anti-VEGF therapy for proliferative diabetic retinopathy (PDR). However, thanks to its structure, the study also revealed insights into the impact of anti-VEGF treatment on DME.

Design. The study compared the safety and efficacy of PRP with intravitreal injections of ran-

Jason S. Calhoun, COA

Originally published in March 2020



LASER. *For many years, focal/grid laser was the leading interventional treatment for DME.*

ibizumab 0.5 mg (Lucentis) in patients with PDR. Secondary outcomes included changes in visual field, development of DME, and rates of vitrectomy for complications.

Findings. "At two years, we showed that treatment with ranibizumab resulted in VA that was noninferior to PRP treatment," said Jeffrey G. Gross, MD, at Carolina Retina Center in Columbia, South Carolina. "Secondary efficacy outcomes in the ranibizumab group included decreased need for vitrectomy and better visual fields at two years, compared to the prompt PRP group."

With regard to DME, fewer eyes in the ranibizumab group developed DME with visual impairment. In addition, for eyes with both PDR and visual loss from DME at baseline, anti-VEGF was given to both the ranibizumab and the PRP groups—yet visual gain appeared to be greater in the eyes receiving anti-VEGF without PRP, suggesting that PRP might diminish the beneficial effects of ranibizumab for the DME.

A follow-up study to Protocol S showed that VA in most of the study eyes remained good at five years and was consistent with the two-year results.[4] However, Dr. Bressler noted that these results should be interpreted with caution since more than one-third of the original participants had died or did not return for the five-year visit.

Nevertheless, the ranibizumab group still had lower rates of DME development with visual loss. They also had less visual field loss at both two and five years, although the difference in visual field loss between the anti-VEGF and PRP groups diminished between the two- and five-year visits.

"These studies also showed that when DME is present in an eye with PDR, it is cost effective, as typically defined in developed nations, to use ranibizumab as an alternative to PRP, since this approach can treat both problems [PDR and DME] simultaneously," Dr. Gross said.

However, in DME eyes without visual impairment at baseline, anti-VEGF treatment was not cost effective compared with PRP. This finding does not reflect all potential benefits of anti-VEGF therapy in this situation, since there were other advantages to anti-VEGF treatment, including less development of DME with visual loss and fewer eyes undergoing vitrectomy for nonclearing vitreous hemorrhage or traction retinal detachment.

Protocol T: Three Anti-VEGF Drugs

Rationale. Is one anti-VEGF drug more effective than another in treating DME? Protocol T[5] was designed to provide some clarity and treatment guideposts for clinicians on this matter.

Keep an Eye on the Big Picture

In the United States alone, 30.3 million patients have diabetes, and another 84.1 million have prediabetes.[1] Globally, an estimated 463 million adults have diabetes, and this is expected to rise to 700 million by 2045.[2]

Holistic perspective needed. As Dr. Wells pointed out, "Unlike AMD, diabetes is a systemic disease. Glucose and hypertension must be controlled, as it makes a difference in the impact on DR and DME. Consequently, ophthalmologists need to be involved from a holistic perspective."

Dr. Wells offered a practical example from his own practice: "For example," he said, "I always look at the ankles of my DME patients to see if they have leg edema and then follow up to see if they are taking diuretics. We often see improvement in DME if the patient's fluid overload is reduced with diuretic therapy."

The QoL challenge. And no matter which current or emerging treatment is used, quality of life is a top concern for patients with DME, many of whom are still working, Dr. Grewal emphasized. "This is a key aspect when analyzing the effectiveness of various agents for DME."

1 CDC. *National Diabetes Statistics Report 2017.* www.cdc.gov/diabetes/data/statistics/statistics-report.html. Accessed Jan. 22, 2019.

2 International Diabetes Foundation. *IDF Diabetes Atlas* 9th edition 2019. www.diabetesatlas.org. Accessed Jan. 22, 2019.

"In developing the study, one of our hypotheses was that there would be differences in efficacy based on VA," said John A. Wells III, MD, at Palmetto Retina Center in Columbia, South Carolina. Specifically, eyes with worse vision might have thicker maculae as a result of higher intraocular VEGF levels, so a drug with the highest VEGF-binding ability might prove more effective.

