Short-Term Outcomes of Aflibercept in Bevacizumab-Resistant Neovascular Age-Related Macular Degeneration

Özlem Bursalı[1], Emine Doğan[1], Kübra Özata Gündoğdu[1], İsa Yuvacı[1]

ABSTRACT

Purpose: To evaluate the short-term anatomical and functional outcomes of aflibercept in patients with neovascular age-related macular degeneration (nAMD) who showed an inadequate response to bevacizumab.

Methods: This retrospective study included 33 eyes with nAMD that were switched to aflibercept after an inadequate response to bevacizumab. Best-corrected visual acuity (BCVA), fundus biomicroscopy, and optical coherence tomography (OCT) findings were assessed at baseline (E1), after the third bevacizumab injection (E2), and one month after the first aflibercept injection (E3). Changes across visits were analyzed, and factors associated with final visual acuity were evaluated using multivariable linear regression.

Results: BCVA was 0.84 ± 0.63, 0.93 ± 0.76, and 0.80 ± 0.71 logMAR at E1, E2, and E3, respectively, with no significant change across visits. Mean central macular thickness (CMT) was 538.7 ± 166.6 µm at E1, 559.7 ± 248.6 µm at E2, and 465.0 ± 202.4 µm at E3, demonstrating a significant reduction following the switch to aflibercept (E2 vs E3, p = 0.007). The prevalence of subretinal fluid decreased significantly from 54.5% at baseline to 21.2% at E3 (p = 0.016). Multivariable regression identified older age (β = 0.342, p = 0.038) and poorer baseline BCVA (β = 0.411, p = 0.015) as independent predictors of worse final visual outcomes.

Conclusion: Aflibercept provided significant short-term anatomical improvement, including reductions in CMT and subretinal fluid, but did not result in significant visual acuity improvement during follow-up. These findings suggest that aflibercept may be an effective option for nAMD patients who are unresponsive to bevacizumab.

Keywords: Aflibercept, bevacizumab, anti-VEGF, neovascular age-related macular degeneration, bevacizumab resistance

INTRODUCTION

Neovascular age-related macular degeneration (nAMD) is a leading cause of irreversible blindness and visual impairment in the elderly population in developed countries.[1] With increasing global life expectancy and lifestyle changes, the prevalence of AMD is expected to rise.

The intravitreal injection of anti-vascular endothelial growth factor (anti-VEGF) agents, which commonly include ranibizumab (Lucentis®), aflibercept (Eylea®), and off-label bevacizumab (Avastin®), can prevent visual loss or improve vision in nAMD.[2] However, the lack of priority reimbursement for ranibizumab and aflibercept significantly burdens patients financially in Turkey. The Turkish Social Security Institution (SSI) has set specific standards for reimbursement of these agents. In public healthcare institutions, the initial treatment protocol for nAMD consists of three intravitreal injections of bevacizumab (at 4–6-week intervals). If significant

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improvement is not achieved, patients become eligible for reimbursement of alternative anti-VEGF agents, upon approval by the Social Security Institution.

Some patients show a suboptimal response to bevacizumab, with persistent fluid on optical coherence tomography (OCT). Aflibercept may be advantageous due to its broader cytokine targeting and higher binding affinity. Unlike bevacizumab and ranibizumab, it binds not only VEGF-A but also VEGF-B and PlGF. Several studies suggest that aflibercept may benefit patients who are refractory to bevacizumab.[3-5]

This study aims to evaluate the short-term anatomical efficacy and OCT changes of aflibercept in nAMD patients who are unresponsive to three consecutive doses of bevacizumab, and to investigate factors associated with final visual acuity outcomes.

MATERIALS AND METHODS

This retrospective study included data from patients with nAMD who had previously been treated with bevacizumab and then switched to aflibercept at Sakarya Education and Research Hospital between January 2020 and September 2023. Prior approval was obtained from the Institutional Review Board (IRB) (IRB number: E-71522473-050.01.04-300122_322), and written informed consent was obtained from all patients. The study was performed in adherence to the Declaration of Helsinki.

