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PART V

AMD DISEASE EDUCATION RESOURCE CENTER

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

Age-related macular degeneration (AMD) is a leading cause of irreversible vision loss in the developed world. It has been estimated that 3 million people in the United States may be affected by AMD in at least one eye by 2020.[1] Until slightly more than a decade ago, there was little that could be done to restore vision in people affected by neovascular AMD. Laser photocoagulation was used for decades to slow the advance of the damage, but it was not until the introduction of VEGF inhibitors that physicians could reverse the loss of vision in patients with AMD.[2] Pegaptanib sodium (Macugen; Bausch + Lomb) was approved by the US Food and Drug Administration (FDA) in 2004, followed by ranibizumab (Lucentis, Genentech) in 2005 and most recently by aflibercept (Eylea, Regeneron) in 2011. The anticancer drug bevacizumab (Avastin, Genentech) is also frequently used off-label as a treatment for neovascular AMD. These anti-VEGF agents have become the standard of care for patients with neovascular AMD.[3]

The FDA approval of aflibercept was supported by data from two parallel phase 3 clinical trials, VIEW 1 and VIEW 2.[4] Investigators continued to follow some patients from the VIEW trials in the open-label VIEW extension trial.[5] Further, some of the VIEW investigators have followed selected patients in yet another extension trial, dubbed RANGE, using a treat-and-extend dosing strategy. In this installment of the AMD Resource Center, W. Lloyd Clark, MD, shares results from the VIEW extension trial and the RANGE trial.

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2. Vedula SS, Krzystolik MG. Antiangiogenic therapy with anti-vascular endothelial growth factor modalities for neovascular age-related macular degeneration. *Cochrane Database Syst Rev*. 2008;(2):CD005139.
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4. Heier JS, Brown DM, Chong V, et al; VIEW 1 and VIEW 2 Study Groups. Intravitreal aflibercept (VEGF Trap-Eye) in wet age-related macular degeneration. *Ophthalmology*. 2012;119(12):2537-2548.
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Taking the Long VIEW in AMD

Two extension studies from the phase 3 clinical trial show long-term stability with aflibercept.

BY W. LLOYD CLARK, MD

Aflibercept (Eylea, Regeneron) is a recombinant fusion protein that consists of portions of human VEGF receptors 1 and 2 fused to the Fc portion of human immunoglobulin G1, formulated for intravitreal injection. It was approved by the US Food and Drug Administration (FDA) in 2011 for the treatment of neovascular, or wet, age-related macular degeneration (AMD), and it is also indicated for treatment of macular edema due to retinal vein occlusion, diabetic macular edema, and diabetic retinopathy in patients with diabetic macular edema.[1]

Aflibercept was approved by the FDA based on the results of two parallel phase 3 randomized, double-masked, multicenter clinical trials, VIEW 1 and VIEW 2.[2,3] Since the completion of these trials, long-term outcomes of aflibercept treatment have been assessed in further clinical trials. In this installment of the AMD Resource Center, I summarize some of the results of an extension study that included patients from the VIEW 1 trial,[4] which accumulated data out to 4 years of follow-up, and the 1-year interim results of a further 2-year treat-and-extend follow-up study called RANGE. When RANGE is complete, we will have detailed results of a total of 6 years of clinical experience with aflibercept for treatment of patients with neovascular AMD.

BACKGROUND: VIEW 1 STUDY

The VIEW 1 study was one of two parallel phase 3 clinical trials, the data from which were submitted to the FDA in support of approval of aflibercept for treatment of neovascular AMD. A total of 2,457 patients were randomized into VIEW 1 and VIEW 2, but this article concentrates on the 1,217 patients randomized into VIEW 1. These patients were randomly assigned in a 1:1:1:1 fashion to four treatment groups: 2.0 mg aflibercept every 4 weeks, 0.5 mg aflibercept every 4 weeks, 2.0 mg aflibercept every 8 weeks (now the labeled dose) after three monthly loading doses, or ranibizumab (Lucentis, Genentech) 0.5 mg every 4 weeks after three initial monthly doses. These patients were followed to week 52 with these treatment regimens, and then all were eligible for modified quarterly dosing out to week 96.[3] The primary endpoint was the maintenance of vision at week 52, and there were a number of other secondary anatomic and functional endpoints, including mean change in best corrected visual acuity (BCVA).