Design. The study provided a head-to-head comparison between aflibercept (Eylea), bevacizumab (Avastin), and ranibizumab for the treatment of center-involved DME in patients with a VA of 20/32 or worse. In addition, the researchers designed Protocol T so that if a difference among the groups was noted, a preplanned secondary outcome would determine the impact of baseline VA. Focal/grid laser beyond six months also was applied for eyes with persistent but stable DME involving the center of the macula.

Findings. The investigators found that all three agents improved vision in patients with DME, and this improvement was maintained at two years. However, the relative effect depended on baseline VA. In eyes with better baseline vision (20/32 to 20/40) there was no significant difference, on average, among the treatment groups at one and two years. However, at worse levels of initial VA (20/50 or worse), patients treated with aflibercept were, on average, more likely to experience improvement in vision at year 1 compared with those who received either bevacizumab or ranibizumab. In addition, at the two-year mark, those who received aflibercept were more likely to experience improvements in vision than were those who received bevacizumab.

"This study tells us that when you are treating patients with DME-causing visual loss—of 20/32 or worse—in your practice, you should use the (patient's) VA at the time of initiating treatment to help guide" the choice of agent, Dr. Wells said. "Protocol T also showed us that persistent but stable edema beyond six months is not associated with visual loss, provided that anti-VEGF was resumed if the VA decreased or the OCT central subfoveal thickness [CST] worsened."

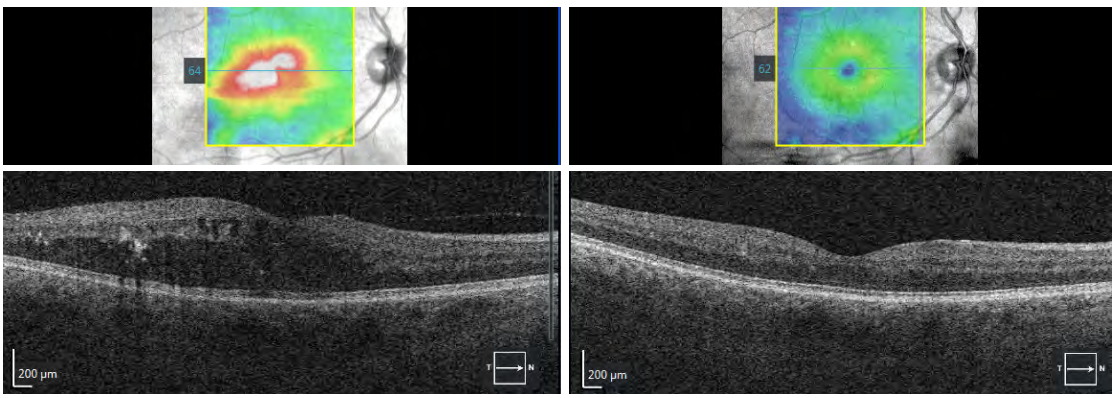
Also of note, in eyes with better baseline vision, bevacizumab reduced edema about 50% less, on average, than the other two drugs through two years. Even so, this did not translate to any less gain in vision for bevacizumab-treated eyes compared with the aflibercept or ranibizumab group when 20/32 to 20/40 at baseline—another example of the potential disconnect between OCT CST outcomes and VA results.

"Yet even through two years, we did not see a lot of severe vision loss" in eyes with chronic persistent edema, Dr. Wells said. "This illustrates that—unlike persistent thickening in neovascular age-related macular degeneration [AMD], where continued anti-VEGF therapy may be necessary to avoid substantial VA loss—such visual loss may not occur in eyes with persistent but stable DME."

Protocol V: Aflibercept, Observation, or Laser

Rationale. "Our goal historically has been to intervene earlier in patients with DME to achieve better outcomes," said Carl W. Baker, MD, with the Paducah Retinal Center in Paducah, Kentucky. That is, he said, "treating an eye at 20/32 is more likely to end up with a better level of VA than treating an eye that walks in at 20/100, even if that 20/100 eye gains 3 lines of vision to 20/50 following anti-VEGF therapy. Yet what should a clinician do if a patient with DME presents with good VA—for example, 20/20? Is anti-VEGF superior to laser or observation for those eyes?"

