Published in final edited form as:

Am J Ophthalmol. 2013 July ; 156(1): 23–28.e2. doi:10.1016/j.ajo.2013.02.009.

Short-term Outcomes of Aflibercept for Neovascular Age-related Macular Degeneration in Eyes Previously Treated with Other Vascular Endothelial Growth Factor Inhibitors

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Abstract

Purpose—To report results of aflibercept therapy in eyes with neovascular age-related macular degeneration previously treated with bevacizumab and/or ranibizumab.

Design—Retrospective, interventional, non-comparative, consecutive case series

Methods—Ninety-six eyes, 85 patients, with neovascular AMD that had previously received bevacizumab and/or ranibizumab were treated with aflibercept monthly for 3 months followed by a fourth injection within 2 months. Outcomes were determined 4 ± 1 months after the first aflibercept dose and included: proportion of patients gaining or losing 2 lines of best corrected visual acuity (BCVA), proportion remaining within ±1 line, mean change in logMAR VA, mean change in central foveal thickness, mean change in macular cube volume, and qualitative anatomic response as assessed by spectral-domain OCT.

Results—At baseline, 82 (85%) eyes had signs of active exudation despite a mean 17 previous anti-VEGF injections. At final visit, 82 (85%) remained stable within ±1 line, 7 (7%) gained and 7 (7%) lost 2 lines of BCVA. Mean logMAR VA showed minimal change 0.02 (range –0.46 to 0.70, $P=0.14$). Mean central foveal thickness decreased –18 microns (range –242 to 198, $P=0.06$). Mean macular volume decreased –0.27 mm³ (95% CI, –0.4 to –0.1, $P=0.004$). On qualitative analysis, 4 (5%) eyes had complete resolution of exudative fluid, 40 (49%) partially resolved, 26 (32%) remained unchanged, and 12 (14%) worsened.

Conclusion—Aflibercept appears to be an effective alternative for neovascular AMD patients previously treated with bevacizumab and/or ranibizumab at 4 months follow-up. The majority of treated eyes demonstrated stable VA and anatomic improvements by SD-OCT.

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INTRODUCTION

Age-related macular degeneration (AMD) is a leading cause of blindness for people over the age of 65 in the United States^{1,2} In the neovascular (wet or exudative) form of AMD, choroidal neovascular membranes disrupt the normal architecture of the choriocapillaris, Bruch's membrane, and the retinal pigment epithelium (RPE) layer leading to retinal edema, submacular hemorrhage, as well as debilitating atrophy and scarring.

The use of intravitreal anti-vascular endothelial growth factor (VEGF) therapy is currently the standard of care for neovascular AMD. The two most commonly used agents, bevacizumab and ranibizumab, reduce exudative fluid and have been shown to improve best-corrected visual acuity (BCVA) in eyes with neovascular AMD compared to controls.^{3,4,5,6,7,8}

The VEGF Trap-Eye: Investigation of Efficacy and Safety in Wet AMD (VIEW 1, VIEW 2) studies led to the U.S. Food and Drug Administration approval of aflibercept (Eylea; VEGF Trap-Eye; Regeneron, Tarrytown, NY and Bayer HealthCare, Berlin, Germany) for the treatment of neovascular AMD in November 2011. These pivotal randomized, multi-center, double-masked, active-controlled studies showed that intravitreal injections of 2 mg every 4 weeks, or 2 mg every eight weeks following a loading dose of 3 monthly injections demonstrated BCVA and anatomic outcomes at years 1 and 2 that were comparable with monthly ranibizumab injections.⁹

Aflibercept is a recombinant soluble decoy receptor fusion protein, consisting of the binding domains of VEGF receptors 1 and 2 fused to the fragment crystallizable (Fc) portion of human immunoglobulin G-1 (IgG-1). This protein binds VEGF-A, VEGF-B, and placental growth factor (PLGF) which inhibits the binding and activation of VEGF receptors.^{9,10,11,12,13,14}

Although aflibercept has shown efficacy as primary therapy for treatment-naïve neovascular AMD, most patients in the clinical setting have previously been treated with other VEGF inhibitors including bevacizumab and/or ranibizumab. We report the short-term efficacy of aflibercept for neovascular AMD in the setting of chronic VEGF blockade in this manuscript.