In the pooled data on BCVA from VIEW 1 and VIEW 2, all patients did well at both week 52 and week 96, regardless of their treatment regimen. Patients, on average, gained between 8 and 10 letters of BCVA regardless of assignment of aflibercept group or ranibizumab, and that treatment effect was maintained out to week 56. Of note, patients treated with aflibercept every 8 weeks showed clinical equivalence to patients treated monthly with ranibizumab over the first 52 weeks.

VIEW 1 EXTENSION

At the conclusion of VIEW 1, patients were offered enrollment into the open-label VIEW 1 extension study to allow investigators to obtain further safety and efficacy data in patients treated long-term with this anti-VEGF therapy.[4] Out of 1,215 patients completing VIEW 1, 323 patients were enrolled in the VIEW 1 extension. These patients were followed for a total of 212 weeks: the combination of 96 weeks in VIEW 1 and 116 weeks in the extension study.

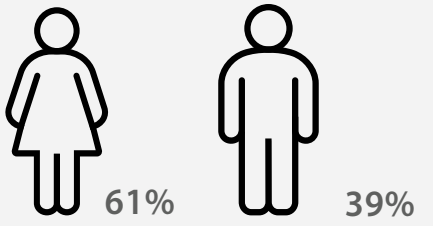
The VIEW 1 extension was an open-label rollover study for patients enrolled in VIEW 1. All patients could receive 2.0 mg intravitreal aflibercept. There were mandatory quarterly visits with modified quarterly dosing; that is, all patients had to receive an injection every 12 weeks, but they could receive more frequent injections if disease activity warranted that treatment. The protocol was modified after the drug was approved by the FDA, requiring treatment every 8 weeks in accordance with the labeling.

Regarding demographics, approximately 61% of patients in the extension study were women, and 97.5% were white. Mean age was 79 years. Baseline characteristics in all groups were fairly well balanced.

For all 323 patients in the extension study, mean BCVA at entry to VIEW 1 was 55.6 ETDRS, and at entry to the extension study it was 65.3 letters. Also for the whole study population, central retinal thickness (CRT) on optical coherence tomography (OCT) was 314.3 µm at VIEW 1 enrollment, and by the time they were enrolled into the extension this had significantly improved to 202.8 µm.

The number of injections during the extension was widely

VIEW 1 EXTENSION DEMOGRAPHICS



white: 97.5% nonwhite: 2.5%

mean age: 79 years

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

REGENERON

01/2016
US-LEA-1648

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

No. of Injections Given During the Extension Study

Minimum	Maximum	Mean
1	41	12.9

distributed, with a minimum of one injection and a maximum of 41. The mean number of injections during the extension was 12.9.

One of the measures of interest in the extension study was the ability to maintain the gains in BCVA that were achieved in VIEW 1. With fixed dosing during VIEW 1, at week 52 patients had had a mean improvement of 10.4 ETDRS letters, and at week 96 that improvement was maintained at 10.2 letters. After patients were enrolled in the extension with its less stringent dosing regimen, some of that improvement was maintained, with a final mean improvement of visual acuity from baseline of 7.1 letters at week 212. That is, only about 3 letters of BCVA gain were lost between week 96 and week 212, with modified dosing as infrequent as quarterly.

Mean BCVA was 66.0 letters at week 52 and 65.8 at week 96 of VIEW 1, and that level was well maintained during the extension, with mean BCVA of 62.7 letters at week 212.