Dr. Baker added that, in the last 10 years, some clinicians have initiated anti-VEGF treatment in these patients despite a lack of supporting evidence because they were concerned that visual outcomes would be worse if anti-VEGF treatment was deferred. Enter Protocol V, the first large randomized trial since anti-VEGF injections were approved



SHIFT TO ANTI-VEGF. *(Left) Before and (right) after treatment of DME with aflibercept. Results such as these have driven the shift to intravitreal injections of anti-VEGF medications.*

to evaluate management strategies for center-involved DME in eyes with good VA.

Design. Protocol V[6] was designed to determine whether initial close monitoring of DME patients with good vision or starting with laser is a more viable treatment strategy, provided that anti-VEGF therapy is initiated as soon as vision loss is noted. The study included patients with center-involved DME and VA of 20/25 or better. The patients were initially managed with aflibercept, laser photocoagulation, or observation. For the latter two strategies, aflibercept was initiated as a rescue treatment if VA loss was noted during follow-up.

Findings. At two years, rates of VA loss of 5 or more ETDRS letters were not significantly different among the three groups of patients.

"With Protocol V, we have found a paradigm where we can observe some DME patients with good vision and wait on treatment until we see a decrease in vision, thus saving them from unnecessary intravitreal anti-VEGF injections. We are becoming more comfortable monitoring them and initiating treatment only when their vision begins to decline," Dr. Baker said.

He added, "At the end of the day, we have learned that paying close attention to vision quality is the most appropriate driver of how we treat DME patients with good vision."

Protocol U: Persistent DME

Rationale. Protocol U[7] added dexamethasone (Ozurdex) to the mix in an effort to address the persistent DME some eyes experience following anti-VEGF therapy.

Design. The phase 2 trial involved patients with a VA of 20/32 to 20/320 who all had received at least three injections of ranibizumab. Eyes that had persistent DME following these injections were randomly assigned to receive dexamethasone or sham as often as every three months. In addition, both groups continued to receive ranibizumab as often as every four weeks.

Findings. The addition of dexamethasone was found to be more likely to reduce retinal thickness, but it did not improve VA at 24 weeks more than continued ranibizumab therapy alone. It also increased intraocular pressure.

"A message here is that clinicians should not get frustrated if their patients aren't experiencing immediate results," said Dr. Wells. "Persistent DME after six injections is common, but visual loss due to persistent DME is very uncommon."

He added, "Protocol U showed that switching to steroids, with its attendant risks, does not lead to better vision outcomes than continuing anti-VEGF therapy. I always tell my patients that they can expect on average to require about nine to 10 injections in the first year and five to six in the second year to control the DME, as this was the median number of injections given with all three agents over two years in Protocol T. "

Initial Treatment: IRIS Registry Results

Researchers assessed treatment patterns for DME in 13,410 treatment-naive patients. This chart presents initial treatment provided within 28 days of diagnosis of DME.

Treatment	% of Patients*
Observation	74.5%
Anti-VEGF	15.6%
Laser	8.5%
Corticosteroids	1%

* The remaining patients received combination therapy (any combination of anti-VEGF drug, corticosteroid, or laser given within a two-week period).

Adapted from Cantrell RA et al. *Ophthalmology.* Published online Oct. 23, 2019.

What's Next in Treatment?

While the current anti-VEGF treatment options for DME are effective, they are short-acting, noted Dilraj S. Grewal, MD, at Duke University in Durham, North Carolina. Consequently, patients must come in frequently, which has resulted in a considerable increase in the treatment burden.

One outcome of this burden: loss to follow-up. "This is especially true of patients who do not receive any noticeable improvement after three months of treatment and become discouraged, even though the treatment effects take time," Dr. Grewal said. "Compliance is a huge challenge."

A look at the pipeline. Drug manufacturers are well aware of the need for longer-acting therapies, Dr. Grewal said. "This is going to be the next big shift in treatment." He provided an overview of several therapies in the pipeline:

Faricimab. In DME, angiopoietin-2 (Ang-2) works synergistically with VEGF-A to drive biological pathways that cause vessel permeability and inflammation. Faricimab (Genentech), formerly known as RG7716, is the first bispecific monoclonal antibody that simultaneously binds to and neutralizes both Ang-2 and VEGF-A. "This drug is designed to affect vascular stability, and its phase 2 trials look promising," Dr. Grewal said.

