

AMD DISEASE EDUCATION RESOURCE CENTER

A multipart case series presented by experts in the management and treatment of wet age-related macular degeneration.

Age-related macular degeneration (AMD) is a progressive disease that attacks the macula. It affects as many as 15 million Americans and is the No. 1 cause of severe vision loss and legal blindness in adults over age 60 years.¹ AMD is commonly classified into three stages: (1) early, at which stage most people have not noticed any vision loss and the disease is diagnosed by the presence of medium-sized drusen; 2) intermediate, when patients may experience some vision loss and the disease is diagnosed by the presence of larger drusen and/or pigment changes; and 3) late, when vision loss has typically become noticeable.

Although the exact cause of AMD is unknown, heredity and environment seem to be key factors in its pathogenesis. Angiogenesis is vital to the development of the eye; VEGF is produced in the eye and regulates the growth of new blood vessels. Elevated levels of VEGF have been found in the vitreous of patients with choroidal neovascularization, a hallmark of wet AMD. Anti-VEGF drugs have been developed to seek out and block harmful VEGF molecules. Treatment with these drugs has become standard of care for AMD, but other options include the use of thermal laser and photodynamic therapy.

In Part 4 of this series, Nancy M. Holekamp, MD, director of retina diseases in the Center for Macular Degeneration at the Pepose Vision Institute, shares her experience managing a patient with what she calls a provocative case of AMD. A video of Dr. Holekamp presenting this case can be viewed online in the AMD Resource Center at bit.ly/AMDresource.

1. Macular Degeneration Partnership. What is macular degeneration? www.amd.org/what-is-macular-degeneration/. Accessed September 14, 2016.

Supported by advertising from Regeneron Pharmaceuticals and Carl Zeiss Meditec



Discover Strength in efficacy

As demonstrated in phase 3 clinical trials in patients with Wet AMD, Macular Edema following RVO, DME, and DR in patients with DME

Choose EYLEA® (aflibercept) Injection from the start

Learn about EYLEA at EYLEA.us/rt

INDICATIONS AND IMPORTANT SAFETY INFORMATION

INDICATIONS

- EYLEA® (aflibercept) Injection 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) in Patients with DME.

CONTRAINDICATIONS

- EYLEA® (aflibercept) Injection 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. 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 floaters, intraocular pressure increased, and vitreous detachment.

Please see brief summary of full Prescribing Information on the following page.

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON

 **EYLEA®**
(aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE



BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

EYLEA® (afibercept) Injection 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) in Patients with DME.

2 DOSAGE AND ADMINISTRATION

2.1 Important Injection Instructions. For ophthalmic intravitreal injection. EYLEA must only be administered by a qualified physician.

2.2 Neovascular (Wet) Age-Related Macular Degeneration (AMD). The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 12 weeks (3 months), followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.3 Macular Edema Following Retinal Vein Occlusion (RVO). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection once every 4 weeks (monthly).

2.4 Diabetic Macular Edema (DME). The recommended dose for EYLEA is (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.5 Diabetic Retinopathy (DR) in Patients with DME. The recommended dose for EYLEA is 2 mg (0.05 mL or 50 microliters) administered by intravitreal injection every 4 weeks (monthly) for the first 5 injections, followed by 2 mg (0.05 mL) via intravitreal injection once every 8 weeks (2 months). Although EYLEA may be dosed as frequently as 2 mg every 4 weeks (monthly), additional efficacy was not demonstrated when EYLEA was dosed every 4 weeks compared to every 8 weeks.

2.6 Preparation for Administration. EYLEA should be inspected visually prior to administration. If particulates, cloudiness, or discoloration are visible, the vial must not be used. Using aseptic technique, the intravitreal injection should be performed with a 30-gauge x ½-inch injection needle. For complete preparation for administration instructions, see full prescribing information.

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

Immediately following the intravitreal injection, patients should be monitored for elevation in intraocular pressure. Appropriate monitoring may consist of a check for perfusion of the optic nerve head or tonometry. If required, a sterile paracentesis needle should be available.

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

Each vial must only be used for the treatment of a single eye. If the contralateral eye requires treatment, a new vial should be used and the sterile field, syringe, gloves, drapes, eyelid speculum, filter, and injection needles should be changed before EYLEA is administered to the other eye. After injection, any unused product must be discarded.

3 DOSAGE FORMS AND STRENGTHS

Single-use, glass vial designed to provide 0.05 mL of 40 mg/mL solution (2 mg) for intravitreal injection.