Patients with prior ocular surgery or systemic/ocular diseases such as glaucoma, diabetic retinopathy, retinal vein occlusion, uveitis, degenerative myopia, or angioid streaks were excluded.

All eyes were initially evaluated for the presence and subtype of macular neovascularization using multimodal imaging. During retrospective review, only a very limited number of eyes were identified as having Type 3 macular neovascularization while also meeting the study criterion of resistance to the initial three loading doses of intravitreal anti-VEGF therapy. Given the small sample size and the distinct pathophysiological and clinical characteristics of Type 3 lesions, these eyes were excluded from the final analysis to avoid additional cohort heterogeneity. Those with RPE tears or dense cataracts affecting OCT image quality were also excluded.

Patients diagnosed with nAMD confirmed by Fundus Fluorescein Angiography (FFA) (Canon CX-1, Tokyo, Japan) and OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA, USA) underwent a detailed ophthalmologic examination, including best-corrected visual acuity (BCVA), anterior and posterior segment findings, and intraocular pressure measurements at baseline and at each follow-up visit. The BCVA values were converted to the logarithm of the minimum angle of resolution (logMAR).

OCT imaging was performed at each clinic visit using a Cirrus HD-OCT to evaluate macular changes. Cirrus HD-OCT images were generated using the Macular Cube 512 × 128 scan. Each image had 5 µm axial and 10 µm transverse resolutions in tissue and consisted of a 512 × 128 volume cube. The scanning area measured 6 × 6 mm, and the cube was composed of 128 horizontal examination lines of 512 A-scans each. The scanning speed was 27,000 A-scans per second. The 1 mm central retinal thickness area is described as the central macular thickness (CMT) in the current study.

In this study, the maximal distance between the outer border of the RPE and the inner border of Bruch's membrane, measured in µm using the software ruler tool on the OCT image, was quantified and termed the pigment epithelium detachment (PED) height. Depending on their location, the presence or absence of fluid, observed as hyporeflective lesions on OCT was recorded as intraretinal, subretinal, or sub-RPE.

Subretinal hemorrhage was defined as blood accumulation between the neurosensory retina and the RPE from choroidal or retinal vessels. Type 1 choroidal neovascularization (CNV) involved occult leakage beneath the RPE, while Type 2 CNV was located above the RPE in the subretinal space.

All patients received a loading course of three consecutive intravitreal bevacizumab (IVB) injections (1.25 mg/0.05 mL) at regular intervals of 4–6 weeks. After the loading phase, persistent or recurrent subretinal fluid (SRF) and/or intraretinal fluid (IRF) presence on OCT and/or a CMT > 250 µm were considered evidence of an inadequate response to bevacizumab treatment. In patients with an inadequate response, treatment was switched to intravitreal aflibercept (2 mg/0.05 mL) 4–6 weeks after the last bevacizumab injection.

Detailed ophthalmic examinations and OCT scans were conducted at three time points: at the initial visit (E1), one month after completing three consecutive bevacizumab injections (E2), and one month after switching to the aflibercept treatment (E3). We compared and analyzed the measurements obtained from these three examinations. We also analyzed the factors associated with the final BCVA, including patient demographics (age, gender); CNV types; the presence of SRF, IRF, and PED; subretinal hemorrhage; CMT; and PED height.