KSI-301. Kodiak Sciences has developed an

antibody biopolymer conjugate (ABC) platform designed to maintain drug levels in ocular tissues for a longer time than is currently available. KSI-301, an anti-VEGF ABC, is designed as a first-line treatment for DME.

Port Delivery System. This technology, from Genentech, is designed to dispense ranibizumab through a refillable, surgically placed implant to achieve sustained delivery. "It has been studied in AMD, and the next phase will move toward evaluating its efficacy in DME," Dr. Grewal said.

AR-13503 SR Implant. This implant, from Aerie Pharmaceuticals, provides sustained release of a small molecule inhibitor of both Rho kinase and protein kinase C. The agent is thought to inhibit angiogenesis, preserve the blood retinal barrier, and reduce retinal fibrosis in DME. It is designed to be administered once every six months via intravitreal injection.

GB-102. An injectable depot version of the anticancer drug sunitinib malate, GB-102 (Graybug) "binds to all VEGF receptors and has been targeted for [treatment of] AMD and DME," Dr. Grewal said. This small molecule receptor tyrosine kinase inhibitor blocks several intracellular receptors associated with angiogenesis, proliferation, vascular permeability, and fibrosis.

RGX-314. Gene therapy is also being explored. One example is RGX-314 (Regenxbio), a one-time subretinal treatment. It contains a gene that encodes for a monoclonal antibody fragment; the expressed protein is designed to neutralize VEGF activity. Disease targets include AMD and DR.

PAN-90806. This once-daily anti-VEGF eyedrop, from PanOptica, is being evaluated for neovascular eye diseases. Results from an initial dose-ranging phase 1/2 trial released in October 2019 demonstrated a biological response as monotherapy in treatment-naive patients with wet AMD.[8]

AI—and more. Dr. Grewal also predicted that artificial intelligence will help ophthalmologists evaluate their patients with DME, determine the best treatment strategy, and match this information with insurance coverage restrictions.

"In addition," Dr. Grewal said, "we will be moving in a more holistic direction, linking patients' eye treatment with their metabolic profile—all through sophisticated smartphone apps."

1 Sun JK, Jampol LM. *Ophthalmic Res.* 2019;62:225-230.
2 Elman MJ et al., for the Diabetic Retinopathy Clinical Research Network. *Ophthalmology.* 2010;117(6):1064-1077.
3 Gross JG et al. *JAMA.* 2015;314(20):2137-2146.
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7 Maturi RK et al. *JAMA Ophthalmol.* 2018;136(1):29-38.
8 www.businesswire.com/news/home/20191010005814/en/PanOptica-Anti-VEGF-Eye-Drop-Shows-Promise-Treatment.

Meet the Experts





Carl W. Baker, MD With the Paducah Retinal Center in Kentucky. *Financial disclosures: Novo Nordisk: C; Regenxbio: C.*

Neil M. Bressler, MD The James P. Gills Professor of Ophthalmology at the Johns Hopkins University School of Medicine in Baltimore and Editor-in-Chief of *JAMA Ophthalmology. Financial disclosures: Bayer: S; Novartis: S; Roche: S; Samsung Bioepis: S. Note: Participation by Dr. Bressler in this activity does not constitute or imply endorsement by the Johns Hopkins University, the Johns Hopkins Hospital, or the Johns Hopkins Health System; nor by the DRCR Retina Network; nor by* JAMA Ophthalmology.

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Jeffrey G. Gross, MD President and managing partner of Carolina Retina Center in Columbia, S.C. *Financial disclosures: BioGenware: O,P; Covalent: O; Heidelberg Engineering: L; Jaeb Center for Health Research: S.*

John A. Wells III, MD With the Palmetto Retina Center and chairman of ophthalmology at the Palmetto Health/USC Medical Group, both in Columbia, S.C. *Financial disclosures: Adverum: S; Genentech: C,S; Iconic Therapeutics: C; Jaeb Center for Health Research: C,S; NEI: S; Ohr Pharmaceuticals: S; Opthea: S; Optos: S; Regeneron: S; ThromboGenics: S.*

See disclosure key, page 5.