4 CONTRAINDICATIONS

EYLEA is contraindicated in patients with

- Ocular or periocular infections
 - Active intraocular inflammation
 - Known hypersensitivity to afibercept or any of the excipients in EYLEA.
- Hypersensitivity reactions may manifest as 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). 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 Dosage and Administration and Patient Counseling Information).

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). Sustained increases in intraocular pressure have also been reported after repeated intravitreal dosing with vascular endothelial growth factor (VEGF) inhibitors. Intraocular pressure and the perfusion of the optic nerve head should be monitored and managed appropriately (see Dosage and Administration).

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. 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 adverse reactions are discussed in greater detail in the Warnings and Precautions section of the labeling:

- Endophthalmitis and retinal detachments
- Increased intraocular pressure
- Thromboembolic events

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 2711 patients treated with EYLEA constituted the safety population in seven phase 3 studies. Among those, 2110 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 floaters, intraocular pressure increased, and vitreous detachment.

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, active-controlled clinical studies (VIEW1 and VIEW2) for 12 months.

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

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

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

Adverse Reactions	CRVO		BRVO	
	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). 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				
Adverse Reactions	Baseline to Week 52		Baseline to Week 100	
	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.

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. Pregnancy Category C. Afibercept produced embryo-fetal toxicity when administered every three days during organogenesis to pregnant rabbits at intravenous doses ≥3 mg per kg, or every six days at subcutaneous doses ≥0.1 mg per kg. Adverse embryo-fetal 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, sternbrae, and ribs; supernumerary vertebral arches and ribs; and complete ossification). The maternal No Observed Adverse Effect Level (NOAEL) in these studies was 3 mg per kg. Afibercept produced fetal malformations at all doses assessed in rabbits and the fetal NOAEL was less than 0.1 mg per kg. Administration of the lowest dose assessed in rabbits (0.1 mg per kg) resulted in systemic exposure (AUC) that was approximately 10 times the systemic exposure observed in humans after an intravitreal dose of 2 mg. There are no adequate and well-controlled studies in pregnant women. EYLEA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

8.3 Nursing Mothers. It is unknown whether afibercept is excreted in human milk. Because many drugs are excreted in human milk, a risk to the breastfed child cannot be excluded. EYLEA is not recommended during breastfeeding. A decision must be made whether to discontinue nursing or to discontinue treatment with EYLEA, taking into account the importance of the drug to the mother.

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). Patients may experience temporary visual disturbances after an intravitreal injection with EYLEA and the associated eye examinations (see Adverse Reactions). 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 10591-6707

All rights reserved.
Issue Date: March 2015
Initial U.S. Approval: 2011

U.S. License Number 1760
EYLEA is a registered trademark of
Regeneron Pharmaceuticals, Inc.
© 2015, Regeneron
Pharmaceuticals, Inc.

Regeneron U.S. Patents 7,070,959;
7,303,746; 7,303,747; 7,306,799;
7,374,757; 7,374,758; 7,531,173;
7,608,261; 7,972,598; 8,029,791;
8,092,803; 8,647,842; and other
pending patents. LEA-0721

A Provocative AMD Case

BY NANCY M. HOLEKAMP, MD



Retina specialists know that wet age-related macular degeneration (AMD), the more advanced form of AMD, affects only 10% to 15% of patients with AMD yet accounts for 90% of the severe vision loss caused by the disease.¹ Abnormal vessels form in the subretinal membrane and often grow and leak or bleed, scarring the macula and causing central vision loss. The

fluid leaking from these vessels is called exudate, and wet AMD is sometimes referred to as exudative AMD. Dry AMD, often the earlier form of the disease, is referred to as nonexudative AMD.

Although there is no approved treatment for patients with dry AMD at this time, several treatment options exist for patients with wet AMD, including the use of a laser with a light-sensitive drug to seal off leaky blood vessels (photodynamic therapy) or, in a more recent advance, pharmacologic anti-VEGF therapy, which can reduce new blood vessel growth and edema. The key to effective treatment involves early detection. Although some vision may be restored in patients who are treated early, no therapy can restore vision in an eye with scarring.

Below I share the case of a patient with AMD that really required some critical thinking on my part. It involves both exudative and nonexudative AMD.

A COMPLEX CASE

An 89-year-old white woman presented with 20/400 visual acuity in the right eye (OD) and 20/40 in the left eye (OS). She had a disciform scar OD, which explained her poor visual acuity. The patient developed exudation OS and was treated with intravitreal ranibizumab (Lucentis, Genentech) as needed, receiving seven injections over the first year of treatment. I saw her monthly, and over the course of these visits the edema would resolve and then return, at which time she would receive another injection.