METHODS

This was a retrospective, interventional, non-comparative, consecutive series of neovascular AMD patients who were previously treated with ranibizumab and/or bevacizumab and transitioned to aflibercept between February 1, 2012 and May 21, 2012. Indications for transition to aflibercept included persistent, recurrent, or worsening exudative fluid or hemorrhage on examination or spectral domain optical coherence tomography (SD-OCT). Patients were also transitioned if they had intolerance to previous bevacizumab or ranibizumab injections. As a general rule, before switching to aflibercept, eyes were treated aggressively with injections of bevacizumab or ranibizumab every 4 – 5 weeks as long as signs of exudation were present. Eyes that received at least 2 aflibercept injections and had follow-up at 4 months ($\pm$ 1 month) were included in the study. Patients with follow-up

intervals outside of this specified time frame, or those who reverted back to another anti-VEGF agent were excluded. Approval for this study of VEGF inhibitors for neovascular AMD was obtained from the Emory University Institutional Review Board before the research was conducted. Patient information was de-identified to remain compliant with the Health Insurance Portability and Accountability Act.

Each eye received intravitreal injections of aflibercept at the recommended dose of 2 mg (0.05mL) every 4 weeks for the first 3 months, followed by a 4th intravitreal injection 1 to 2 months later.⁹ Variations in this protocol occurred based on the discretion of the treating physician or if patient follow-up precluded monthly injections.

Office-based Snellen VA measurements using best spectacle-corrected or pinhole visual acuities were obtained on the day of aflibercept initiation, subsequent follow-up visits, and at the patient's final follow-up appointment. The study's primary outcomes were the mean change in logarithm of the minimum angle of resolution (logMAR) VA and the percentage of patients with improved, stable, or worsened Snellen VA at 4 ± 1 months after starting aflibercept injections.¹⁵ *Improvement* and *worsening* were defined as gaining or losing 2 lines of Snellen VA. *Stabilization* was defined as remaining within ± 1 line of baseline Snellen VA. The number of eyes with baseline and final VA $\geq 20/40$ as well as the number of aflibercept injections were also quantified.

Additional outcomes include the mean change in central foveal thickness, macular cube volume, as well as qualitative changes of intraretinal fluid (IRF), subretinal fluid (SRF), pigment epithelial detachments (PEDs), subretinal hemorrhage (SRH), and overall response to therapy on Cirrus SD-OCT (Carl Zeiss Meditec Inc., Dublin, CA). Changes in the degree of fluid by SD-OCT from respective baseline images were classified as *complete resolution*, *partial resolution*, *unchanged*, or *worse*. *Complete resolution* was defined as resolution of all intraretinal fluid, subretinal fluid, pigment epithelial detachments, and subretinal hemorrhage. Any adverse events such as endophthalmitis, retinal detachment, sustained increase in intraocular pressure requiring topical ocular hypertensive medications, uveitis, and thromboembolic events (nonfatal stroke, nonfatal myocardial infarction or vascular death including deaths of unknown cause) were also recorded. Statistical analyses were performed using Microsoft Excel (Microsoft Corporation, Redmond, WA) and a two-tailed, paired T-test was applied to compare means of continuous variables.

RESULTS

Demographics and Clinical Characteristics

One hundred twenty-three eyes of 107 patients were transitioned from bevacizumab and/or ranibizumab to aflibercept between February 1, 2012 and May 21, 2012. A total of 27 eyes were excluded from the study for the following reasons. Four eyes received only a single aflibercept injection. Fourteen eyes had follow-up outside the designated 4 ± 1 month window. Nine eyes reverted back to bevacizumab or ranibizumab. Of these, 6 were due to subjective declines in vision that were not supported by objective BCVA testing and 2 were related to expense. A final patient experienced a drop in Snellen acuity from 20/50 to 20/400 (remained 20/40 by potential acuity meter) 1 month after his second aflibercept injection so

the third injection was held. When he returned two weeks later with BCVA of 20/70, he was reverted back to ranibizumab injections. Ultimately, 96 eyes of 85 patients, 34 males and 51 females, were included in the study. Of these, 77 eyes had central foveal thickness and 67 eyes had macular cube volume values documented at both baseline and final exams.

