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Neovascular age-related macular degeneration: 18-month outcomes of aflibercept treatment in patients resistant to ranibizumab

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ABSTRACT

Objectives: Aim of this study is to investigate the effect of intravitreal aflibercept therapy in an 18-month period in patients with recurrent neovascular age-related macular degeneration resistant to intravitreal ranibizumab.

Methods: This is a prospective study of eyes with neovascular age-related macular degeneration switched to intravitreal aflibercept with at least 18 month of follow-up after the switch. All patients had had a minimum of 6 injections of ranibizumab before the switch. All patients received a loading dose of three intravitreal 2 mg aflibercept injections at 4-week intervals. Changes in best-corrected visual acuity, central macular thickness and the frequency of injections were compared.

Results: The study included 39 patients, each with one diseased eye. The studied eyes had received an average of 10.74 ± 4.38 previous intravitreal ranibizumab injections over a period of 28.31 ± 18.08 months. During the study, an average of 6.94 ± 2.58 intravitreal aflibercept injections were given in a period of 18 months. Mean central macular thickness at baseline, before switching to aflibercept, 6, 12, and 18 months after the aflibercept injection were 327.44 ± 120.57, 354.50 ± 127.79, 290.20 ± 112.25, 311.70 ± 119.47, and 299.29 ± 98.38 µm, respectively. A significant change was found in the macular thickness measured at intervals throughout the study. However, no significant improvement was found in visual acuity after 18 month after switching to aflibercept.

Conclusions: Switching from intravitreal ranibizumab, an inhibitor of vascular endothelial growth factor-A, to aflibercept, another inhibitor for such factors, has increased central macular thickness significantly without changes in visual acuity.

Keywords: age-related macular degeneration, aflibercept, ranibizumab, switch

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Age-related macular degeneration (AMD) is indicated as the leading cause of age-related severe vision loss in developed countries, especially in patients over 55 years [1]. Treatments involving the intravitreal administration of inhibitors of vascular endothelial growth factor-A (VEGF-A) have

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transformed the management of neovascular AMD (nAMD). Two such VEGF-A-inhibiting agents are ranibizumab (Lucentis®; Genentech, South San Francisco, CA, USA) and aflibercept (Eylea® ;Regeneron, Tarrytown, NY, USA). Both were approved by the United States Food and Drug Administration (FDA) for the treatment of various retinal diseases, the latter being the latest drug approved for the treatment of nAMD. Aflibercept is a recombinant protein produced by fusion of the VEGF-binding sequences of human VEGF receptors 1 and 2 along with the Fc backbone of human immunoglobulin G1 (IgG1) [2]. Aflibercept binds and inhibits the VEGF-A and VEGF-B isoforms as well as the placental growth factor, which is another member of the VEGF family, although binding of ranibizumab is restricted to VEGF-A isoform (2). In addition, aflibercept was reported to have a significantly higher binding affinity for VEGF compared to ranibizumab and bevacizumab, another such agent that had not been yet approved by the FDA but used off-label to treat retinal diseases [3]. Several studies have shown that anatomic response for ranibizumab and bevacizumab in n-AMD can be reduced over time, a phenomenon known as tolerance, tachyphylaxis, or resistance [4]. In this study, we aimed to investigate the efficacy of intravitreal aflibercept (IVA) in patients with nAMD who had been previously treated with intravitreal ranibizumab (IVR) but developed resistance to treatments. We have switched to and applied an 18-month aflibercept treatment, evaluating the changes in patients central macular thickness (CMT) along with their visual acuity in the course of treatment.

METHODS

The study adhered to the Declaration of Helsinki, and obtained exemption from full review by the local ethics committee. This is a prospective study of eyes with neovascular age-related macular degeneration switched to intravitreal aflibercept with at least 18 month of follow-up after the switch.All patients had had a minimum of 6 injections of ranibizumab before the switch. All patients received a loading dose of three intravitreal 2 mg aflibercept injections at 4-week intervals. Changes in best-corrected visual acuity (BCVA), central macular thickness (CMT) and the frequency of injections were compared.

Inclusion criteria were as follows: persistent intraretinal or subretinal fluid, at least six consecutive monthly injections with ranibizumab, and last injection of ranibizumab within one month of switching to aflibercept. We recorded demographic data, the total number of intravitreal ranibizumab injection, the time since initiation of anti-VEGF therapy, the interval between the last intravitreal ranibizumab injection and the first aflibercept injection.

All patients received a loading dose of three monthly aflibercept injections (2 mg/0.05 ml) and were followed up monthly. Retreatment with a single aflibercept injection was performed according to any of the following: visual acuity loss of at least five letters, with optical coherence tomography (OCT) evidence of fluid in the macula; persistent or recurrent intraretinal or subretinal fluid on OCT; new subretinal hemorrhage from choroidal neovascularization (CNV).

Fundus fluorescein angiography and indocyanine green angiography-ıf nessesary-were performed at the baseline visittoconfirmthe presence of AMD-related CNV and to exclude potential masquerade lesions such as polypoidal vasculopathy. At each visit, a full ophthalmic examination, including BCVA and IOP (intraocular pressure) assessment with Goldman applanation tonometry, spectral-domain optical coherence tomography (Heidelberg Spectralis; Heidelberg Engineering, Heidelberg, Germany) measurement of both eyes were conducted.

