Insert to

November/December 2015

RETINA TODAY

AN UPDATE ON THE LATEST CLINICAL TRIALS ON DME:

ARE THEY APPLICABLE TO OTHER DISEASE STATES?

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® (aflibercept) Injection
For Intravitreal Injection

TARGETED SCIENCE

EYLEA is a registered trademark of Regeneron Pharmaceuticals, Inc.

REGENERON

05/2015
LEA-0756

EYLEA® (aflibercept) Injection For Intravitreal Injection

BRIEF SUMMARY OF FULL PRESCRIBING INFORMATION

For complete details, see Full Prescribing Information.

1 INDICATIONS AND USAGE

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.

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 should 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 aflibercept 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 edothelial 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. Aflibercept 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, 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 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 aflibercept 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

U.S. License Number 1760

Issue Date: March 2015
Initial U.S. Approval: 2011

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

AN UPDATE ON THE LATEST CLINICAL TRIALS ON DME:

ARE THEY APPLICABLE TO OTHER DISEASE STATES?

A roundtable discussion about recent clinical trials and their impact on treatment of various retinal conditions.

PANELISTS:

Dante J. Pieramici, MD, Moderator
Dr. Pieramici is a partner in California Retina Consultants and director of the California Retina Research Foundation, both in Santa Barbara. He is a paid consultant and receives research funds from Genentech/Roche and receives a speaking honorarium and research funds from Regeneron/Bayer. He may be reached at dpieramici@yahoo.com.

Gregory R. Blaha, MD, PhD
Dr. Blaha is the director of the vitreoretinal service and vitreoretinal fellowship at Lahey Medical Center in Peabody, Massachusetts. He is an assistant professor at Tufts University School of Medicine. Dr. Blaha is a consultant for Regeneron. He may be reached at Gregory.Blaha@lahey.org.

David Eichenbaum, MD
Dr. Eichenbaum practices at Retina Vitreous Associates of Florida in Tampa Bay, and he is an affiliate assistant professor of ophthalmology at the University of South Florida. Dr. Eichenbaum is a speaker for Allergan and Genentech, and he has served as an advisor, consultant, and clinical expert for Allergan, Genentech, and ThromboGenics. He conducts contracted research for Alcon, Allergan, Genentech, and ThromboGenics. He may be reached at deichenbaum@retinavitreous.com.

Rishi P. Singh, MD
Dr. Singh is a staff surgeon at the Cole Eye Institute, Cleveland Clinic, medical director of the Clinical Systems Office, and assistant professor of ophthalmology at the Case Western Reserve University in Cleveland. He is a consultant for Alcon, Genentech, Regeneron, Shire, and ThromboGenics. He conducts contracted research for Alcon, Genentech, Ophthotech, and Regeneron. He may be reached at drrishisingh@gmail.com.

Dante J. Pieramici, MD: Let us begin by discussing our impressions of the top-line results from the Protocol T study.[1] To recap, the Protocol T study found that intravitreal aflibercept (Eylea, Regeneron), bevacizumab (Avastin, Genentech), or ranibizumab (Lucentis, Genentech) improved vision in eyes with center-involving diabetic macular edema (DME), but the relative effect depended on baseline visual acuity. When the initial loss of visual acuity was mild, there were no apparent differences, on average, among study groups. At worse levels of initial visual acuity, aflibercept was more effective at improving vision.

Dr. Singh, is visual acuity a fair measure to evaluate patients with DME?

Rishi P. Singh, MD: If visual acuity were reproducible, I believe it would be; however, many retina specialists, myself included, no longer perform refractions. We are now testing pinhole acuity and Snellen acuity at distance, which may not correlate with the studies.

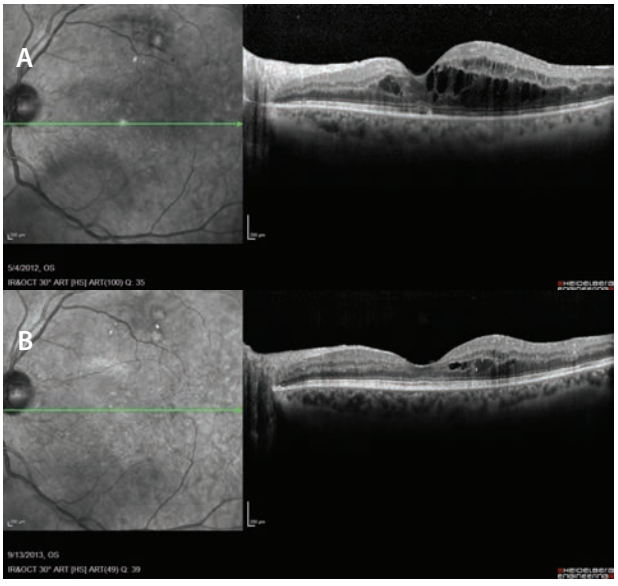
Gregory R. Blaha, MD, PhD: Snellen visual acuity is quite variable in the clinic, and it is difficult to compare with the ETDRS visual acuities used in studies, but vision is what our patients care about. Visual acuity is important to have in any study, as long as we recognize that it may not be the same as what we see in the clinic.

Dr. Pieramici: Do you use visual acuity to decide if you will use one drug or another?

David Eichenbaum, MD: In general, I use visual acuities reported in studies as a guide. We currently have 1-year data from Protocol T, which is a 2-year study. We should consider those results, but I believe visual acuity of 20/50 is not a definitive cut-off, although it may be a trend. When I examine a patient who is generally seeing worse—I, too, do not perform refractions—I consider what we have learned thus far from Protocol T.

Dr. Pieramici: Patients may have visual acuities of 20/50 at one visit and 20/70 at the next visit, but they say they are seeing better at the second visit. It is difficult to rely only on nonrefracted Snellen visual acuity to guide treatment. I tend to rely more on the quantitative data provided by optical coherence tomography (OCT) to drive my decision-making.

Dr. Eichenbaum: As people who like definitive things—and we all know that vision is variable—retina specialists put a lot of faith in OCT, although we do have cases where the edema flattens out while the visual acuity decreases significantly or vice versa (Figure 1). I think, in general, we put more stock in the drying effect of the anti-VEGF agents than we do in the visual acuity.



Courtesy of David Eichenbaum, MD.

Figure 1. This patient presented with significant leakage and edema and visual acuity of 20/125 (A). After 13 injections of ranibizumab over approximately 14 months, some fluid persists (B), but visual acuity has improved to 20/32.

Dr. Blaha: Although macular thickness does not always directly correlate with visual acuity,[2] we use OCT because measurements are objective and easily obtained, and we can use OCT to show patients their posttreatment changes.

Dr. Singh: What we do in clinical practice often differs from the clinical trial protocols. For example, strictly following the Branch Vein Occlusion Study protocol, patients had to demonstrate visual acuities of 20/40 or worse for 3 months before they could receive argon laser treatment.[3] In clinical practice, visual acuity is not always the driver for therapy.

