

Original research

The results of aflibercept therapy as a first line treatment of age-related macular degeneration

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Received 2 August 2018; revised 27 October 2018; accepted 5 November 2018

Available online 27 November 2018

Abstract

Purpose: To report the results of aflibercept treatment in treatment-naïve neovascular age-related macular degeneration (AMD) patients and suggest a suitable treatment algorithm for routine clinical practice.

Method: The medical charts of patients treated with intravitreal aflibercept for neovascular AMD were reviewed retrospectively. Best corrected visual acuity, slit-lamp examination, dilated fundus examination, applanation tonometry, and a total number of aflibercept injections were recorded. Aflibercept therapy was applied in an as-needed algorithm after three monthly loading dose. Additionally, optic coherence tomography data, including presence or absence of macular fluid and central macular thickness were recorded.

Results: Thirty-eight eyes of 36 patients were included in this study. The mean number of aflibercept injections was 4.86 ± 2.76 (3–18). Mean follow-up time was 12.1 ± 5.7 months (6–26). Thirty-seven eyes (97.3%) achieved maintenance of vision. The mean best corrected visual acuity (logMAR) increased from 0.98 ± 0.56 (0.2–2.4) to 0.57 ± 0.31 (0.1–1.3), ($P = 0.001$). Mean visual acuity gain was 15.86 ± 12.18 letters at the end of the study. The mean central macular thickness decreased from $327.9 \pm 56.5 \mu\text{m}$ (219–474 μm) to $277.0 \pm 53.0 \mu\text{m}$ (197–405 μm), ($P = 0.016$).

Conclusions: Aflibercept therapy appears to be a safe and effective treatment for neovascular AMD. Injections applied in an as-needed algorithm after three monthly loading doses were successful to maintain and improve visual acuity.

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Keywords: Age-related macular degeneration; Aflibercept; Neovascular (wet); AMD

Introduction

Age-related macular degeneration (AMD) is the most important cause of blindness in the industrialized world.^{1,2} It is a chronic, degenerative condition and is divided into non-neovascular atrophy (dry) type and the neovascular (wet) type. Neovascular macular degeneration is responsible for 80% of significant visual loss related to AMD.²

The vascular endothelial growth factor is the main mediator in the pathogenesis of neovascular AMD. It induces

angiogenesis and increases vascular permeability.³ Therefore, anti-vascular endothelial growth factor agents have been the mainstay of the therapy for neovascular AMD in the last decade.³ Three anti-vascular endothelial growth factor agents, pegaptanib (Macugen; Eyetech Pharmaceuticals, Inc. New York, NY), ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA), and bevacizumab (Avastin®, Genentech) have been shown to be effective in treating neovascular AMD.^{4,5} Pegaptanib is a ribonucleic acid aptamer which blocks the main pathologic isoform of vascular endothelial growth factor 165, ranibizumab is an affinity matured, humanized, monoclonal antibody fragment to vascular endothelial growth factor, and bevacizumab is a full-length, humanized, monoclonal antibody to vascular endothelial growth factor.^{4,5} Ranibizumab and bevacizumab block the receptor binding domain of all

Conflicts of interest: Authors declare that they have no conflict of interest.

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Peer review under responsibility of the Iranian Society of Ophthalmology.

isoforms of vascular endothelial growth factor-A.^{4,5} Aflibercept (Eylea; Regeneron, Tarrytown, New York, USA, and Bayer, Berlin, Germany) is a new anti-vascular endothelial growth factor agent that binds to all vascular endothelial growth factor-A and vascular endothelial growth factor-B isoforms and also placental growth factors 1 and 2 with high affinity.⁶ Similar efficacy and safety outcomes as monthly ranibizumab were determined with intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses.^{7,8} The long-term effects, the optimal dose, and the best treatment regimen of aflibercept therapy were still controversial, particularly in the real world.

We aimed to present our results of aflibercept treatment in patients with no previous treatment for neovascular AMD and suggest a suitable treatment algorithm.