Statistical Analysis

All statistical analysis was performed using Statistical Package for the Social Sciences (SPSS) software (v22.0 for Windows; SPSS Inc., Chicago, IL, USA). Visual and anatomical outcomes comparing mean values was conducted by two-sample, two-sided t test. Statistical significance was defined as $p < 0.05$.

RESULTS

The study included 39 patients, each with one diseased eye. Throughout the study, the patients were given intravitreal injection of 2 mg/0.05 mL

Table 1. Desciriptive characteristics of the patient cohort at baseline

Characteristics	Data of the patients (n = 39)
Age, years (mean ± SD, range)	72.20 ± 7.14 (59-86)
Gender distribution, male / female n (%)	17 (44) / 22 (56)
Follow-up before switch, months (mean ± SD, range)	28.31 ± 18.08 (8-67)
Number of ranibizumab injections previous swicth (mean ± SD, range)	10.74 ± 4.38 (6-23)
BCVA, log MAR (mean ± SD)	0.98 ± 0.62
CMT (mean ± SD)	327.44 ± 120.57

BCVA = best-corrected visual acuity, CMT = central macular thickness, SD = standard deviation

aflibercept to the diseased eye to replace the ranibizumab injections. The mean age was 72.20 ± 7.14 years (range; 59-86 years). Of the patients, 22 were women and 17 were men. At enrollment, study eyes had an average of 10.74 ± 4.38 previous IVR injections over a period of 28.31 ± 18.08 months (range; 8-67 months).

The mean number of IVA injections during 18 months was 6.94 ± 2.58. At baseline, CMT was 327.44 ± 120.57 µm and best-corrected visual acuity (BCVA) was 0.98 ± 0.62 logMAR log of the Minimum Angle of Resolution) (Table 1). Before switching to aflibercept, CMT was 354.50 ± 127.79 µm and BCVA was 1.02 ± 0.49 logMAR. Mean CMT 6, 12, and 18 months after the aflibercept injection were 290.20 ± 112.25, 311.70 ± 119.47, and 299.29 ± 98.38 µm, respectively (Table 2). A significant difference in CMT was found between the visits (p = 0.02). The CMT was significantly lower at 6 months and 18 months after switching to aflibercept than that before switching ($p < 0.01$ and p = 0.04, respectively). Mean BCVA values 6, 12, and 18 months after the aflibercept injection were 0.87 ± 0.46, 0.97 ± 0.50, and 0.97 ± 0.50 logMAR, respectively (Table 2). No significant improvement in visual acuity was found in the 18-month period after switching to aflibercept (p = 0.59). No serious ocular and systemic side effects were reported during the 18-month period.

Table 2. Mean central macular thickness and best-corrected visual acuity

	CMT (mean ± SD)	BCVA (mean ± SD)
At baseline	327.44 ± 121.20	0.98 ± 0.62
Before switch	354.50 ± 127.79	1.02 ± 0.49
Six months after switch	290.2 0 ± 112.25	0.87 ± 0.46
Twelve months after switch	311.70 ± 119.47	0.97 ± 0.50
Eighteen months after swicth	299.29 ± 98.38	0.97 ± 0.50
p values	**0.02**	0.59

SD = standard deviation

DISCUSSION

In this prospective study, we investigated the anatomic and functional response to aflibercept treatment in patients with refractory nAMD after switching from intravitreal ranibizumab to aflibercept injection. Several studies have reported treatment outcomes after switching to aflibercept from other drugs [5-7].

Cho *et al*. [8] reported that the CMT was reduced from 295 µm to 274 µm through an average of 4.4 aflibercept injections over a period of 6 months. Grewal *et al*. [9] found that the initial CMT of 329 µm decreased to 292 µm through an average of 10.2 ± 1.2 aflibercept injections over a period of 12 months. Bakall *et al*. [10] reported that the CMT was reduced by 65 mm after 3 injections with no significant change in visual acuity. In our study, the average number of IVR injections before switching to aflibercept was 10.74. All of the patients were found to have persistent

subfoveal subretinal and/or intraretinal fluid in the diseased eye despite multiple injections.

In our study, the average CMT value of 349.97 ± 122 μm before switching to aflibercept was decreased to 299.29 ± 98.38 μm in the course of 18-month treatment. The results demonstrate that switching to aflibercept provided significant improvements in CMT, which were maintained during the longer follow-up periods up to 18 month.

Comparison of anatomical results showed that switching from ranibizumab to aflibercept delivered a significant decrease in CMT. Molecular and pharmacological characteristics of aflibercept might have contributed to improved outcomes [11]. Aflibercept was known to have a higher binding affinity for VEGF-A compared to ranibizumab or bevacizumab. In addition, it also binds and inhibits VEGF-B and placental growth factor, which were shown toinfluence neovascularization [12]. Our study provides evidence that there is a significant anatomical effect, resulting in decreased CMT after switching. Our study also indicated a modest improvement in BCVA after switching to aflibercept, albeit not significant. Significant foveal photoreceptor loss and development of subretinal scarring at an earlier stage of the disease might have contributed to the divergent results in terms of the anatomic improvement and functional outcome.

Limitations

Limitations of the current study include small sample size.

CONCLUSION

In conclusion, switching to aflibercept produced a significant decrease in central macular thickness after 6, 12, and 18 months. However, there was no significant change in visual acuity.

Conflict of interest

The authors disclosed no conflict of interest during the preparation or publication of this manuscript.

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