Dr. Pieramici: We must remember that patients in studies may be different from the patients we see every day in the clinic. We use the studies as guidelines to help us make decisions. We do not use them like a cookbook that tells us we must have a specific amount of edema or visual acuity to use a particular agent. I believe Protocol T has given us some insight into the relative potency of these drugs overall.

Are there any parallels between Protocol T and the VIVID and VISTA[4] results in the worse-vision groups?

Dr. Eichenbaum: I think Protocol T, as it was written and reported, had more of a signal with visual acuity than VIVID and VISTA did, perhaps because Protocol T split the groups by visual acuity at the beginning of the study.

CASE REPORT

Presented by: Rishi P. Singh, MD

This 49-year-old woman with poorly controlled type 2 diabetes, hypertension, and cataracts was referred to our clinic. Her chief complaints were decreased vision for 8 months (worse in the left eye), photophobia, flashes, and floaters. Her entering visual acuities were 20/125 OD and 20/100 OS. She has severe nonproliferative diabetic retinopathy and florid diabetic macular edema in both eyes. The patient has no healthcare insurance.

Based on our baseline retina evaluation and the patient's financial situation (Figure 1), we treated both eyes with bevacizumab (Avastin, Genentech), which produced a good response (Figure 2).

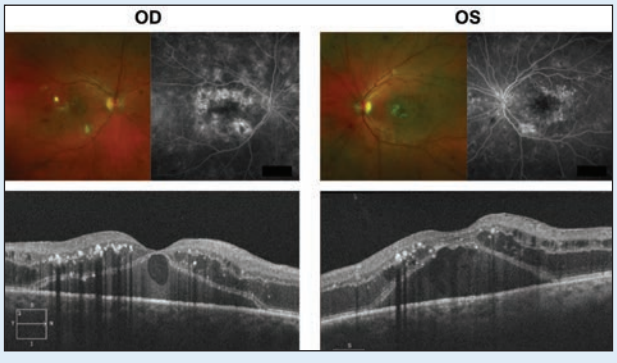


Figure 1. Baseline retina evaluation.

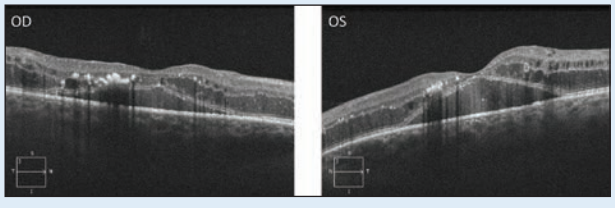


Figure 2. Both eyes responded well to initial treatment with bevacizumab.

A second round of bilateral bevacizumab injections produced a good response, with improved visual acuity; however, some residual edema persisted (Figure 3). We treated both eyes with focal laser and 1 month later saw reduced subretinal fluid on OCT (Figure 4). Visual acuities at this visit were 20/40+1 OD and 20/70-1 OS. We did not treat at this visit.

Two months later, the macular edema had worsened and significant exudates were present. Visual acuities had decreased to 20/60+/-1 OD and 20/125-1 OS. We administered bilateral bevacizumab, which produced a significant improvement (Figure 5). At this visit, we treated the left eye only with bevacizumab.

At the patient's next follow-up visit, visual acuity and edema had improved in the right eye, while the left eye had worsened significantly (Figure 6). We decided to treat the left eye with aflibercept (Eylea, Regeneron). One month later, we saw a significant improvement in the left eye, while the right eye remained stable (Figure 7). Visual acuities were 20/30-2 OD and 20/60-2 OS.

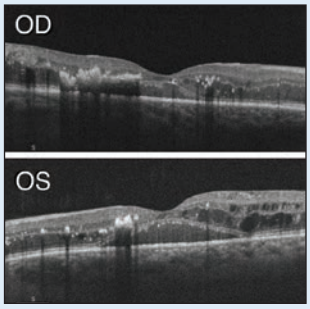


Figure 3. After bilateral bevacizumab, some edema persisted.

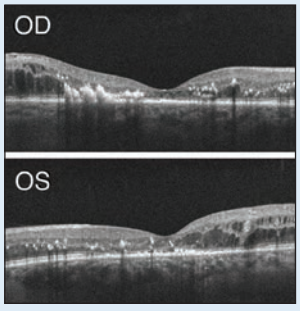


Figure 4. After focal laser, subretinal fluid improved.

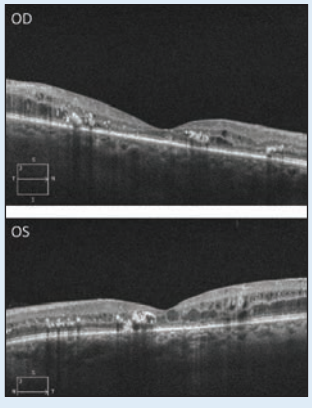


Figure 5. We decided to treat only the left eye with bevacizumab at this visit.

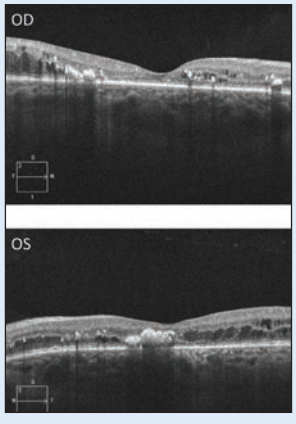


Figure 6. As bevacizumab was not producing a good response in the left eye, we switched to aflibercept.

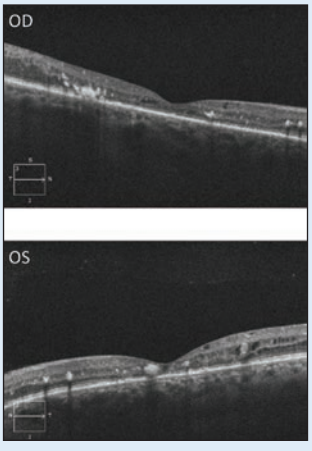


Figure 7. Aflibercept produced a significant improvement in the right eye.

Despite the initial OCT and visual acuity, the patient improved significantly with anti-VEGF therapy. Protocol T showed that patients with baseline visual acuity of 20/50 or worse experienced a greater improvement when treated with aflibercept versus ranibizumab or bevacizumab. Given this patient's acuity level, she was transitioned to aflibercept.

If the year-2 results support the year-1 results and maintain statistical significance, Protocol T would speak more toward visual acuity than VIVID and VISTA do.

Dr. Blaha: In Protocol T, the patients in the lower vision group who received aflibercept gained more letters as compared to patients in the VIVID and VISTA studies, but VIVID and VISTA had a 20/40 cut-off, while in Protocol T, the cut-off was 20/50. If there is a ceiling effect, then patients with 20/40 visual acuity can improve only so much, and that may be why patients are gaining more letters in the 20/50-and-worse group in Protocol T.