MYSTERY IMAGE

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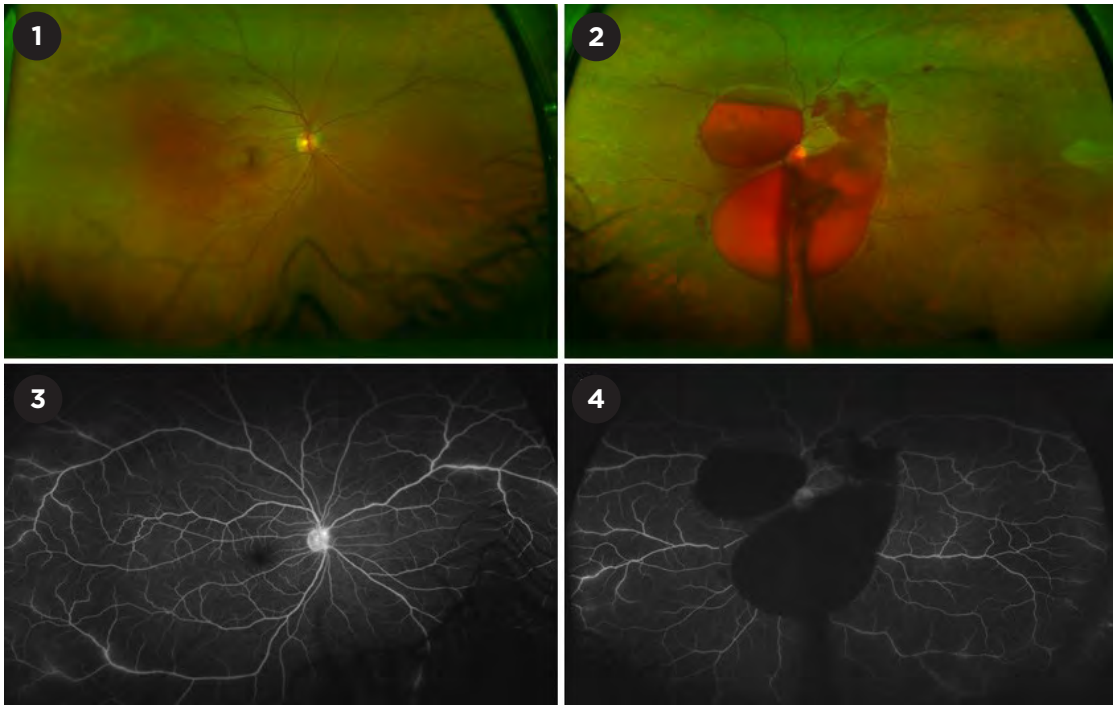

Varun Shrestha, MD. Sagarmatha Chaundhary Eye Hospital. Lahan. Nepal.

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

LAST MONTH'S BLINK

An Unusual Presentation of Sarcoidosis

Originally published in March and April 2020

A 29-year-old man with a history of chronic cough, pleuritic chest pain, night sweats, and multiple hospitalizations for pneumonia presented with a one-day history of sudden-onset decreased vision in his left eye. He also had a history of working in methadone clinics, and his tuberculosis status was unknown.

His visual acuity was 20/20 in the right eye and counting fingers at 3 inches in the left. Examination revealed 1+ vitreous cells and perivenous sheathing in his right eye (Fig. 1). In his left eye, 2+ vitreous cells, large preretinal vitreous hemorrhage overlying the macula and surrounding the optic nerve, intraretinal dot-and-blot hemorrhages, and perivenous sheathing in the peripheries were evident (Fig. 2). The right fluorescein angiography demonstrates hyperfluorescence of the optic nerve and late leakage of the peripheral vessels (Figs. 3, 4).

Initial workup was significant for indeterminate Quantiferon Gold testing and elevated levels of angiotensin-converting enzyme. Chest X-ray and computed tomography revealed bilateral hilar lymphadenopathy and a 5-mm nodule in the right lower lobe of the lung. Syphilis, HLA-B27, Lyme disease, and antineutrophil cytoplasmic antibody tests were negative. The patient's pulmonologist eventually performed a lung biopsy, and the findings were consistent with sarcoidosis.

