Published in final edited form as:

Ophthalmic Surg Lasers Imaging Retina. 2016 March ; 47(3): 245–251. doi:
10.3928/23258160-20160229-07.

Evaluating Efficacy of Aflibercept in Refractory Exudative Age-Related Macular Degeneration With OCT Segmentation Volumetric Analysis

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Abstract

BACKGROUND AND OBJECTIVE—To use automated segmentation software to analyze spectral-domain optical coherence tomography (SD-OCT) scans and evaluate the effectiveness of aflibercept (Eylea; Regeneron, Tarrytown, NY) in the treatment of patients with exudative age-related macular degeneration (AMD) refractory to other treatments.

PATIENTS AND METHODS—Retrospective chart review of 16 patients refractory to bevacizumab (Avastin; Genentech, South San Francisco, CA)/ranibizumab (Lucentis; Genentech, San Francisco, CA) treatment was conducted. Visual acuity, central foveal thickness (CFT), maximum fluid height, pigment epithelial detachment (PED) volume, sub-retinal fluid (SRF) volume, fluid-free time interval, and adverse effects were evaluated. Automated segmentation analysis was used to quantify improvement.

RESULTS—With aflibercept treatment, there was a statistically significant improvement in visual acuity by 1 line ($P = .020$), in CFT by $74.02 \mu\text{m}$ ($P = .001$), and in maximum fluid height by $31.9 \mu\text{m}$ ($P = .011$). Total PED and SRF volume also decreased significantly by $1.50 \mu\text{m}^3 \times 10^8 \mu\text{m}^3$ ($P = .013$). Anatomic improvement was confirmed by automated segmentation analysis.

CONCLUSION—This study demonstrates utility of automated segmentation software in quantifying anatomic improvement with aflibercept treatment in exudative AMD refractory to other anti-vascular endothelial growth factor treatments.

INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of vision loss in patients older than 60 years of age and is newly diagnosed in more than 2 million people older than 55 years of age per year in the United States alone.¹ As AMD is estimated to affect more than 6 million people by the year 2020 and anticipated to cause a global economic burden of more than \$300 billion in the near future,¹ the significance of improved treatments is becoming ever more apparent.

Current treatment options for exudative AMD include anti-vascular endothelial growth factor (VEGF) agents such as bevacizumab (Avastin; Genentech, South San Francisco, CA), ranibizumab (Lucentis; Genentech, South San Francisco, CA), and aflibercept (Eylea; Regeneron, Tarrytown, NY). Aflibercept, also known as VEGF Trap-Eye, is a recombinant fusion protein that binds all isomers of the VEGF-A family (ie, 121 and 165), as well as placental growth factor (PLGF).² It also has a higher binding affinity for VEGF and a longer half-life than both bevacizumab and ranibizumab.²

Many studies in the literature have described that a subset of patients with exudative AMD demonstrate diminished responses to bevacizumab and/or ranibizumab over time,^{3–6} demonstrated by persistence of sub-retinal or intraretinal fluid despite treatment. Possible mechanisms for this phenomenon include chronic alteration of vessel architecture and increased fibrosis causing barriers to fluid resorption.³ Switching therapy in these nonresponder patients has proven some benefit in approximately 80% of patients.⁴

With the advent of the newest anti-VEGF agent, aflibercept, many authors have described improved responses to therapy in patients referred to as refractory to treatment with either ranibizumab or bevacizumab.^{4–9} Hypothetically, patients no longer responsive to either bevacizumab or ranibizumab may respond better to aflibercept, either because of its broader mechanism of action or instead because of the patient's lack of response to the former drugs.

Optical coherence tomography (OCT) has in recent years been a critical tool used to manage patients with exudative AMD and to help guide treatment decisions. The advent of spectral-domain OCT (SD-OCT) has allowed the acquisition of true 3-D volumetric scans of the retina.¹⁰ Since thickness changes of the retinal layers are one indicator of disease status, the segmentation of retinal layers in OCT scans proves to be a clinically significant application. The Iowa group¹¹ was the first to report a true 3-D approach for segmentation of retinal layers on SD-OCT scans in a simultaneous fashion (PMID: 2062510, PMID: 18815101, PMID: 17354964, PMID: 18051065), which has since been improved for the outer retina (PMID: 24569576) and was superior compared to manufacturer specific algorithms (PMID: 26336634). We employ this algorithm to investigate the clinical utility of such segmentation software in evaluating whether aflibercept is effective in treatment of exudative AMD previously refractory to treatment with bevacizumab and/or ranibizumab. To our knowledge, this study is the first to use automated OCT segmentation and volumetric analysis to document anatomic improvement with aflibercept in this patient population.