CATT VERSUS PROTOCOL T

Dr. Pieramici: Are there any consistencies or extrapolations that one can make between the CATT[5] and Protocol T, remembering that these studies investigated two different disease processes?

Dr. Blaha: The differences between CATT and Protocol T are significant, making comparisons difficult. In addition to the different disease processes, different doses of ranibizumab (Lucentis, Genentech) were administered (0.5 mg versus 0.3 mg), and CATT is a noninferiority study while Protocol T is not. All three agents appear to be efficacious, although bevacizumab (Avastin, Genentech) does not dry quite as well as the other agents.

Dr. Pieramici: I agree. Although there may be relative differences among the agents when used to treat DME versus AMD, in general, both studies are reassuring in that they support the safety and efficacy of these agents in these two disease processes.

Dr. Eichenbaum: The only real parallel I drew was that patients needed about the same number of injections in the p.r.n. arms of both studies in the first year. That was interesting, even though the studies looked at two different diseases, used different drugs, and had different inclusion and exclusion criteria.

Dr. Singh: In the first year, CATT showed differences in p.r.n. bevacizumab versus p.r.n. ranibizumab not meeting its noninferiority mark. Therefore, as p.r.n. bevacizumab users in neovascular AMD, we do not know if there was equivalence between p.r.n. and monthly ranibizumab. I look at the p.r.n. phases of the study, because I think that is probably the only aspect of the CATT and Protocol T studies that we can correlate with our own clinical practices.

EXTRAPOLATING PROTOCOL T DATA

Dr. Pieramici: Assuming cost is not an issue, have the Protocol T results for DME changed how you select your primary agent for treating AMD?

Dr. Blaha: Cost is always an issue. Whether the patient, the insurance carrier, the government, or the drug company is paying for a drug, cost is a factor along with other practical considerations. For example, if I want to treat a patient on the same day as the visit but I do not have samples in the office, I may start treating with bevacizumab, regardless of the disease. In diabetes, I may be more likely to switch to aflibercept if I am not seeing the response I want. Whereas in AMD, I am more comfortable staying with bevacizumab for several months to give it a chance to have an effect, assuming the patient is doing well and I am seeing an anatomic response. I tend to think of AMD and DME slightly differently. I think VEGF levels are higher in DME and that DME is a more multifactorial process.

Dr. Pieramici: Would that thought process influence your decision for retinal vein occlusions (RVOs)?

Dr. Blaha: Perhaps. Although I believe a small amount of fluid may be tolerated in RVOs as in DME, while I aim for complete resolution in AMD.

Dr. Eichenbaum: Does Protocol T influence my primary agent selection in other disease processes? My short answer is: not so much. I prefer to evaluate individual patients and their unique situations and start them on the agent that best suits them, whether that has to do with the retinal pathology under treatment, costs, systemic risk factors, or personal preferences. I value the choices we have. For example, if a patient has significant sub-RPE fluid, and the treating physician has read some literature reporting that sub-RPE fluid responds to aflibercept (Eylea, Regeneron), he or she may wish to try that agent.[6] On the other hand, however, the HARBOR[7] study showed that ranibizumab effectively treats sub-RPE fluid as well, so agent preference for sub-RPE fluid is not clear.

When looking at agents, we must perform ongoing evaluations and consider the response instead of taking a strict on-label approach, as individual patients are not direct translations of registration study populations. Switching between agents should be an option under consideration after a reasonable trial of any given agent, because individual patients likely have biologic factors that we do not completely understand that may favor a response to one agent over another.

Dr. Pieramici: Dr. Singh, have the Protocol T results influenced how you decide on an AMD drug?

Dr. Singh: To some extent, yes. With aflibercept, we are delivering the highest molar dose possible in a drug right now. In studies of neovascular AMD and RVO that have p.r.n. phases, such as CATT and HARBOR, we see

Setting Patients' Expectations

Dr. Eichenbaum: Another takeaway message from Protocol T is to try to keep things simple when setting patients' expectations. I tell my patients, "You are going to get to know me really well, because in this first 6 to 12 months, you will see me a lot. The good news is, after the first year, you will probably start seeing me less often." Somewhere between 12 and 24 months, I can usually reduce the frequency of injections, based on findings from Protocol I and other studies, such as RISE and RIDE.

Dr. Pieramici: Do you find it is more difficult for patients with diabetes to maintain continued therapy for DME as opposed to patients with AMD?

Dr. Singh: Yes. I think the number of visits for diabetic patients at their stage of the disease and their stage of life is much higher than we ever anticipated. We only look at their eye problems, but these patients have multiple systemic comorbidities that require care from many other physicians. If we put ourselves in that position—most of us are in the age group of the average patient with diabetes—I think we would have difficulty adhering to that regimen. A differentiating point about diabetic patients is that they are much more difficult to treat. That is why we look for more sustained-release delivery options.

Dr. Blaha: Younger patients are often working, so that is another issue for them versus the older population of patients with AMD. In addition, we often tolerate some fluid in DME, so patients may not feel the pressure to see us quite as often.

Dr. Eichenbaum: I agree. It is important to note from Protocol T that there is no magic bullet that will give patients a meaningful reduction in dose requirement for the first year. If they want to optimize their vision, we have to encourage them to keep their appointments. Great data were presented at ARVO last year that talked about the overall visit burden of patients with diabetes with and without DME, considering the different medical disciplines they must see regularly for optimum health.[1] A patient with DME may be seeing a doctor as often as every 2 weeks. Advanced diabetes is a remarkably high-burden disease for patients' healthcare.

Dr. Pieramici: With respect to that, patients who have complications from diabetes are more likely to be those who did not take care of their disease, as opposed to patients with AMD. Therefore, in diabetes, we have a self-selecting group of people who do not follow instructions and do not like to visit doctors. Again, this is where studies differ from what we see in our clinics. Study participants are the most motivated of patients, whereas, I think we all have had nonstudy patients who disappear for 6 months and then return with neovascular glaucoma or some other serious complication. We have to accept that it will be difficult to maintain a high number of injections in some patients, particularly those with bilateral disease who are difficult to begin with.

Dr. Blaha: On the other hand, I have found a subset of patients take their DME diagnosis as a call to action. Once they need injections in their eyes, they realize they have to take care of their diabetes better than they have in the past.