The patient continued to be seen monthly throughout year 2. Early in year 2, fundus photography and optical coherence tomography (OCT) revealed a hint of glaucoma and a Drance hemorrhage at the nasal margin of the optic nerve (Figure 1). Macular degeneration with drusen and areas of focal hyperpigmentation were noted in the macula, as was a zone of juxtafoveal geographic atrophy (GA). Although the patient's visual acuity was 20/40 OS, her OCT showed a big cystic area overlying the GA (Figure 2). Late in year 2 of follow-up she developed chronic cystoid macular edema (CME) overlying the zone of GA, and the CME remained unchanged despite monthly intravitreal injections of ranibizumab.

Through all this, the patient's visual acuity remained good at 20/40, despite the chronic CME. This is not uncommon, as chronic CME is thought to represent malfunction of retinal pigment epithelial cells or perhaps Müller cells that are no longer able to resorb the intraretinal fluid.

DISCUSSION

Management of this patient was not straightforward, which is why I consider the case to be provocative in nature. When the details of the case are considered, several management questions arise. Should I continue the monthly injections, even though the CME does not get better, because the patient is monocular and I do not want the CME to get worse? Should I discontinue the injections in order to find out if the CME gets worse, because this level of CME could simply be her new baseline? Should I stop the injections because of the risk of promoting GA? Should I get a fluorescein angiogram (FA) to determine whether the CME represents true leakage?

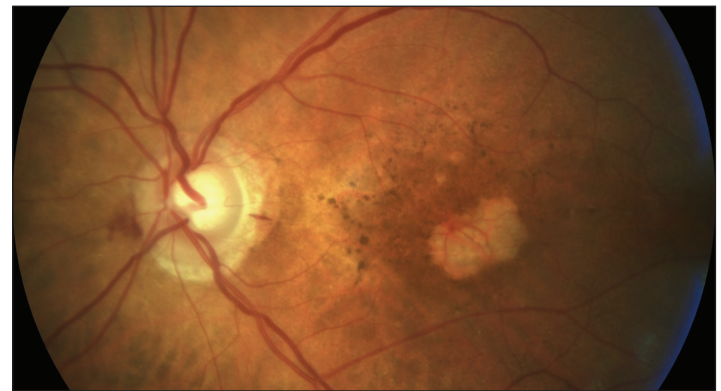


Figure 1. Fundus photo OS shows juxtafoveal GA. Patient's visual acuity at the time was 20/40 OS.

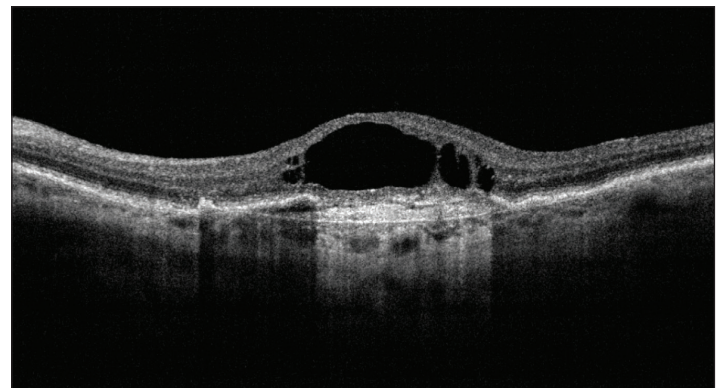


Figure 2. OCT scan OS shows CME overlying GA.

“ Think about your patients and carefully review their OCT findings at each visit. If you are not sure what to do, start by getting an FA.

Not many retina specialists get FAs anymore, but the procedure is always helpful when you are not sure what to do. In this case, I did order an FA, and the result was consistent with leakage; therefore, I continued the patient on monthly injections of ranibizumab. To my surprise, the CME had completely resolved by year 3, and the GA zone had grown only slightly larger. The patient's visual acuity is now 20/63 OS, but she is able to read with a magnifier, and she has been happy with our management strategy. The CME did eventually respond to monthly anti-VEGF injections, and the vision decline was consistent with the natural history of untreated GA.