PATIENTS AND METHODS

The study design was a retrospective chart review approved by the institutional review board of the University of Florida and in accordance with principles set forth by the Declaration of Helsinki. Patients included in the study were treated by four independent vitreoretinal surgeons in an outpatient clinic setting. All patients had previously demonstrated lack of sufficient response to either bevacizumab and/or ranibizumab and were subsequently switched to treatment with aflibercept. The aflibercept treatment period varied for each patient but was an average of 35 weeks (range: 8 weeks to 49 weeks; standard deviation [SD]: 12.89 weeks). Seventeen eyes of 16 patients were evaluated. Eleven patients were female and five were male between the ages of 64 years and 90 years.

Visual acuity (converted from Snellen chart acuity to logMAR scale),¹² central foveal thickness (CFT), maximum fluid height, pigment epithelial detachment (PED) volume, subretinal fluid (SRF) volume, fluid-free time interval, and adverse effects (ie, infection, inflammation) were analyzed. OCT imaging was obtained with Spectralis HRA + OCT (Heidelberg Engineering, Heidelberg, Germany) (resolution: 1,024 × 496; 19 lines – 25 lines). Automated segmentation of OCT (Figure 1A) was performed using the Iowa Reference Algorithms (Retinal Image Analysis Lab, Iowa Institute for Biomedical Imaging, Iowa City, IA) (Figure 1B), a set of fully automated 3-D segmentation algorithms for analysis of retinal structures in normal subjects and patients with various ocular diseases^{10,11} available online at <https://www.iibi.uiowa.edu/content/shared-software-download>, and automated quantification of CFT, maximum fluid height, SRF and PED volume was performed using a customized version of the algorithms. The Iowa Reference Algorithms are not approved for clinical use. Segmentation was performed on all data from the 17 eyes included in this study, and manual correction was not performed on any of the segmentation results.

CFT was also measured manually using digital calipers on the Heidelberg Spectralis as the distance from outer Bruch's membrane to the internal limiting membrane at the level of the fovea. Maximum fluid height was defined as the distance from the base to the height of the fluid or from Bruch's membrane to the maximum height of the PED.

Parameters were compared from first visit (pre-aflibercept treatment) to last documented visit (post-aflibercept treatment). Exclusion criteria included vision-impairing pathology other than exudative AMD (ie, dense vitreous hemorrhage or corneal edema) and lack of follow-up.

All patients included in our study were treated with 2 mg aflibercept for an induction interval of 3 months with an injection every 4 weeks. The treatment period was then extended to 8 weeks for all patients, and then future treatment intervals were titrated based on subsequent OCT appearance.

All statistical analyses were completed with a two-sample, two-sided paired *t* test by Microsoft Excel software (Microsoft, Redmond, WA), and significance was defined as a *P* value of less than .05.

RESULTS

Among our study patients, 10 out of 17 eyes (58.8%) had previously been treated with ranibizumab, and seven of 17 eyes (41.2%) had been previously treated with bevacizumab. All of these eyes were refractory to treatment with ranibizumab and/or bevacizumab after multiple (at least three) injections, as evidenced by persistent intraretinal ($n = 10$) or subretinal fluid ($n = 8$) on OCT. They were all switched to treatment with aflibercept. Figure 2 illustrates changes in OCT appearance in a sample of our patients before and after treatment with aflibercept.

Visual acuity on a logMAR scale overall improved by 1 line and this was statistically significant ($P = .020$) (Figure 3). Visual acuity improved in 11 of 17 eyes treated with aflibercept.