1. Wallick CJ, Hansen RN, Campbell J, et al. Increased Health Care Utilization Among Patients With Diabetic Macular Edema Compared With Diabetic Patients Without Edema. Presented at: Annual Meeting of the Association for Research in Vision and Ophthalmology; May 2014; Orlando, FL.

a wide array of treatment, ranging from one to six injections, and as many as 21 injections in the first or second year. So, the treatments we are providing for those conditions are highly variable. To what is that related? Perhaps we are not saturating or hitting enough of the VEGF, and a higher molar dose in those circumstances might be beneficial, particularly in patients for whom a high frequency of treatment is beneficial. That is where I think it has influenced me. If patients need multiple treatments, it may not necessarily be because they are nonresponders but because they need a higher molar dose of drug to inhibit VEGF, and that may prompt me to switch to aflibercept.

Dr. Pieramici: Do you think the advantages seen for aflibercept in Protocol T are applicable to pigment epithelial detachments (PEDs) and polypoidal choroidal vasculopathy?

Dr. Singh: We saw some potential benefits of treating PEDs with intravitreal aflibercept.[8] However, I question the rigor of those analyses. PEDs are notoriously difficult to measure in general. Therefore, I think we need more data to verify its efficacy.

Dr. Blaha: I agree. It is difficult to compare the drug's effect on other diseases. There is a trend regarding its drying ability, but what that means in different diseases is difficult to say.

Dr. Eichenbaum: AMD may be categorized as intraretinal, subretinal, and sub-RPE disease. If a particular molecule confers an advantage in the space anterior to the RPE, it may follow that it performs better in certain subtypes of AMD. If a molecule could be placed into the sub-RPE space, would that confer some advantages in other types of wet AMD? That question is fun to think about, but we have little evidence to support the superiority of one drug over another in the different subtypes of AMD. As we develop better databases of SD-OCT images of wet AMD lesions in ongoing Phase 2 and Phase 3 studies, we may have a better idea.

Dr. Blaha: All of these studies report averages for all patients, and patients are different. Some patients may have high VEGF levels, while some may have low levels. Patients with AMD may have different types of lesions and PEDs. The devil is in the details.

SWITCHING AGENTS IN DME

Dr. Pieramici: In Protocol T, investigators did not switch from one drug to another, but I believe the Protocol T results influence how we think about initiating treatment and how we switch agents.

Dr. Blaha: When patients are not responding as well as I or they may like—either functionally or anatomically—I sometimes consider switching to aflibercept. Investigators in Protocol T did not switch agents, so we do not know how patients who are started with one agent and switched to another agent will respond. We do know that patients who are not treated for 6 months or a year and then are started on therapy do not do as well.

Switching between agents must be done on a personalized basis per patient. We must individualize treatment, looking at vision and fluid. I often switch to aflibercept to try to dry fluid better if a patient is not doing as well as I think he or she could be. Each patient is different, and we have to personalize therapies. We need to have the choices available to us.

Dr. Singh: Protocol T also shows us that a loading dose is probably unnecessary. I think that is a key takeaway. For the most part, the reality in clinical practice is that we do not use loading doses. What we are seeing, at least in Protocol T, is more of a real-life scenario of how we deliver anti-VEGF therapy. We treat patients based on their responses as shown by OCT, and we continue to treat based on that. I believe we may be switching therapies too frequently. To me, switching after two or three doses of an anti-VEGF agent seems like undertreatment or a low threshold for moving to a new drug. I think we need to establish better guidelines for frequency of treatment and when to switch agents.

Dr. Eichenbaum: I agree with Dr. Singh. There is very little prospective data in the literature on switching. Thorell and colleagues looked at switching in AMD after 6 months of treatment with no less than injections every 6 weeks of bevacizumab or ranibizumab, which is similar to the time frame in AMD when I think about switching.[9] In my opinion, 6 months of consistent therapy in AMD is a reasonable test of an agent.

Protocol T did change my thinking about switching agents when I have a phakic patient with DME. In these cases, I switch to aflibercept prior to using a steroid. I think phakic patients deserve the chance to fail aflibercept before switching classes of agents, based on the Protocol T results thus far. That does not mean I necessarily start treating patients with aflibercept, and I do not switch patients wholesale if they are doing well on another agent, particularly if I am treating them less than monthly. However, it is another option if treatment response with bevacizumab or ranibizumab is unsatisfactory.

Dr. Pieramici: I believe Protocol T provides us with a hierarchy of how we will switch agents. For example, if a patient is not responding 100% to aflibercept, I do not switch to bevacizumab. For that type of patient, I consider a steroid. I may switch from bevacizumab to ranibizumab to aflibercept, but I probably will not go the other way, unless there is a potential safety concern.

INJECTION FREQUENCY

Dr. Pieramici: In Protocol T, patients received a median of about nine injections during the first year, regardless of the agent used. What does this tell us about how we are treating our patients in the "real world?"

Dr. Singh: This is the second study that provides good data showing that an as-needed treatment regimen results in fewer injections per year. Protocol I also validated the same number of treatments.[10] The reality, according to some claims studies, is that we are administering fewer injections than in the studies. One study looked at EMR data, which is a good way of collating injections and visual acuity, and found patients were receiving a mean of 2.7 injections per year.[11] Based on these data, we are probably undertreating across the board.

Dr. Blaha: I agree. The Protocol T retreatment criteria are fairly complicated, and I think no one is following those criteria in clinic. In general, patients probably need more injections, on average, than they are receiving.

Dr. Pieramici: Strictly speaking, Protocol T did not include a loading dose, but it set a fairly high bar for retreatment during the first 6 months. Basically, visual acuity had to be 20/20 and the macula had to be dry or patients would receive an injection.

Dr. Eichenbaum: Although I agree, I also think assessing codes and databases may be problematic, because physicians may code for DME when the edema is in the peripheral macula and has been there for years, or even if the edema is resolved. Removing that confounder, however, I still think physicians in the retina community generally undertreat. For this reason, when I speak to community physicians, I recommend a loading phase, because I am concerned that if we move away from loading, there will be even more problems with undertreatment. I do not think physicians do foveal assessments often enough to say we can treat less often than the literature's general guidelines.

Dr. Pieramici: I recently saw data from the 2015 Preferences and Trends Survey by the American Society of Retina Specialists in which members were asked how many anti-VEGF injections they administer before switching therapy. The average was approximately three injections, and more than 80% of the respondents switch after five injections. This also underscores the importance of discussing with patients up front the number of injections they may require at the start of their therapy, although we hope that number will decrease over time.

AFLIBERCEPT'S EFFICACY IN PROTOCOL T

Dr. Pieramici: Let us switch gears and discuss the advantages shown by aflibercept in Protocol T. Why do you think this drug was more efficacious?

Dr. Eichenbaum: I believe there are various possible reasons why aflibercept's top-line results in the first year were better in worst-seeing eyes. One factor could be variability in the poor-vision group that drove the result. If the 1-year data are substantiated in year 2, however, we will know the drug is likely responsible for these results, because Protocol T is a well-controlled, well-designed study.

Dr. Blaha: I think we can assume part of the reason is aflibercept's higher binding affinity and higher molar equivalent.