The average patient age was 79 (range 62–91) years old. For the entire study population, the mean number of any previous anti-VEGF injections was 17 (range 1–60). Thirty eyes were previously treated exclusively with bevacizumab (mean 14 injections, range 1–53), 43 eyes exclusively with ranibizumab (mean 19 injections, range 1–49), and 23 eyes with both intravitreal agents (mean 13 injections of bevacizumab, range 1–32 and mean 8 injections of ranibizumab, range 1–36). At the time of transition to aflibercept, 82 (85%) eyes had evidence of active exudation in the form of SRF, IRF, PED, or subretinal hemorrhage. Mean follow-up for study eyes was 114 days (range 90–133). The mean number of aflibercept injections from initiation of therapy to last follow-up appointment, excluding the injection at the last visit, was 2.6 (range 1–4). No patients received less than 2 injections before the last follow-up appointment (Table 1).

Visual Outcomes with Aflibercept after Prior Therapies

The average VA at the time of first treatment with aflibercept ranged from 20/40 to 20/50 in the groups receiving prior bevacizumab or ranibizumab monotherapy and was 20/60 for the group who received both prior bevacizumab and ranibizumab. For the group as a whole, the mean baseline VA was 20/50 and of these 96 eyes, 7 (7%) gained ≥ 2 lines, 82 (85%) remained stable within ± 1 line, and 7 (7%) lost ≥ 2 lines of Snellen VA. The mean gain in logMAR VA was 0.02 (range -0.46 to 0.70 , $P=0.14$), (Figure 1). Thirty-eight (83%) out of 46 eyes with $\geq 20/40$ vision at baseline maintained this level of acuity and 8 eyes improved to this range by the end of the study.

Of the 30 eyes previously treated exclusively with bevacizumab, 1 (3%) gained ≥ 2 lines, 27 (90%) remained stable within ± 1 line, and 2 (7%) lost ≥ 2 lines of Snellen VA. The mean change in logMAR acuity for this group was -0.03 (range -0.38 to 0.12 , $P=0.26$). Fourteen (78%) out of 18 eyes with $\geq 20/40$ vision at baseline maintained this level of acuity by the end of the study.

Of the 43 eyes previously treated exclusively with ranibizumab, 3 (7%) gained ≥ 2 lines, 36 (84%) stabilized within ± 1 line, and 4 (9%) worsened by ≥ 2 lines of Snellen VA. The mean change in logMAR acuity for this group was -0.004 (range -0.46 to 0.47 , $P = 0.8$). Twenty-two (85%) out of 26 eyes with $\geq 20/40$ vision at baseline maintained this level of acuity and 3 eyes improved to this range by the end of the study.

In the 23 eyes whose prior treatment consisted of both bevacizumab and ranibizumab, 3 (13%) improved by ≥ 2 lines, 18 (78%) remained stable within ± 1 line, and 2 (9%) worsened by ≥ 2 lines of Snellen VA. There was a statistically significant improvement in mean logMAR VA of 0.13 (95% confidence interval [CI], 0.06 to 0.20 , $P = 0.003$). All 3 eyes with $\geq 20/40$ vision at baseline maintained this acuity and 3 eyes improved to this level at last follow-up.

Anatomic Outcomes with Aflibercept after Prior Therapies

Central Foveal Thickness (CFT)—The mean CFT of 77 eyes at the time of first treatment with aflibercept was 276 (range 130–559) microns for the entire study population, 278 (range 130–459) microns in the bevacizumab-only group, 258 (range 165–348) microns in the ranibizumab-only group, and 299 (range 181–559) microns for the group that previously received both agents. The mean change in central foveal thickness at the end of follow-up for the study population was –18 (range –242 to 198) microns ($P = 0.06$) (Figure 2), –20.4 (range –168 to 198) microns ($P = 0.26$) for the bevacizumab-only group, –11.2 (range –109 to 54) microns ($P = 0.07$) in the ranibizumab-only group, and –28.9 (range –242 to 123) microns ($P = 0.2$) for eyes that received both agents.