CONCLUSION

The take-home message from this case? Do not become an injecting machine in the office. Think about your patients and carefully review their OCT findings at each visit. If you are not sure what to do, start by getting an FA. In this case, the FA demonstrated active leakage and encouraged me to keep up monthly anti-VEGF injections in this patient. The strategy paid off: The CME is gone and her macula has achieved a dry state. Of course, monocular patients continue to require close surveillance, and this patient continues to see me on a regular basis for monitoring of her macular degeneration. Furthermore, she understands that she could once again require injections if her macula develops recurrent exudative disease. ■

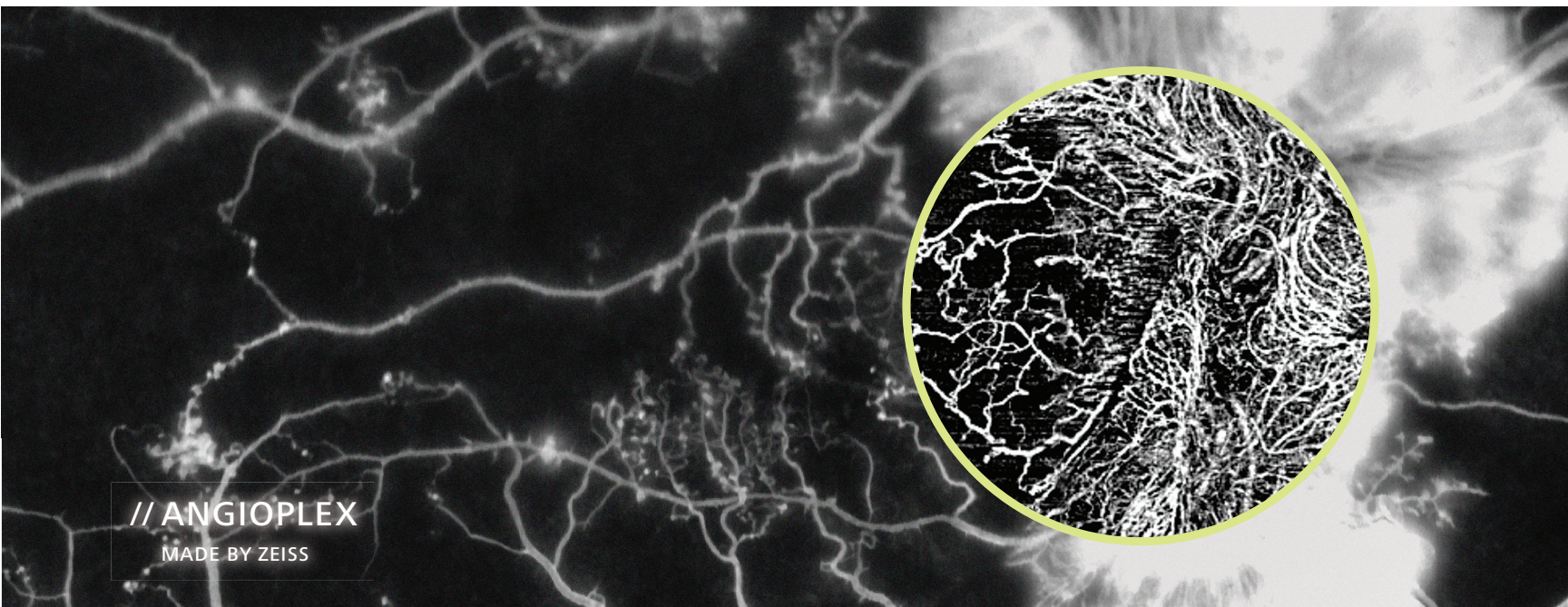
1. Macular Degeneration Partnership. Wet AMD. www.amd.org/what-is-macular-degeneration/wet-amd/. Accessed September 14, 2016.

Nancy M. Holekamp, MD

- director of retina diseases, Center for Macular Degeneration, Pepose Vision Institute, in Chesterfield, Mo.
- financial disclosure: speaker, Regeneron, Genentech, Allergan, and Alimera Sciences; consultant, Regeneron, Genentech, Allergan, and Alimera Sciences; research funds, Allergan and Alimera Sciences
- nholekamp@gmail.com

The moment that revolutionary insight
becomes a routine part of every day care.

Introducing ZEISS AngioPlex™ OCT Angiography



ZEISS AngioPlex OCT Angiography **Making the revolutionary, routine.**

A new era in retinal care—right now.

- **New vascular information** with ultra-clear 3D microvascular visualizations
- **Enhanced workflow** with non-invasive, dye-free, single-scan angiography
- **Advancing OCT** with ZEISS' powerhouse CIRRUS™ OCT platform



Visit www.zeiss.com/octangio
to find out more!