Dr. Singh: In addition, we are learning more about placental growth factor and that levels are higher in the aqueous of patients who have neovascular glaucoma and proliferative diabetic retinopathy. This is another factor we did not realize plays a role, and in the diabetic eye, it may be a bigger player than we first thought. That might be another benefit of aflibercept over the other two drugs.

Dr. Pieramici: If molar equivalence is an issue, what do you think about the 0.3-mg dose of ranibizumab, which we use in the United States, versus the 0.5-mg dose, which is available in Europe?

Dr. Blaha: One advantage to the 0.3-mg dose of ranibizumab is that costs less than aflibercept. If you are treating in a stepwise fashion, ranibizumab 0.3 mg may make sense as a middle step, because it is less expensive than aflibercept and it dries better than bevacizumab. However, I think there is a concern that we may be underdosing with 0.3 mg.

Dr. Singh: Prior to approval of the 0.3-mg dose of ranibizumab for DME, some of my patients were receiving the 0.5-mg dose as part of a compassionate care program. Those patients did really well. When the 0.3-mg dose was approved, I switched many patients to that dose, but I was underwhelmed by their response. I saw a decline in some patients, and I ended up switching to a different drug. I believe there is a slight difference between the 0.3-mg and 0.5-mg doses of ranibizumab. The question remains: Is it a tangible difference in clinical practice?

Dr. Eichenbaum: That is a good point. We have some information on how ranibizumab 0.5 mg performs in the longer term in the extension of RISE and RIDE.[12] I believe those patients remained on the 0.5-mg dose in the extension arm. Whether or not it is a tangible difference is a difficult question to answer. If we put stock in the increased molar activity of aflibercept, it would follow that ranibizumab 0.5 mg would be better, but I do not think we can assume the molar activity is a clear win at this point. There are other factors to consider, including the placental growth factor binding affinity that aflibercept exhibits. We need to watch and wait, but I agree with Dr. Singh that it would be difficult to compare outcomes from the 0.3-mg dose with outcomes from the 0.5-mg dose without a new trial.

Dr. Pieramici: In the RISE and RIDE trials, investigators did not find a difference in efficacy between the drugs, and the FDA actually approved either dose. It was Genentech that decided to market the 0.3-mg dose, but it certainly makes you wonder about using higher doses of ranibizumab.

LASER

Dr. Pieramici: Based on Protocol T results, how are you using focal laser in your practices? If a patient presents with central DME that is affecting his or her visual acuity, for example, how do you use anti-VEGF agents, and when do you introduce laser therapy?

Dr. Singh: All of the trials we have been discussing were not solely anti-VEGF studies. They were combination studies. Therefore, to achieve the benefits shown in the trials, we must treat in the same fashion. I often combine laser and anti-VEGF therapy. Some of my patients travel

SAFETY

Dr. Pieramici: Protocol T clearly was not a safety trial, however, there are no major safety signals to date, except for one small post-hoc analysis. In your DME patients, do you consider the molecules differently in a patient who is at a particularly high risk for a cardiovascular event, such as someone who had a recent stroke or heart attack? Does this influence your treatment choice?

Dr. Singh: Data from IVAN and other studies show systemic VEGF suppression was not seen to the same extent with ranibizumab versus bevacizumab.[13] Therefore, if I am concerned about an at-risk patient, I consider those results. If any possibility of an adverse event exists, eliminating anti-VEGF altogether may be the best course. Again, there are no data to support that. All I know is that systemic VEGF suppression is much more common with full-length antibody agents versus single-chain fragments that are degraded faster. So I might consider selecting a drug for that sort of indication because of a systemic-related issue.

Dr. Blaha: Theoretically, based on molecular structure, there are reasons why there may be safety differences, but no study has shown that, so it does not affect my decision-making.

Dr. Pieramici: Do you consider efficacy primarily when deciding on a drug, even for a high-risk patient?

Dr. Blaha: I think efficacy has been shown to potentially be different in different studies, whereas safety has not. So I go with the studies and let efficacy drive my medicine selection, even though there may be theoretical reasons why one agent might be safer than another.

Dr. Eichenbaum: Like many of the topics we are discussing today, this is a "connect the dots" kind of question. We know the fragment does not suppress systemic VEGF as much as long-chain antibodies. We know that in trials, patients requiring bilateral treatment, as well as patients who had arterial thrombotic events within 90 days of treatment were excluded from randomization. Clinical science gives us systemic safety data in the ideal scenario, but in practice, there is systemic suppression, we do bilateral treatments, and patients have strokes, heart attacks, and amputations, so I do think about these issue. How I proceed depends on numerous factors: whether patients have monocular or binocular disease, for example, or if they have been prescribed a blood thinner or have undergone a surgical revascularization procedure. I definitely think about the systemic safety of the drugs in high-risk patients, particularly if they are receiving bilateral treatment, which is much more common in DME than in AMD.

Dr. Blaha: In some studies, patients in the p.r.n. arms had higher potential safety issues than those receiving monthly treatment. How do you factor that into your assessment of the risk of anti-VEGF exposure?

Dr. Eichenbaum: Again, the studies enrolled a relatively "safe" patient population who were undergoing monocular treatment, and the overall risk of adverse events is low across all treatment groups.

Dr. Pieramici: I agree. Patients who had recent heart attacks or strokes were excluded from the studies, as were patients undergoing dialysis and those with active proliferative disease, the sickest patients.

several hours to see me. To commit them to a monthly treatment regimen would not be possible, so sometimes I use focal laser to maintain visual stability, even though visual gain may be minimal.

Dr. Blaha: I use focal laser for focal areas of DME away from the fovea. As Dr. Singh noted, most of the studies have some sort of laser rescue, but it is difficult to determine if the laser is having a beneficial effect when it is being used to treat patients who have failed another therapy. I do not use laser therapy often, because I worry about its long-term effects, such as atrophy.

Dr. Eichenbaum: A preponderance of evidence informs us that to achieve the best vision with center-involving symptomatic or significant DME, antiangiogenic agents are superior to laser, and I think in 2015, they should be the standard of care as first-line treatment. I think we also have good evidence—the 5-year data from Protocol I, for example—of a widening delta between patients who have laser too soon and patients who have laser later, perhaps when the resistant focal lesions are more visible or easier to treat with less power. Therefore, guided by Protocol I as well as the evidence in RISE and RIDE, VIVID and VISTA, and all of the smaller DME studies, I tend to use anti-VEGF therapy for center-involving edema for at least 6 months before considering laser. I have a strong preference to defer macular laser based on the good early results with anti-VEGF therapy and the bigger difference in later results. I think it is important to give patients

CASE REPORT

Presented by: David Eichenbaum, MD

This 68-year-old man with diabetic macular edema (DME) was previously treated with focal laser and bevacizumab (Avastin, Genentech), with the last injection 2 to 3 months before I saw him (Figure 1). He recently had cataract surgery and is pseudophakic. Visual acuity in his left eye was 20/32 with symptomatic distortion. Early and late-phase fluorescein angiography (FA) showed mild epiretinal membrane (ERM) and center-involving DME (Figure 2) without focal treatable leaks. I began monthly treatment with ranibizumab (Lucentis, Genentech).