Macular Cube Volume—The mean standard macular cube volume of 67 eyes at the time of first treatment with aflibercept was 9.8 (range 7.7–13.80) mm³ for all patients, 9.8 (8.2–13.3) mm³ in the bevacizumab-only group, 9.7 (range 7.8–12.2) mm³ for the ranibizumab-only group, and 9.8 (7.7–13.8) mm³ for patients whom received bevacizumab and ranibizumab. The mean change in macular cube volume at the end of follow-up was –0.27 mm³ (95% CI, –0.4 to –0.1, $P = 0.004$) overall (Figure 3), –0.35 mm³ (95% CI, –0.53 to –0.11, $P = 0.007$) for bevacizumab-only eyes, –0.02 (range –1.5 to 0.7) mm³ ($P = 0.12$) for ranibizumab-only eyes, and –0.53 mm³ (95% CI, –1.02 to –0.04, $P = 0.02$) for eyes that previously received both bevacizumab and ranibizumab.

SD-OCT Segmentation Analysis after Treatment with Aflibercept—Eighty-two eyes showed evidence of exudative fluid and/or hemorrhage in one or more layers before switching to aflibercept (31 with intraretinal fluid, 49 with subretinal fluid, 73 with pigment epithelial detachment, and 18 with subretinal hemorrhage).

Among the 31 eyes with baseline intraretinal fluid, 13 (42%) had complete resolution, 6 (19%) had partial resolution, 10 (32%) remained unchanged, and 2 (6%) worsened. Of the 49 eyes with baseline SRF, 17 (35%) had complete resolution, 12 (25%) had partial resolution, 11 (22%) remained unchanged, and 9 (18%) worsened. Among the 73 eyes with PED, 2 (3%) had complete resolution, 17 (23%) had partial resolution, 50 (69%) remained unchanged, and 4 (5%) worsened. Of the 18 eyes with subretinal hemorrhage, 11 (61%) had complete resolution, 3 (17%) had partial resolution, and 4 (22%) remained unchanged.

Overall, among the 82 eyes with any baseline exudative fluid or hemorrhage, 4 (5%) had complete resolution, 40 (49%) had partial resolution, 26 (32%) remained unchanged, and 12 (14%) worsened (Table 2). This trend was consistent among all 3 subgroups treated with previous bevacizumab, ranibizumab, or both agents (data not shown). Of note, 3 eyes (1 in each bevacizumab-only, ranibizumab-only, and both agent group) had complete resolution during the course of treatment but developed fluid again when the treatment interval for aflibercept was extended.

Adverse Events

Two hundred and forty-five injections were performed in this study. No ocular adverse events including endophthalmitis, retinal detachment, retinal pigment epithelial tears,

massive submacular hemorrhage, uveitis, or sustained elevated intraocular pressure requiring topical ocular hypertensive mediations were observed. Four eyes developed focal areas subretinal hemorrhage during the study, of which 1 worsened, 1 remained unchanged, and 2 resolved by the end of the study period. Systemic complications including thromboembolic events like myocardial infarction or stroke were not observed during the study period.

DISCUSSION

Aflibercept, which was FDA-approved for the treatment of neovascular AMD in November 2011, has previously demonstrated efficacy for neovascular AMD in treatment-naïve patients.⁹ The results of this study provide insight into the outcomes of transitioning to aflibercept for eyes previously treated with bevacizumab and/or ranibizumab injections.

The majority of eyes in this study maintained stable VA following conversion to aflibercept. Eighty-five percent of eyes remained stable within ± 1 lines and 7% gained 2 lines of Snellen VA. Eighty-three percent of eyes with 20/40 vision at baseline maintained this level of acuity at last follow-up. A statistically significant improvement in logMAR VA was found in the subgroup of 23 eyes that received prior bevacizumab and ranibizumab.