There was a statistically significant decrease in average CFT by both Iowa Reference Algorithms and manual Spectralis measurement. Average CFT decreased by $74.02 \mu\text{m}$ after treatment with aflibercept as measured by the Iowa Reference Algorithms ($P = .001$) (Figure 4), with an average CFT pretreatment of $289.24 \mu\text{m}$ (95% CI, $226.62 \mu\text{m} - 351.86 \mu\text{m}$) and an average CFT post-treatment of $257.35 \mu\text{m}$ (95% CI, $202.39 \mu\text{m} - 312.31 \mu\text{m}$). If measured manually, there was still a decrease in average CFT of $92.94 \mu\text{m}$, but less significant at $P = .004$. Measured manually, the average CFT pretreatment was $422.76 \mu\text{m}$ (95% CI, $351.54 \mu\text{m} - 493.99 \mu\text{m}$) and the average CFT post-treatment was $329.82 \mu\text{m}$ (95% CI, $285.17 \mu\text{m} - 374.48 \mu\text{m}$). A decrease in CFT was found in all 17 eyes after treatment with aflibercept.

There was also a statistically significant decrease in average maximum fluid height of $31.9 \mu\text{m}$ after treatment with aflibercept as measured by the Iowa Reference Algorithms ($P = .011$) (Figure 5). Average maximum fluid height pretreatment was $418.14 \mu\text{m}$ (95% CI, $359.95 \mu\text{m} - 476.33 \mu\text{m}$) and average maximum fluid height post-treatment was $344.12 \mu\text{m}$ (95% CI, $292.16 \mu\text{m} - 396.08 \mu\text{m}$). Maximum fluid height was reduced in 13 of 17 eyes after treatment with aflibercept.

Combined PED and SRF volume decreased significantly from average pretreatment volume ($7.68 \times 10^8 \mu\text{m}^3$; 95% CI, $3.45 \times 10^8 \mu\text{m}^3 - 1.19 \times 10^9 \mu\text{m}^3$) to average post-treatment volume ($6.18 \times 10^8 \mu\text{m}^3$; 95% CI, $2.40 \times 10^8 \mu\text{m}^3 - 9.97 \times 10^8 \mu\text{m}^3$), a difference of $1.50 \times 10^8 \mu\text{m}^3$ ($P = .013$) (Figure 6). There was a decrease in combined PED and SRF volume in eight of 13 eyes that had PED and/or SRF at the time of initiating aflibercept treatment.

There was a decrease in average pretreatment PED volume ($5.56 \times 10^8 \mu\text{m}^3$; 95% CI, $1.73 \times 10^8 \mu\text{m}^3 - 9.40 \times 10^8 \mu\text{m}^3$) versus post-treatment PED volume ($4.92 \times 10^8 \mu\text{m}^3$; 95% CI, $1.22 \times 10^8 \mu\text{m}^3 - 8.62 \times 10^8 \mu\text{m}^3$), although this result was not statistically significant ($P = .33$). Similarly, though there was an absolute decrease in average pretreatment SRF volume ($2.12 \times 10^8 \mu\text{m}^3$; 95% CI, $2.24 \times 10^7 \mu\text{m}^3 - 4.02 \times 10^8 \mu\text{m}^3$) versus post-treatment SRF volume ($1.26 \times 10^8 \mu\text{m}^3$; 95% CI, $1.81 \times 10^7 \mu\text{m}^3 - 2.35 \times 10^8 \mu\text{m}^3$), the difference was not statistically significant ($P = .16$).

After initial induction treatment, our study patients were all extended to 8 weeks between aflibercept injections. The frequency of injections was then titrated according to presence of sub-retinal or intra-retinal fluid on OCT. We found that among our patients, we could not extend treatment intervals to greater than 7.1 weeks on average without fluid recurrence. The treatment interval was shortened for those patients who could not be extended to 8 weeks without fluid recurrence.

There were no adverse events such as injection-induced inflammation, endophthalmitis, retinal detachment, vitreous hemorrhage, or intraocular pressure elevation in any of the patients included in our study.

DISCUSSION

To our knowledge, this is the first study in the literature that demonstrates the utility of segmentation software and automated volumetric analysis — such as the Iowa Reference Algorithms — in quantification of anatomical improvements with aflibercept treatment in exudative macular degeneration. At least for CFT, where a comparison is available, confidence intervals were tighter when measured automatically than when measured manually. In our study, OCT volumetric analysis was performed with the Iowa Reference Algorithms and allowed for rapid, automated analysis of clinically acquired SD-OCT volume scans.