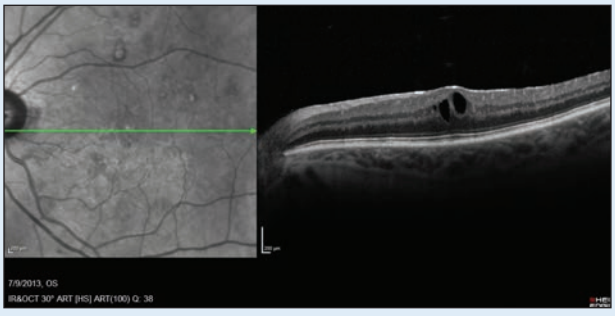


Figure 1. Patient was previously treated with laser and bevacizumab.

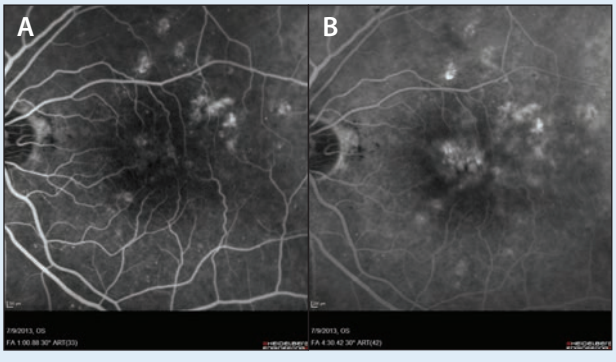


Figure 2. Early (A) and late-phase (B) FA showed mild epiretinal membrane and center-involving DME.

One year later, after 11 ranibizumab injections, the patient's visual acuity with posterior capsule opacification was 20/63. Optical coherence tomography (OCT) showed persistent DME (Figure 3). I administered a twelfth ranibizumab injection and referred the patient to his cataract surgeon for YAG laser capsulotomy.

Two months later, after a thirteenth ranibizumab injection, OCT showed persistent DME (Figure 4), and I administered the dexamethasone intravitreal implant (Ozurdex, Allergan).

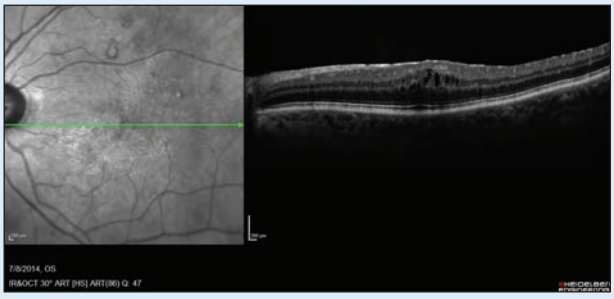


Figure 3. Despite 11 near-monthly ranibizumab treatments, the DME persisted.

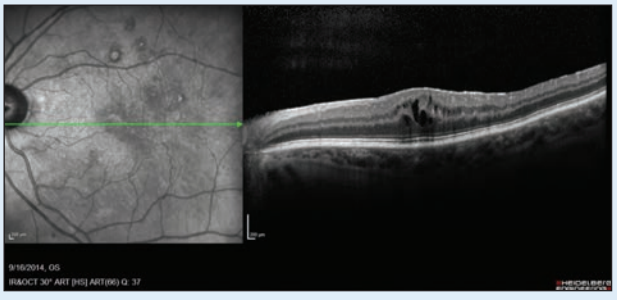


Figure 4. As the edema persisted, I administered the dexamethasone intravitreal implant at this visit.

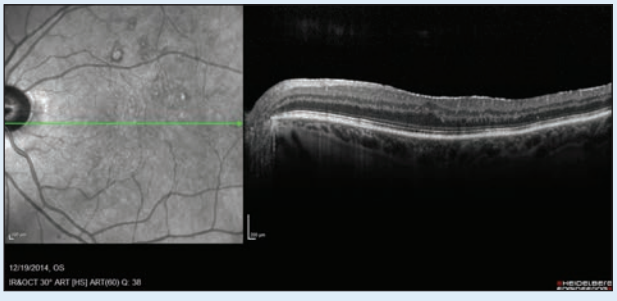


Figure 5. The patient was unhappy with his visual acuity of 20/40 after treatment with ranibizumab and the dexamethasone intravitreal implant, despite the improvement in DME.

Two months later, after treatment with the dexamethasone intravitreal implant and a fourteenth ranibizumab injection, the patient's visual acuity was 20/40, and OCT showed a persistent dry macula with ERM (Figure 5). I administered ranibizumab injection No. 15.

Approximately 18 months since I began treating this patient, and after 19 ranibizumab injections, his visual acuity was 20/40. OCT with early and late-phase FA showed reduced but persistent center-involving DME (Figure 6) and continued absence of focal treatable leaks. We discussed the option of vitrectomy and pucker peel, but the patient deferred vitrectomy, not wishing to risk decreased efficacy of potential future intravitreal treatment. I administered ranibizumab No. 20.

At the patient's next follow-up visit, and after 21 ranibizumab

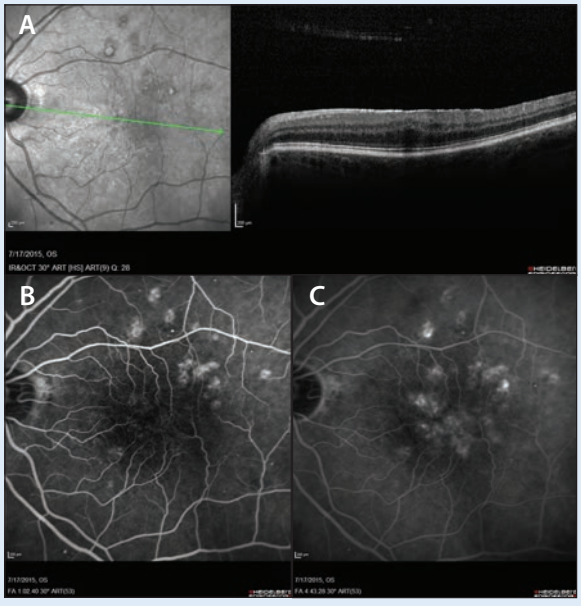


Figure 6. OCT with early and late-phase FA showed center-involving DME after more than 1 year of treatment with ranibizumab, as well as the dexamethasone intravitreal implant.