Methods

In this retrospective study, the functional and anatomic outcomes of intravitreal aflibercept as a first-line therapy in patients with neovascular AMD were evaluated. The medical charts of patients treated with intravitreal aflibercept for neovascular AMD from September 2014 to January 2017 were reviewed retrospectively. Ethical approval was obtained from the local ethics committee. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Consent was taken from all patients about the side effects of the drug and its application.

Two inclusion criteria were defined: 1) eyes were diagnosed as subfoveal choroidal neovascularization secondary to neovascular AMD based on exam, optical coherence tomography (OCT) and fluorescein angiography (FA), and 2) patients without macular scar and/or atrophy detected by fundus examination were included in the study. We defined 7 exclusion criteria: 1) missing data about previous injections, 2) eyes treated with anti-vascular endothelial growth factor other than aflibercept elsewhere during the study period, 3) eyes treated previously with photodynamic therapy, or else 4) eyes treated with ocular procedures other than uncomplicated cataract surgery or Nd:YAG laser posterior capsulotomy, 5) the choroidal neovascular vessel was secondary to some other disease than exudative age related macular degeneration, 6) patients diagnosed as polypoidal choroidal vasculopathy (PCV) or retinal angiomatous proliferation (RAP), and 7) patients with a follow-up shorter than 6 months under aflibercept treatment. Indocyanine Green (ICG) was performed in patients with suspected PCV or RAP. Patients with suspected PCV, RAP, subretinal hemorrhage with etiologic factors other than choroidal neovascular membrane, diabetic retinopathy, poor OCT images quality, history of laser therapy, or any intravitreal injections were excluded from the study.

Aflibercept treatment (2 mg/0.05 cc) were performed in three monthly loading doses. If complete resolution of intraretinal and subretinal fluid (both) was not achieved, injections were continued until complete resolution was obtained.

After complete retinal dryness, the injections were applied in an as-needed algorithm, and patients were followed up with OCT every 4 weeks. We also performed fundus fluorescein angiography (FFA) before the beginning of the therapy and after the therapy in any suspected OCT of activity. Complete ophthalmological examinations of all the patients including best corrected visual acuity, slit-lamp examination, dilated fundus examination, applanation tonometry and a total number of aflibercept injections were recorded from the medical charts. OCT, FFA data were also reviewed.

Recurrent activity was defined as the re-appearance of intraretinal or subretinal fluid on OCT and/or leakage on angiography following a previous fluid-free and/or leakage-free interval and/or new-onset macular hemorrhage typically accompanied by visual symptoms. Re-treatment was performed in patients with recurrent activity.

Best corrected visual acuity was measured by using Early Treatment Diabetic Retinopathy Study (ETDRS) chart. ETDRS letter score was converted into a Snellen and logarithm of the minimum angle of resolution or recognition (logMAR) for statistical analysis.

OCT was performed with the same OCT device (Optovue optic coherence tomography V 5.1, RTVue 100-2; Optovue, Fremont, CA, USA) after pupillary mydriasis, and analysis of all OCT images was performed by the same retina specialist (E.U.) The distance between the internal limiting membrane (ILM) and Bruch membrane in the central point of fovea was defined as central macular thickness.

All injections were performed in an operating room with topical anesthesia (0.5% proparacaine hydrochloride, Alcaine; Alcon) by the same person. After conjunctiva was irrigated with the povidone-iodine solution (5%), anti-vascular endothelial growth factor agent (2 mg/0.05 ml aflibercept) injection was performed via the pars plana, 3.5–4 mm posterior to limbus using a syringe with 30 gauge needle. After the procedure, moxifloxacin eye drop (Vigamox; Alcon, USA) was applied 4 times daily for 5 days. Additionally, we also aimed to assess the long-term effect of aflibercept on intraocular pressure. Thus, intraocular pressure measurement was performed by the same person with Goldmann applanation tonometer before each aflibercept injection, the first day after injection, and at the first-week visit.

Statistical Package for the Social Sciences version 20.0 software was used for all statistical analyses. Descriptive statistics are presented as minimum, maximum, and mean \pm standard deviation. The normality of data was confirmed using the Kolmogorov-Smirnov test. Wilcoxon signed rank test and paired *t*-test were used for paired samples. Pearson correlation analysis was used to show the linear correlation between the total number of aflibercept injections and the increase of best corrected visual acuity. *P* values < 0.05 were accepted as statistically significant.