Anatomically, patients in this study experienced a trend toward decreased mean central foveal thickness, and a statistically significant mean decrease in macular cube volume, -0.27 mm^3 ($P = 0.004$) after switching to aflibercept. Trends toward anatomic improvements were apparent regardless of prior treatment regimen (data not shown). Intraretinal fluid responded well with 61% exhibiting at least a partial response, of which 42% exhibited a complete resolution. Subretinal fluid responded similarly with 60% of eyes demonstrating at least a partial response, of which 35% demonstrated a complete response. The majority of PEDs (69%) in the study remained unchanged, but interestingly, 23% showed a partial response and 3% had a complete response, while only 5% worsened. Subretinal hemorrhages responded well with 78% exhibiting at least a partial response, of which 61% completely resolved. Overall, a favorable response was observed on SD-OCT segmentation analysis in 54% of eyes, with 49% exhibiting a partial response and 5% exhibiting a complete response. These favorable anatomic responses are particularly interesting because our cohort reflected a selection bias toward patients with persistent, recurrent, or worsening exudation or hemorrhage despite previous anti-VEGF therapy. Patients in this study by in large had received aggressive previous treatment with other anti-VEGF agents (mean 17 injections) prior to transitioning to aflibercept.

There are three potential explanations for the overall anatomic success of aflibercept therapy in this setting. First, studies suggest patients treated with repeat intravitreal bevacizumab and ranibizumab injections may develop tachyphylaxis over time.^{16,17} Following intravitreal injection, a systemic immune response to VEGF inhibitors in patients' serum as well as a local immune response from a compromised blood-ocular barrier may contribute to the formation of measurable, neutralizing antibodies to bevacizumab or ranibizumab. Such a response may also account for the occurrence of sterile uveitis after repeated injections with anti-VEGF agents.^{2,18} Additionally, chronic VEGF blockade may attract and induce

macrophages in choroidal neovascular tissue that upregulate the production of VEGF and overwhelm the effects of anti-VEGF agents.^{16,19, 20,21} By changing to aflibercept, less initial immunogenicity associated with a new agent may theoretically lead to sustained benefits in eyes refractory to bevacizumab and/or ranibizumab.

A second explanation for the favorable responses may be related to the binding properties of aflibercept. Bevacizumab is a humanized full-length IgG1 monoclonal antibody and ranibizumab is a humanized IgG1 kappa isotype monoclonal antibody fragment. Aflibercept, on the other hand, is created by fusing the second immunoglobulin (Ig) domain of human VEGF receptor (VEGFR) 1, the third Ig domain of human VEGFR-2, and the Fc region of human IgG-1 to create a protein that binds VEGF-A with 100 times greater affinity than bevacizumab or ranibizumab.^{10,12}

In addition, aflibercept targets other VEGF family members including VEGF-B and placental growth factor (PLGF) that are not inhibited by bevacizumab and ranibizumab.^{10,11,12,13,14} Such binding properties may account for positive anatomic effects that were seen in this study, including improvement of chronic fluid and PEDs, despite treatment with prior anti-VEGF therapy.

This study has several limitations inherent to its retrospective design. These include incomplete follow-up, non-standardized follow-up intervals, differences in prior VEGF inhibitor regimens, the use of Snellen VA, and statistical analysis of a relatively small number of eyes for endpoints that were not pre-specified before initiating therapy. Nevertheless, this study offers valuable insight into initial experience with aflibercept in a cohort of patients previously treated with other VEGF inhibitors.

In conclusion, aflibercept appears to be an effective alternative for neovascular AMD patients previously treated with bevacizumab and/or ranibizumab. The majority of eyes in this study maintained stable VA and showed anatomic improvement. The mechanism for these effects is not well understood. One theory would be that tachyphylaxis to a specific agent is alleviated and this may explain the anatomic improvements seen in patients with recurrent fluid after multiple injections of bevacizumab or ranibizumab. For patients with persistent exudative fluid that never fully responded to bevacizumab or ranibizumab, it is possible that the greater binding affinity of aflibercept and its ability to block multiple molecular targets may explain the observed results. Larger studies and longer follow-up are needed to determine whether these anatomic gains and VA findings can be sustained.