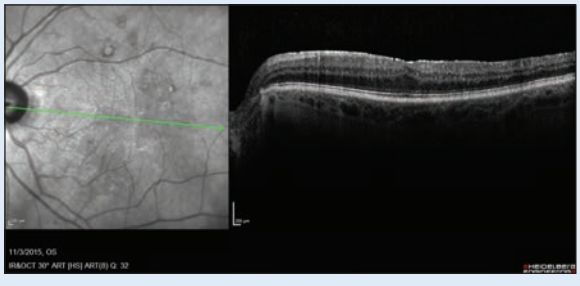


Figure 7. After switching from ranibizumab to aflibercept, the patient visual acuity improved to 20/20 and the macula was dry with mild ERM persisting.

injections, OCT showed persistent DME, and I decided to switch to aflibercept (Eylea, Regeneron). Two months later, OCT showed a dry macula (Figure 7), and the patient's visual acuity had improved to 20/20.

The patient was subjectively improved at his last follow-up visit, and reports that his central distortion is decreased. The patient elected to continue with aflibercept treatment, and extension will be considered if the macula remains dry.

that long-term shot at better vision, particularly because patients with diabetes usually have a longer life expectancy than patients with AMD, and we must think 10 to 20 years out.

STEROIDS

Dr. Pieramici: When do you consider introducing steroids into your treatment regimen? At what point do you believe anti-VEGF therapy is not producing the desired outcome? As a follow-up question: do you just stop anti-VEGF agents and switch or do you add a steroid?

Dr. Blaha: Sometimes, I bring a patient back a week or so after an anti-VEGF injection to determine if his or her edema is anti-VEGF responsive. If there is no response, I try a steroid, as there is some evidence that chronic DME may become driven more by inflammatory factors.[14] Whether I switch depends on a patient's lens status and history of glaucoma. Usually, I switch, as opposed to add, in order to decrease the number of injections, but I think either approach is acceptable.

Dr. Singh: In one study, researchers found the majority of patients who respond best to combination treatment are those who had the worst visual acuity and retinal thickness above a certain threshold.[15] That may be because VEGF is not the only mediator. Those patients may have chronic inflammation. I also consider duration of disease activity. If a patient has had a year of active treatment and is not achieving the visual gains or the OCT thickness I want, I may switch to combination treatment.

Dr. Eichenbaum: I believe there is a disease-modifying component to anti-VEGF agents as well as an inflammatory component to DME. In addition, I believe we have much better steroids today than in the past. I also may consider combination therapy when I cannot reduce the dosing interval to a level that a patient can live with, or if I cannot dry the macula effectively with intense anti-VEGF treatment. I often use an alternating strategy between steroids and antiangiogenic agents in an effort to reduce the burden and keep the retina from being "soggy," while hopefully still realizing some of the benefits of the disease modification achieved with anti-VEGF therapy.

Dr. Pieramici: In Protocol T, success did not mean a completely dry retina or visual acuity of 20/20. It meant a point of stability had been reached, which could have been a fair amount of edema remaining in the retina. That leaves me wondering if we could do better in these patients by adding something with a different mechanism of action.

DIABETIC RETINOPATHY

Dr. Pieramici: What is your opinion of the beneficial effect of anti-VEGF agents on diabetic retinopathy? Are you monitoring this effect in your patients? How does that influence your use of steroids?

Dr. Blaha: Reducing diabetic retinopathy may be one benefit of anti-VEGF agents over steroids, but I do not use that to guide my therapy. I think it is an important side benefit, and I do inform patients of that benefit.

Dr. Eichenbaum: I think the published evidence of a disease-modifying characteristic to the anti-VEGF class of drugs is a biomarker of a benefit that you don't necessarily get as profoundly with steroid monotherapy, and from which you get zero benefit with laser alone. An elegant paper published last year looked at the fluorescein angiograms in RISE and RIDE.[16] Researchers showed an essential cessation of the advancement of retinal nonperfusion when antiangiogenics were used monthly in RIDE and RISE. This speaks to an important biologic effect of relatively high doses of antiangiogenic therapy, particularly in the first year or two in diabetic patients.

Dr. Pieramici: Some evidence suggests steroids may also have an effect on diabetic retinopathy. We saw that in Protocol I, although to a lesser extent than with the anti-VEGF agents. When treating DME, knowing anti-VEGF agents have some effect on diabetic retinopathy may influence me to consider combination therapy instead of switching from one agent to another.

Dr. Blaha: Initially, there was some concern that anti-VEGF agents might worsen nonperfusion, which is why I am happy to know the overall level of diabetic retinopathy may improve with anti-VEGF treatment.

Dr. Pieramici: I tell my patients, "It is as if we can turn back the clock on your retinopathy." It is rare in life, at least with diabetes, that we can do this.

CONCLUSION

Dr. Pieramici: Today, we have a variety of agents with which to treat a patient with center-involving diabetic macular edema. For the most part, anti-VEGF agents have become the first line of therapy and can be effective in many patients. Protocol T gives us some insight into the relative effectiveness of the various agents after a year of therapy. It will be interesting to see if these relative differences hold up or increase during the second year of this study. In addition, the second year of therapy should give us more insight into the relative durability of these agents.

Dr. Blaha: I think the 1-year results of Protocol T are very interesting and suggest that there are differences between the current anti-VEGF agents in DME. I look forward to the 2-year results. Having options for treatment is most important, as each patient is unique. They do not always match those in a study.