Results

Thirty-eight eyes of 36 patients fulfilled the inclusion criteria and were included in this study. The demographic

Table 1
Demographic characteristics.

Parameters	Values	Range
Mean age (y)	74.5 ± 6.8	61–87
Patients/eye	36/38	
Female/male	20/16	
Mean follow-up time (m)	12.1 ± 5.7	6–26
Mean number of aflibercept injections	4.86 ± 2.76	3–18
Phakia/pseudophakia	24/14	
History of glaucoma	3	
Diabetic retinopathy	0	

y: Year; m: Month.

characteristics of patients and the mean follow-up time are shown in Table 1.

At the end of the study, 33 eyes had improvement of one line or more in vision (86.8%), and 4 eyes (10.5%) achieved maintenance of vision. The mean best corrected visual acuity (logMAR) was 0.98 ± 0.56 (0.2–2.4), (39.07 ± 21.43 letters) before the initiation of aflibercept therapy. The last best corrected visual acuity (logMAR) increased to 0.57 ± 0.31 (0.1–1.3) (54.94 ± 15.70 letters) with a mean aflibercept injections 4.86 ± 2.76, which was statistically significant compared to baseline (Table 2), ($P = 0.001$). The monthly follow-up of best corrected visual acuity is shown in Table 2. The mean best corrected visual acuity was significantly improved in all visits except the first two months visit. Twenty-eight eyes of 38 (73.6%) gained 1 or more line at last follow-up. Mean visual acuity gain was 15.86 ± 12.18 letters at the end of the study. The visual acuity gain continued to increase after loading phase (Table 2). There was no improvement in visual acuity of 4 eyes (10.52%), and only one of these had a decrease in visual acuity. A visual acuity gain of equal or more than 3 lines was observed in 22 eyes at last follow-up. Loss of one line of visual acuity was observed in one eye. The mean central macular thickness increased in 3 of these 4 eyes. There is no correlation between the total number of aflibercept injections and the increase of best corrected visual acuity, ($r = -0.201$, $P = 0.225$).

The mean central macular thickness was 327.9 ± 56.5 μm (219–474) before initiating treatment with aflibercept. At last follow-up after aflibercept therapy, the mean central macular thickness decreased to 277.0 ± 53.0 μm (197–405) which was statistically significant compared to baseline ($P = 0.016$) (Table 2). The mean decrease of central macular thickness was 51.9 ± 58.2 μm (157 ± 119). Monthly follow-up of central macular thickness is shown in Table 2. Central macular thickness increased in three eyes, one of them had 7, one had 3, and one had 5 aflibercept injections. The best corrected visual acuity did not improve in these patients. No correlation was observed between the total number of injections and the decrease in central macular thickness ($r = 0.227$, $P = 0.19$). Thirty-four eyes were without fluid in OCT at last follow-up. In 15 eyes no additional anti-vascular endothelial growth factor injection was required after 3 loading doses. In 7 eyes, because the subretinal fluid was not cleared after the loading dose, more injections were needed. There was still subretinal fluid in 4 eyes at the last follow-up.