Patients with ocular sarcoidosis often present with uveitis; retinopathy and vitreous hemorrhage constitute rare clinical presentations of the disease. This case illustrates the importance of considering sarcoidosis as an etiology of vitreous hemorrhage in the setting of posterior uveitis.

WRITTEN BY **RACHEL H. LEE, MD, MPH, JEROME GIOVINAZZO, MD, RICHARD M. FRANCE, MD, AND STEPHANIE LLOP, MD,** NEW YORK EYE AND EAR INFIRMARY OF MOUNT SINAI. PHOTO BY MEDICAL PHOTOGRAPHY DEPARTMENT AT NEW YORK EYE AND EAR INFIRMARY OF MOUNT SINAI.

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:

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 CRVO in 2 clinical studies (COPERNICUS and GALILEO) and 91 patients following 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.19.07.0306

FDA approved for several indications, including Diabetic Retinopathy (DR)[1]

With demonstrated outcomes for members backed by extensive clinical experience, EYLEA delivers

PROOF RIGHT BEFORE YOUR EYES

EYLEA®
(aflibercept) Injection
For Intravitreal Injection

IMPORTANT SAFETY INFORMATION AND INDICATIONS

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.

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TRUST the Clinical Evidence and Flexibility of EYLEA[1]

Get the facts at:
EYLEAMarketAccess.com

*__Wet Age-related Macular Degeneration (AMD):__ The recommended dose of EYLEA is 2 mg administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 3 months, followed by 2 mg via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every-4-week (monthly) dosing after the first 12 weeks (3 months). Although not as effective as the recommended every-8-week dosing regimen, patients may also be treated with one dose every 12 weeks after one year of effective therapy. Patients should be assessed regularly. **Diabetic Macular Edema (DME) and DR:** The recommended dose of EYLEA is 2 mg administered by intravitreal injection every 4 weeks (approximately every 28 days, monthly) for the first 5 injections, followed by 2 mg via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (approximately every 25 days, monthly), additional efficacy was not demonstrated in most patients when EYLEA was dosed every 4 weeks compared to every 8 weeks. Some patients may need every-4-week (monthly) dosing after the first 20 weeks (5 months).

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.

INDICATIONS

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

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

References: 1. EYLEA® (aflibercept) Injection full U.S. Prescribing Information. Regeneron Pharmaceuticals, Inc. August 2019. **2**. Data on file. Regeneron Pharmaceuticals, Inc.

11/2019
EYL.19.11.0003

EYLEA COPAY CARD

EYLEA4U® Copay Card Program

Eligible patients may pay as little as a

$0 copay for each EYLEA treatment.*

Subject to annual assistance limit.

The patient is responsible for any additional copay costs that exceed the program assistance limit.

The program covers up to*

$15,000

in assistance per year

toward product-specific copay, coinsurance, and insurance deductibles for EYLEA treatments. No income eligibility requirement.

Patient eligibility

- Must have commercial or private insurance that covers EYLEA
- Must have a copay for EYLEA
- Must be a resident of the United States or its territories or possessions

To learn more about the EYLEA Copay Card, call EYLEA4U at 1-855-EYLEA4U (1-855-395-3248), Option 4, Monday–Friday 9AM–8PM Eastern Time or visit EYLEA.com.

For patients with insurance not funded through a government healthcare program.

*Subject to annual assistance limit. Not an insurance or debit card program. This program is not valid for prescriptions covered by or submitted for reimbursement under Medicaid, Medicare, VA, DOD, TRICARE, or similar federal or state programs. This program does not cover or provide support for supplies, procedures, or any physician-related service associated with EYLEA. General, non-product-specific copay, coinsurance, or insurance deductibles are not covered. This program is not valid where prohibited by law, taxed, or restricted. EYLEA4U reserves the right to rescind, revoke, terminate, or amend this offer, eligibility, and terms of use at any time without notice. Additional program conditions apply. See EYLEA.com.

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EYLEA® (aflibercept) Injection 4U℠

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