Acknowledgments

a. Supported in part by an Unrestricted Grant from Research to Prevent Blindness Inc. (New York, NY) and NIH Core Grant EYO 6360 (Bethesda, MD)

b. GBH receives a consulting fee from the Children's Hospital of Philadelphia Research Institute as a consultant/expert reader for the Telemedicine Approaches to Evaluating Acute-phase Retinopathy of Prematurity Study (eROP Study). He also has financial activity outside the submitted work involving expert witness testimony. There were no other financial disclosures from the remaining authors.

c. Design and conduct of the study (VYH, SY, GBH); Collection (VYH, SY, GBH, CSB, JY, BEC, TWO); Management (SY, GBH, TWO, CSB, JY, BEC); Analysis (VYH, SY, GBH, TWO); Interpretation of the data

(VYH, GBH, SY, TWO); Preparation, review, or approval of the manuscript (VYH, GBH, SY, TWO, CSB, JY, BEC)

d. Other acknowledgements: None

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Figure 1.
Final vs. Baseline Logarithm of the Minimum Angle of Resolution Visual Acuity after
Transitioning to Aflibercept Injections to Treat Neovascular Age-related Macular
Degeneration

Figure 2.
Final vs. Baseline Central Foveal Thickness (microns) after Transitioning to Aflibercept
Injections to Treat Neovascular Age-related Macular Degeneration

Figure 3.
Final vs. Baseline Macular Cube Volume (mm³) after Transitioning to Afibercept Injections
to Treat Neovascular Age-related Macular Degeneration

Table 1

Demographics and Clinical Characteristics of Patients Transitioned to Aflibercept from Bevacizumab and/or Ranibizumab to Treat Neovascular Age-related Macular Degeneration

	Value (Range)
No. of eyes	96
No. of patients	85
Gender	
Male	34
Female	51
Age (mean, years)	79 (62–91)
Interval between last agent and aflibercept (days)	49 (18–355)
Mean follow-up after initiation of aflibercept (days)	114 (90–133)
Mean number of aflibercept injections prior to last follow-up visit	2.6 (1–4)
No. of eyes with exudative fluid and/or hemorrhage at first aflibercept injection	82
Mean number of prior anti-VEGF injections for all study eyes	17 (1–60)
Bevacizumab-only group (No. of eyes)	30
Mean bevacizumab injections	14 (1–53)
Ranibizumab-only group (No. of eyes)	43
Mean ranibizumab injections	19 (1–49)
Bevacizumab and ranibizumab group (No. of eyes)	23
Mean bevacizumab injections	13 (1–32)
Mean ranibizumab injections	8 (range 1–36)
Other prior treatment modalities (No. of eyes)	
Photodynamic therapy	5
Pegaptanib injections	1
Other ocular conditions (No. of eyes)	
Epiretinal membrane	4
Glaucoma	5
Idiopathic polypoidal choroidal vasculopathy	1
Central serous chorioretinopathy	2
Presumed ocular histoplasmosis syndrome	1

Spectral Domain Optical Coherence Tomography Segmentation Analysis from Time of First Aflibercept Injection to 4-month Follow-up Visit after Prior Vascular Endothelial Growth Factor Inhibitors for Treating Neovascular Age-related Macular Degeneration.

Table 2

SD-OCT Segmentation	Baseline eyes	Worse (%)	Unchanged (%)	Partial Resolution (%)	Complete Resolution (%)
IRF ^a	31	2 (6)	10 (32)	6 (19)	13 (42)
SRF ^b	49	9 (18)	11 (22)	12 (25)	17 (35)
PED ^c	73	4 (5)	50 (69)	17 (23)	2 (3)
SRH ^d	18	0 (0)	4 (22)	3 (17)	11 (61)
Overall	82	12 (14)	26 (32)	40 (49)	4 (5)

^a Intraretinal fluid (IRF)

^b Subretinal fluid (SRF)

^c Pigment epithelial detachment (PED)

^d Subretinal hemorrhage (SRH) – assessment based on fundus examination