Table 2

Comparison of the mean best corrected visual acuity (logMAR), central macular thickness (μm), and intraocular pressure (mmHg) values at the beginning of the aflibercept therapy and follow-up months.														
Parameters	PreAf	PostAf 1. M	PostAf 2. M	PostAf 3. M	PostAf 4. M	PostAf 5. M	PostAf 6. M	PostAf 7. M	PostAf 8. M	PostAf 9. M	PostAf 10. M	PostAf 11. M	PostAf 12. M	PostAf Final
Best corrected visual acuity (logMAR), Mean±SD (Min–Max)	0.98 ± 0.56 (0.2–2.4)	0.92 ± 0.47 (0.2–2.0) $P^* = 0.28$, $n = 38$	0.89 ± 0.44 (0.2–2.0) $P^* = 0.19$, $n = 38$	0.76 ± 0.36 (0.1–1.3) $P^* = 0.04$, $n = 38$	0.73 ± 0.34 (0.1–1.3) $P^* = 0.03$, $n = 38$	0.66 ± 0.29 (0.1–1.0) $P^* = 0.007$, $n = 38$	0.68 ± 0.33 (0.1–1.3) $P^* = 0.001$, $n = 38$	0.61 ± 0.29 (0.1–1.0) $P^* = 0.006$, $n = 32$	0.58 ± 0.28 (0.1–1.0) $P^* = 0.002$, $n = 30$	0.58 ± 0.29 (0.1–1.0) $P^* = 0.002$, $n = 28$	0.55 ± 0.26 (0.1–1.0) $P^* = 0.004$, $n = 27$	0.58 ± 0.25 (0.1–0.8) $P^* = 0.004$, $n = 24$	0.58 ± 0.25 (0.2–1.0) $P^* = 0.009$, $n = 22$	0.57 ± 0.31 (0.1–1.3) $P^* = 0.001$
Central macular thickness, μm Mean ± SD (Min–Max)	327.9 ± 56.5 (219–474)	303.7 ± 70.4 (195–469) $P^* = 0.19$, $n = 38$	297.2 ± 55.7 (216–444) $P^* = 0.03$, $n = 38$	284.3 ± 55.2 (186–420) $P^* = 0.025$, $n = 38$	288.3 ± 57.2 (197–426) $P^* = 0.022$, $n = 38$	286.6 ± 52.1 (202–411) $P^* = 0.018$, $n = 38$	286.5 ± 46.3 (213–387) $P^* = 0.021$, $n = 38$	280.5 ± 48.8 (215–376) $P^* = 0.007$, $n = 32$	281.2 ± 51.3 (201–379) $P^* = 0.006$, $n = 30$	272.3 ± 45.4 (209–321) $P^* = 0.001$, $n = 28$	275.7 ± 49.8 (198–409) $P^* = 0.002$, $n = 27$	280.3 ± 48.8 (189–404) $P^* = 0.04$, $n = 24$	269.1 ± 43.0 (203–376) $P^* = 0.014$, $n = 22$	277.0 ± 53.0 (197–405) $P^* = 0.016$
Intraocular pressure, mmHg Mean ± SD (Min–Max)	16.08 ± 2.11 (11–20)	16.13 ± 2.22 (12–20) $P^* = 0.1$, $n = 29$	16.06 ± 2.34 (12–19) $P^* = 0.1$, $n = 38$	16.18 ± 2.36 (11–21) $P^* = 0.09$, $n = 38$	16.29 ± 2.32 (11–19) $P^* = 0.008$, $n = 38$	16.38 ± 2.28 (11–19) $P^* = 0.005$, $n = 38$	16.25 ± 2.31 (11–20) $P^* = 0.01$, $n = 38$	16.49 ± 2.24 (11–21) $P^* = 0.003$, $n = 32$	16.33 ± 2.18 (12–19) $P^* = 0.001$, $n = 30$	16.40 ± 2.31 (11–20) $P^* = 0.001$, $n = 28$	16.33 ± 2.45 (12–19) $P^* = 0.001$, $n = 27$	16.66 ± 2.18 (11–20) $P^* = 0.001$, $n = 24$	16.58 ± 2.22 (12–20) $P^* = 0.001$, $n = 22$	16.43 ± 2.17 (12–19) $P^* = 0.001$

SD: Standard deviation; Af: Aflibercept; M: Month; n: Number of eyes; P^* :Wilcoxon signed rank test, ($P < 0.05$ indicates statistical significance according to Bonferroni adjustment).

After excluding patients with glaucoma, while baseline intraocular pressure value of all eyes was measured as 16.08 ± 2.11 (11–20) mmHg, the final intraocular pressure value of all eyes was 16.43 ± 2.17 (12–19) mmHg. The increase of mean intraocular pressure was statistically significant under aflibercept treatment ($P = 0.001$) (Table 2), although the values of intraocular pressure were between 11 and 21 mmHg.

No ocular or systemic side effect due to intravitreal injections was observed during follow-up.