Regarding change in visual acuity outcomes from VIEW 1 baseline to week 212, patients did quite well. At week 212, 73% of eyes had gained some BCVA (≥ 0 letters) compared with baseline. Further, 61% of eyes gained 5 or more letters, and 30% gained 15 or more letters. By contrast, relatively few patients experienced significant vision loss: 20% of eyes lost 5 or more letters of BCVA, 13% lost 10 or more letters, and 8% of eyes lost 15 or more letters.

Looking at changes in visual acuity outcomes during the extension only (ie, from extension study baseline to week 212), again the results are quite good, although one must keep in mind that these patients had already previously received 2 years of primary therapy for active disease. Despite that caveat, 42% of eyes gained at least some BCVA during the extension, 17% of eyes gained 5 or more letters, and 3% gained 15 or more letters. And again, there were relatively favorable results regarding vision loss, with 35% percent of eyes losing 5 or more letters, 17% of eyes losing 10 or more letters, and only 8% of eyes losing 15 or more letters.

No great safety concerns were encountered in the VIEW 1 extension. There was a total of 12 ocular serious adverse events during the extension with an array of different causes, none of which was clinically significant. Intraocular inflammation occurred in 16 out of 4,128 injections, a rate of 0.39%. There were 105 systemic serious adverse events during the extension study, again involving a wide variety of causes. The most common were cardiac disorders, infections, injuries to the patient, and nervous system disorders, but there were no significant safety signals thought to be due to the drug under study.

There were a total of 20 arterial thromboembolic events, as defined by the Antiplatelet Trialists' Collaboration, during the almost 2 years of the extension, affecting 6.2% of trial participants. There were eight nonfatal myocardial infarctions, five nonfatal strokes, and nine vascular deaths. Total deaths during the protocol were 17, or 5.3% of trial participants.

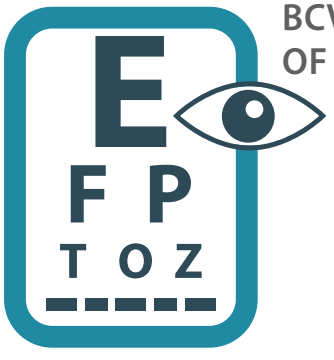
RANGE, YEAR 1

The RANGE study was designed to evaluate long-term treatment with intravitreal aflibercept injection in patients who had completed the VIEW 1 and VIEW 1 extension studies. As noted above, the mean change in visual acuity from VIEW 1 baseline to the end of the VIEW 1 extension study was +7.1 letters. Good maintenance of visual acuity was achieved in the extension study, even though treatment intervals were extended to between 8 and 12 weeks in most patients.

Based on the excellent visual acuity data from the VIEW 1 extension, with nearly 4 years of maintenance of visual acuity gains, the RANGE study was designed to evaluate the long-term safety and efficacy of intravitreal aflibercept out to 6 years. Below I discuss the 1-year results of this 2-year study. RANGE investigators used a treat-and-extend treatment protocol, and the study included patients previously treated in the VIEW 1 extension study.

RANGE was a multicenter study conducted at six clinical sites that had participated in both VIEW 1 and the VIEW 1 extension study. The primary outcome measure was the proportion of patients who maintained visual acuity, defined as a loss of 5 or fewer ETDRS letters, from baseline to the end of year 1. Secondary outcome measures included mean change in BCVA from baseline, proportions of patients with visual gain or visual loss, proportions of patients with BCVA better than 20/70 or less than 20/200, mean change in CRT from baseline on OCT, and mean number of injections.

Entry criteria included previous enrollment in the VIEW 1 extension study, and enrollment in the RANGE study within 90 days of the site's activation. Patients could have received no previous therapy for wet AMD other than anti-VEGF therapy. They could have no history of vitrectomy, no concurrent ocular condition that would limit their ability to participate in the trial, and no history of intraocular inflammation.



BCVA DURING YEAR 1 OF THE RANGE STUDY

- **Mean entry BCVA:** 61.5 ETDRS letters
- **BCVA at week 24:** 61.2 ETDRS letters
- **BCVA at week 52:** 61.4 ETDRS letters

Visual acuity remained stable throughout the first year of the study.