Our results show a significant improvement in visual acuity, CFT, maximum fluid height, and combined PED and SRF volume due to aflibercept treatment in those patients demonstrating declining responses to bevacizumab and/or ranibizumab in exudative AMD. Anatomic improvement was confirmed using automated segmentation software. Although patients who were switched from either ranibizumab or bevacizumab could typically be extended to longer intervals between treatment and without recurrence in fluid compared to prior treatment intervals with ranibizumab or bevacizumab, we also found that treatment intervals in these patients could not be extended to greater than 7.1 weeks on average without fluid recurrence. These findings are similar to other studies in the literature.^{4,9}

The decrease in combined SRF and PED volumes after aflibercept treatment achieved statistical significance, whereas individual measurements of SRF and PED volumes did not, likely due to a larger effect size.

Automated fluid analysis is currently being used to predict treatment intervals in CNV management, efforts funded by the National Eye Institute. Intensity-based analysis can also be performed using this segmentation software in order to examine the local intensity changes on the retinal pigment epithelium or basement membrane secondary to retinal disease.

Limitations of our study include its retrospective nature, small sample size, and relatively short duration of treatment and follow-up. The subset of patients evaluated in our study were refractory to prior treatment with either ranibizumab or bevacizumab; however, treatment intervals were variable on these drugs, and it is certainly possible that lack of response may have been secondary to inadequate treatment regimens. Thus, our findings cannot be

extrapolated to make any statements on comparing these drugs in treatment-naïve patients in a head-to-head fashion. Given the retrospective nature of this study, the four independent vitreoretinal specialists managing these patients could determine criteria for deciding that a patient was “refractory” to prior treatment, and these criteria were not clearly defined as would be required in a prospective trial. We determined that all patients included in this analysis who were termed “refractory” did exhibit persistent intraretinal or subretinal fluid despite multiple treatments (at least three injections) with either bevacizumab and/or ranibizumab; however, treatment intervals were variable. Finally, it is important to note that at this time, no algorithms for automated segmentation are U.S. Food and Drug Administration-approved or currently available for clinical use, although we believe that utilization of this technology may have clinical utility, and further analysis in the setting of a prospective trial would be useful.

This study describes the use of automated OCT segmentation analysis to evaluate the effectiveness of aflibercept in patients with exudative AMD refractory to other anti-VEGF treatments. Most importantly, it demonstrates how automated OCT segmentation analysis is useful in the management of patients and may inform treatment decisions. Future prospective studies should continue to evaluate the clinical utility of OCT segmentation analysis as an outcome measure.

Acknowledgments

Supported in part by a grant from Foundation Fighting Blindness (PI: Christine Kay); Arnold and Mabel Beckman Initiative for Macular Research, (PI: Abramoff); and National Institutes for Health R01-EY017066 and R01-EY018853 (PI: Abramoff and Sonka) and R01-EB004640 EY018853 (PI: Sonka).

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Figure 1.

Figure 1A. The Iowa Reference Algorithms: (1) One example B-scan from a Spectralis optical coherence tomography image. (2) The same B-scan with the segmentation from the Iowa Reference Algorithms.

Figure 1B. Segmentation of internal limiting membrane (ILM), upper surface of fluid, and Bruch's membrane at the level of the fovea: (1) Original central B-scan from optical coherence tomography image. (2) The same B-scan with the segmentation from the Iowa Reference Algorithms.

Figure 2.

Optical coherence tomography resolution of subretinal fluid and flattening of pigment epithelial detachment in a patient before (A) and after (B) treatment with aflibercept in patient A. Red lines indicate internal limiting membrane and Bruch's membrane as segmented by the Iowa Reference Algorithms respectively.

Figure 3.
Optical coherence tomography resolution of subretinal fluid in patient B before (A) and after (B) treatment with aflibercept.

Figure 4.
Optical coherence tomography resolution of subretinal fluid in patient C before (A) and after (B) treatment with aflibercept.

Figure 5.

Comparison of visual acuity (VA) before and after treatment with aflibercept in non-responders to bevacizumab and/or ranibizumab. VA improved by 1 line ($P = .020$).

Figure 6.
Decrease in central foveal thickness (in microns) after treatment with aflibercept ($P = .001$).

Figure 7.

Decrease in maximum fluid height (in microns) after treatment with aflibercept ($P = .011$).

Figure 8.

Decrease in combined subretinal fluid and pigment epithelial detachment volume (cubic microns) comparing pre- and post-aflibercept treatment ($P = .013$).