Discussion

Clinical trials showed similar efficacy and safety outcomes of intravitreal aflibercept as monthly ranibizumab.^{7,8} However, achieving same results in a real world usually may not be possible. A more heterogeneous group of patients and under-treatment of AMD due to the difficulties to follow optimal treatment regimens could cause different results of studies designed in a real world.⁹

Intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses produced similar efficacy and safety outcomes as monthly ranibizumab in clinical trials.^{7,8} Nevertheless, injections with bi-monthly intervals may not be applicable for all clinics. Therefore, we applied aflibercept in an as-needed algorithm, after three monthly loading doses.

Our study presents a successful, long-term morphologic and functional treatment. Outcomes can be achieved when treating AMD eyes with aflibercept in an as-needed algorithm. Thirty-three eyes had improvement of vision (86.8%), and 4 eyes (10.5%) achieved maintenance of vision. Mean visual acuity gain was 15.86 ± 12.18 letters compared with 8.4 letters in the integrated analysis of the VIEW 1 and VIEW 2 studies: 7.9 letters in VIEW 1 and 8.9 letters in VIEW 2. The mean best corrected visual acuity was improved from 0.98 ± 0.56 to 0.57 ± 0.31 with a mean aflibercept injections 4.86 ± 2.76 . Our mean injection number was lower than VIEW 1 and VIEW 2 (7.5 injections) due to the as-needed algorithm, and our mean visual acuity gain was higher. We thought that the low baseline visual acuity of our patients could be the reason for higher visual acuity gain because it was already known that a patient who starts with poor vision is likely to gain more.^{8,10} Additionally, while we excluded all patients with suspected RAP and PCV, in the VIEW studies,^{7,8} there is not enough information about this group of patients.

The reported visual acuity gain reported by the real-life studies range from 4 letters to 8 letters.^{10–14} Almuhtaseb et al.¹¹ reported 8 mean letters gain after 7 aflibercept injections. The visual acuity improvement that they reported was lower from the current study.¹⁰ Their injection number was higher because they used the therapy algorithm defined in VIEW.¹⁰ They suggested that the regimen defined in VIEW study decreased the visit number.¹⁰ However, we suggested that the as-needed algorithm decreased the number of injections with a higher visit number, and therefore, both the cost of aflibercept

therapy and the complication risks of each intravitreal injections were reduced with a comparable visual acuity gain.

Eleftheriadou et al.¹² presented 7.3 mean letters gain with fixed dosing in year 1 as per the VIEW studies after they continued their study with the treat and extend algorithm. In the second year, they could achieve the stability of visual acuity with 7.1 mean letters gain from baseline.¹² Their number of injections were 8.6 ± 1.1 for the first year and 13.5 ± 2.4 for the whole 2 years.¹² Additionally, they showed 3.1 mean letters gain in the subgroup analysis of patients treated with pro re nata with 8.7 ± 3.4 mean numbers of injections in 2 years follow-up.¹² In the current study, we had a mean visual acuity gain 15.86 ± 12.18 letters with a mean injection number 4.86 ± 2.76 . Although our injection number in one-year follow-up was similar to Eleftheriadou et al.,¹² mean visual acuity gain of our patients was higher.

Mean visual acuity gain is the main primary visual outcome of the current study. However, secondary outcomes such as the OCT-based monitoring of the fluid status of the macula after loading and at the end of the study are as crucial as visual acuity improvement. In the current study, the mean central macular thickness decreased from 327.9 ± 56.5 μm (219–474 μm) to 277.0 ± 53.0 μm (197–405 μm) which was statistically significant ($P = 0.016$). The decrease of mean central macular thickness began in the third month of the study and continued to decrease until the end of the study; however, the improvement of visual acuity stopped after the tenth month (Table 2). Thirty-five eyes (92.1%) had a decrease in central macular thickness. The mean decrease of central macular thickness was 51.9 ± 58.2 μm . However, a mean reduction of 139 μm was reported in the integrated analysis of the VIEW 1 and VIEW 2 studies at 52 weeks and 133 μm at 96 weeks.⁸ The higher improvement of central macular thickness reported in VIEW studies was not a surprise because it was a clinical trial with a rigid treatment algorithm. Additionally, in a real-life study, Eleftheriadou et al.¹² reported that the mean decrease of central macular thickness was 79.0 ± 101.6 μm . Similarly, Frame et al.¹⁴ presented that the mean decrease of central macular thickness was 78.3 ± 113.9 μm in the regular treated group and 75.3 ± 126.1 μm in irregular treated group. These results were comparable to our results (51.9 ± 58.2 μm).^{12,14,15}