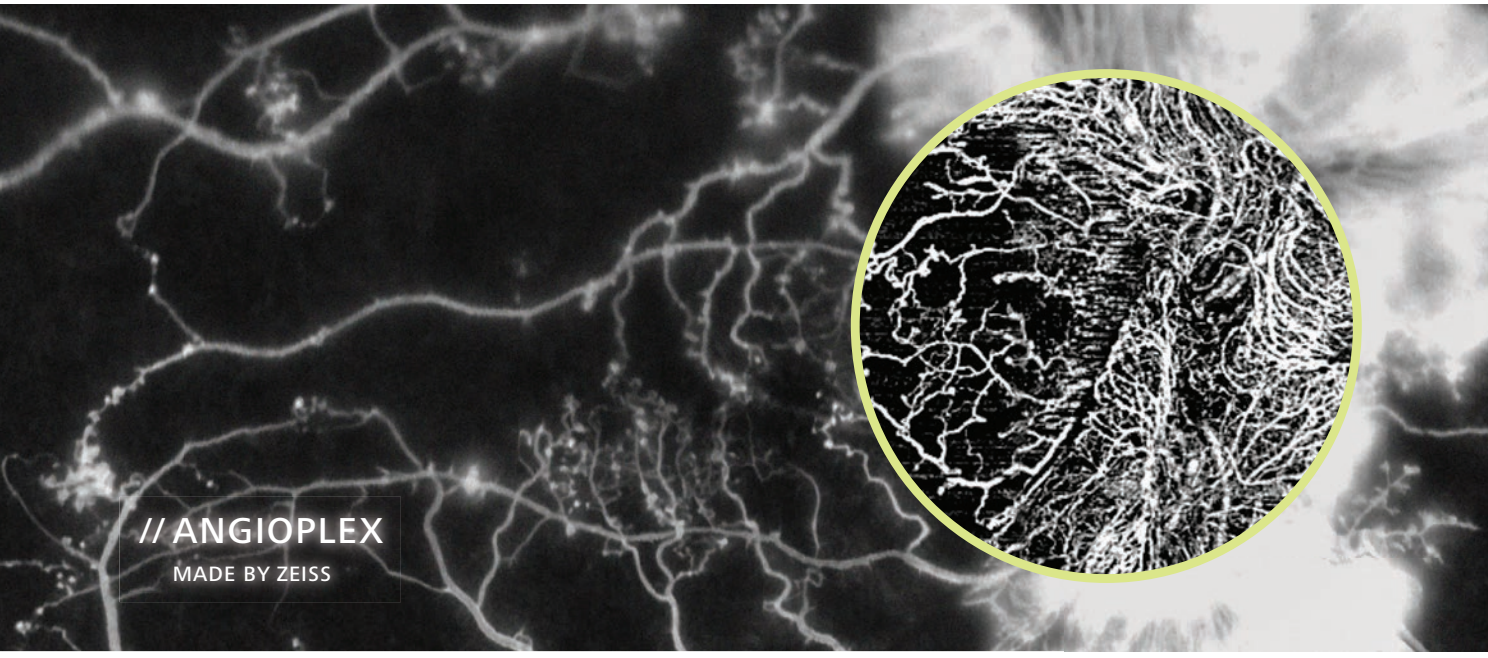
Dr. Singh: Our newest tools for taking care of diabetic patients are impressive. Both patients and physicians should be reassured by the impressive studies that have been released recently. The average patient will now be able to experience visual stability late into life, provided they have close and constant follow-up.

Dr. Eichenbaum: We are fortunate in many ways to practice in a revolutionary era, as we have a growing armamentarium of commercially available medications for our subspecialty. Comparative studies like Protocol T will help guide us regarding agent selection and the relative strengths and weaknesses of our weapons against disease. We must always remember that trials serve as a guidebook more than a roadmap, and thoughtful interpretation with the help of our colleagues can help us make the most of the recommendations. ■

1. Wells JA, Glassman AR, Jampol LM, et al; Diabetic Retinopathy Clinical Research Network. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema. *N Engl J Med*. 2015;372:1193-1203.
2. Browning DJ, Glassman AR, Aiello LP, et al; Diabetic Retinopathy Clinical Research Network. Relationship between optical coherence tomography-measured central retinal thickness and visual acuity in diabetic macular edema. *Ophthalmology*. 2007;114:525-536.
3. Argon laser photocoagulation for macular edema in branch vein occlusion. The Branch Vein Occlusion Study Group. *Am J Ophthalmol*. 1984;98:271-282.
4. Brown DM, Schmidt-Erfurth U, Do DV, et al. Intravitreal aflibercept for diabetic macular edema: 100-week results from the VISTA and VIVID studies. *Ophthalmology*. 2015;122:2044-2052.
5. Martin DF, Maguire MG, Ying GS, et al; CATT Research Group. Ranibizumab and bevacizumab for neovascular age-related macular degeneration. *N Engl J Med*. 2011;364:1897-1908.
6. Gambon R, Barthelmes D, Amstutz C, et al. Preliminary results of aflibercept in treatment-naive choroidal neovascularization of wet age-related macular degeneration. *Klin Monbl Augenheilkd*. 2014;231:423-426.
7. Ho AC, Busbee BG, Regillo CD, et al. HARBOR Study Group. Twenty-four-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. *Ophthalmology*. 2014;121:2181-2192.
8. Patel KH, Chow CC, Rathod R, et al. Rapid response of retinal pigment epithelial detachments to intravitreal aflibercept in neovascular age-related macular degeneration refractory to bevacizumab and ranibizumab. *Eye* (Lond). 2013;27:663-667.
9. Thorell MR, Nunes RP, Chen GW, et al. Response to aflibercept after frequent re-treatment with bevacizumab or ranibizumab in eyes with neovascular AMD. *Ophthalmic Surg Lasers Imaging Retina*. 2014. 45:526-533.
10. Elman MJ, Ayala A, Bressler NM, et al; Diabetic Retinopathy Clinical Research Network. Intravitreal ranibizumab for diabetic macular edema with prompt versus deferred laser treatment: 5-year randomized trial results. *Ophthalmology*. 2015;122:375-381.
11. Kiss S, Liu Y, Brow J, et al. Clinical utilization of anti-vascular endothelial growth-factor agents and patient monitoring in retinal vein occlusion and diabetic macular edema. *Clin Ophthalmol*. 2014;8:1611-1621.
12. Brown DM, Nguyen QD, Marcus DM, et al; RIDE and RISE Research Group. Long-term outcomes of ranibizumab therapy for diabetic macular edema: the 36-month results from two phase III trials: RISE and RIDE. *Ophthalmology*. 2013;120:2013-2022.
13. Chakravarthy U, Harding SP, Rogers CA, et al; IVAN study investigators. Alternative treatments to inhibit VEGF in age-related choroidal neovascularisation: 2-year findings of the IVAN randomised controlled trial. *Lancet*. 2013;382:1258-1267.
14. Funatsu H, Noma H, Mimura T, et al. Association of vitreous inflammatory factors with diabetic macular edema. *Ophthalmology*. 2009;116:73-79.
15. Maturi RK, Bleau L, Saunders J, et al. A 12-month, single-masked, randomized, controlled study of eyes with persistent diabetic macular edema after multiple anti-VEGF injections to assess the efficacy of the dexamethasone-delayed delivery system as an adjunct to bevacizumab compared with continued bevacizumab monotherapy. *Retina*. 2015;35:1604-1614.
16. Campochiaro PA, Wykoff CC, Shapiro H, et al. Neutralization of vascular endothelial growth factor slows progression of retinal nonperfusion in patients with diabetic macular edema. *Ophthalmology*. 2014;121:1783-1789.

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!

ZEISS

We make it visible.

Carl Zeiss Meditec, Inc. 800 342 9821 www.zeiss.com/cirrus

Avanti Widefield OCT

- **Visualize** more pathology with 12mm x 9mm widefield scan
- **Analyze** individual layers of the retina with en face view
- **Personalize** patient care with retinal trend analysis that may aid in treatment decisions and improve disease management

Avanti is the platform for future technology innovation that also meets the challenges of today's comprehensive practice.

Optovue.com/products/Avanti

optovue®
Your OCT specialist

300-50885 Rev. A