Watch the Video

To view Dr. Clark presenting the information from these studies, visit the AMD Resource Center.

Patients received open-label treatment with 2.0 mg intravitreal aflibercept. They got a mandated injection at day 0 and at week 8, plus an injection at week 4 at the investigator's discretion. The idea behind this was to ensure disease stability at the beginning of this long-term observation trial.

Beginning at week 8, after a maximum of three injections, a treat-and-extend regimen was begun using prespecified criteria:

- absence of macular fluid, defined as intraretinal, subretinal or sub–retinal pigment epithelium (RPE) fluid;
- absence of new macular hemorrhage; and
- absence of vision loss of 5 letters or more from previous visit due to disease activity.

If these criteria were met, then the patient's treatment interval was extended by 2 weeks. If the criteria were not met, the treatment interval was reduced by 1 week.

From the 323 patients who participated in the VIEW 1 extension, the six RANGE clinical sites enrolled 37 patients for this long-term follow-up study. Of those 37, 35 were retained to the week 52 visit. Mean patient age was 68.2 years, and 61% were women. Mean entry BCVA was 61.5 ETDRS letters, and mean CRT on OCT was 216 µm, demonstrating minimal disease activity at baseline.

The mean number of injections in year 1 was 7.2 (range, 4-14) in this cohort utilizing the treat-and-extend strategy. The mean treatment interval was 59 days. Although there was a wide distribution of number of injections, approximately 43% of the eyes received seven injections during this, the fifth year of their aflibercept therapy. This was a fairly heavy treatment burden, as determined by the study's treat-and-extend criteria.

Of the 35 patients who completed week 52 of RANGE, 30 (85.7%) maintained vision, the primary outcome measure of less than 5 letters lost. Mean BCVA at baseline was 61.5 letters, at week 24 it was 61.2 letters, and at week 52 it was 61.4. That is, visual acuity remained stable throughout the first year of RANGE.

Regarding BCVA change from baseline, 60.0% of patients gained some BCVA (≥ 0 letters) during year 1 of RANGE; 14.3% gained 5 letters or more, and 5.7% gained 15 letters or more. In contrast, relatively few patients lost BCVA, with 20% losing 5 or more letters and 5.7% losing 15 or more. Visual acuity gains in the earlier protocols were well maintained.

The study also looked at the percentages of patients who ended the study outside certain visual acuity limits. At baseline, 21 patients (60.0%) had BCVA of 20/70 or better; by week 52, the number had increased to 23 patients (65.7%). By contrast, at baseline, four patients (11%) and at week 52 seven patients (20%) had BCVA of 20/200 or worse.

Anatomic data showed that CRT was quite stable during year 1 of RANGE. Mean baseline CRT was 221 µm; at week 24, mean CRT was 205 µm; at week 52, it was 213 µm. This indicates good maintenance of disease control through week 52.

In terms of safety, there were no ocular serious adverse events through week 52. Two patients discontinued the study, one due to death from hypoxia, and one due to worsening dementia.

CONCLUSIONS

The VIEW 1 extension study demonstrated excellent maintenance of the visual acuity gains seen during the VIEW 1 trial in patients with wet AMD. It also demonstrated an excellent safety profile, giving retina specialists confidence that patients can be well managed on a long-term basis with intravitreal aflibercept.

In the RANGE study, after long-term anti-VEGF therapy of AMD, maintenance therapy utilizing a treat-and-extend approach with intravitreal aflibercept injection was safe and effective through week 52. In the first year of RANGE, 85.7% of patients lost less than 5 letters of visual acuity. Mean change in BCVA was -0.1 letters, and there was essentially no change in CRT. After nearly 5 years of anti-VEGF therapy, 65.7% of patients maintained 20/70 or better BCVA. The mean number of injections during year 1 of RANGE was 7.2, and mean interval of treatment was 57 days. Continued follow-up of these patients through year 2 will provide additional insights into the long-term treatment efficacy and safety of intravitreal aflibercept injection. ■

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