In treatment-resistant cases, there is no consensus in the literature about how many doses should be applied before the decision of switching to another anti-vascular endothelial growth factor molecule. Additionally, there is no clear definition and a definite ratio of resistance in the literature.^{7,8,11–14} Hence, despite the increase in central macular thickness, one of our patients had 7 and one had 5 aflibercept injections, and although there is a limited response, four of our patients had subretinal fluid in 4 eyes at the last follow-up.

Ito et al.¹⁶ reported that best corrected visual acuity significantly improved from 0.37 ± 0.04 logMAR units (mean \pm standard error) to 0.25 ± 0.04 after the loading phase (3 months after starting treatment; $P < 0.001$) and maintained at

Table 3
Summarizing the previous studies of real world on aflibercept injections and comparing them with our results.

Authors	Year	Number of eyes	Design	Injection frequency	Visual outcome	Central macular thickness outcome	Follow-up time
Almuhaseb	2017	255	Retrospective	Fixed 8-weekly	8 letters gain	100 μ decrease	11 month
Eleftheriadou	2017	66	Retrospective	First year fixed 8 weekly Second year treat and extend	First year 7.3 letters gain Second year 7.1 letters gain	First years 74 μ decrease Second year 77 μ decrease	24 months
Ito	2017	61	Retrospective	Treat and extend	−0.14 logMAR gain	165 μ Decrease	24 months
Current study	2018	38	Retrospective	As-needed	15.8 letters gain	51.9 μ decrease	12 months

0.21 ± 0.04 (*P* < 0.001) after 1 year and 0.23 ± 0.05 (*P* < 0.001) after 2 years by using the treat and extend algorithm. They also reported that central macular thickness significantly decreased from 338 ± 19 μm (mean ± standard error) to 179 ± 10 μm after the loading phase (*P* < 0.001) and maintained at 171 ± 7 μm (*P* < 0.001) after 1 year and 173 ± 8 μm (*P* < 0.001) after 2 years. The mean number of injections was 8.1 ± 0.2 (mean ± standard error) in the first year and 5.4 ± 0.2 in the second year. Additionally, Haga et al.¹⁷ reported that best corrected visual acuity significantly improved from 0.56 ± 0.42 logMAR units (mean ± standard error) to 0.24 ± 0.28 treatment after 1 year by using the treat and extend algorithm. The mean number of injections was 7.5 ± 1.2 (mean ± standard error) in the first year. In the present study, the mean best corrected visual acuity (logMAR) significantly improved from 0.98 ± 0.56 to 0.57 ± 0.31 with a mean aflibercept injections 4.86 ± 2.76, (*P* = 0.001). In the current study, the improvement of visual acuity was higher, and the number of injections was lower than the literature. We thought that the low visual acuity scores of our patients caused a higher visual acuity gain. The lower number of injection could be the result of as-needed treatment algorithm. Additionally, it is possible that the different population of the selected patients and study protocols could cause these different results.

Table 3 summarizes the previous studies on aflibercept injections and compares them with our results.

Although the previous literature suggested that using post-injection topical antibiotic drops does not reduce the risk of endophthalmitis developing,¹⁸ we applied topical antibiotic after intravitreal therapy due to poor hygiene conditions of our patients.

The most important limiting factor is the retrospective design of our study. The low number of patients included in the current study is another limiting factor. Additionally, although an experienced retina specialist masked to visual acuity reviewed the images, the absence of a second grader may induce some bias in the measurements.

In conclusion, the present study showed the efficacy of aflibercept treatment in eyes with naive neovascular AMD. A significant anatomical and functional improvement was presented with as-needed treatment algorithm after three loading doses. Although this therapy algorithm increased our number of visits, it decreased the number of injections and, therefore, the cost of therapy and the complication of injections.

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