The Statistical Package for the Social Sciences (SPSS Inc., Chicago, IL, USA) version 21.0 software was used for statistical analysis. The distribution of continuous variables was assessed using the Shapiro–Wilk test. Central macular thickness (CMT) values demonstrated normal distribution across all examination time points ($p > 0.05$). Longitudinal changes in continuous variables were evaluated using repeated-measures analysis of variance (ANOVA). Mauchly's test was used to assess the assumption of sphericity, and when this assumption was violated, Greenhouse–Geisser correction was applied. Although BCVA values showed mild deviation from normality due to low-vision outliers, parametric methods were considered appropriate given the robustness of repeated-measures ANOVA to moderate deviations from normality. Categorical variables were analyzed using Cochran's Q test for overall comparisons across the three examination time points, followed by McNemar exact tests for pairwise comparisons when appropriate. To identify factors independently associated with final visual acuity, a multivariable linear regression analysis was performed. Due to the limited sample size and the risk of model overfitting, only clinically relevant baseline variables (age, baseline BCVA, and baseline CMT) were included in the final regression model. Post hoc pairwise comparisons were adjusted using the Bonferroni correction. A p-value < 0.05 was considered statistically significant.

RESULTS

The study included 33 eyes of 33 patients (22 males and 11 females) with a mean age of 74.00 ± 6.41 (65–87) years. The right eye was involved in 51.5% of patients (n = 17), and the left eye in 48.5% (n=16). Systemic hypertension was the most common comorbidity. The study included 12 patients (36%) with Type 1 CNV and 21 (63%) with Type 2 CNV.

The mean BCVA (logMAR) was 0.84 ± 0.63 at E1, 0.93 ± 0.76 at E2, and 0.80 ± 0.71 at E3 (Figure 1). The observed changes in BCVA were not statistically significant. Similarly, there were no significant changes in the intraocular pressure measurements (Table 1).

The mean CMT was 538.71 ± 166.60 µm at E1, 559.72 ± 248.63 µm at E2, and 465.00 ± 202.43 µm at E3 (Figure 2). The change in CMT between baseline and post-bevacizumab measurements was not significant; however, a significant reduction was observed after switching from bevacizumab to aflibercept (E2 vs E3, Greenhouse–Geisser corrected $p = 0.007$).

At the initial examination, SRF was observed in 18 patients (54.5%), in 14 patients (42.4%) after three bevacizumab injections, and in seven patients (21.2%) after one aflibercept injection (Table 1). Pairwise post hoc comparisons verified that the reduction in SRF prevalence was statistically significant between baseline and post-aflibercept evaluations (McNemar test, $p = 0.016$).

At E1, E2 and E3 examinations, the rates of IRF presence were 27.3% (nine patients), 27.3% (nine patients), and 18.2% (six patients), respectively. There were no significant differences among the groups.

The mean PED height was 295.48 ± 252.31 µm at the baseline. This decreased to 253.43 ± 246.17 µm after three bevacizumab injections and 230.41 ± 194.33 µm after one aflibercept injection. This decrease was not significant ($p = 0.439$).

The presence of subretinal hemorrhage was observed in 12 patients (36%) at E1 and in four patients (12%) at E2 ($p = 0.008$). At E3, there were three (9%) patients with subretinal hemorrhages. Significant reductions in subretinal hemorrhage prevalence were observed between E1 and E2 ($p=0.008$) and between E1 and E3 ($p=0.004$), whereas no significant change was found between E2 and E3 ($p=1.000$).

To identify clinical parameters independently associated with 4-month final BCVA, a multivariable linear regression model was executed. Multivariable regression identified advanced age ($\beta= 0.342$, $t = 2.21$, $p = 0.038$) and poorer

baseline BCVA (β = 0.411, t = 2.64, p = 0.015) as significant independent predictors of higher 4-month logMAR values (poorer visual preservation). Baseline anatomical metrics, including CMT (p = 0.279) and PED height (p = 0.469), demonstrated no independent statistical association with short-term functional outcomes.

In addition to the multivariable model, 4-month final BCVA outcomes were compared across different demographic, clinical, and anatomical subgroups. Although final logMAR BCVA tended to be lower (better clinical vision) in patients with Type 1 CNV (0.51 ± 0.19) compared to Type 2 CNV (0.87 ± 0.77), this group variance did not cross the threshold of statistical significance in our cohort (p = 0.731). Similarly, no statistically significant differences in 4-month visual outcomes were observed based on gender (p = 0.836), presence or absence of SRF (p > 0.05), or IRF (p > 0.05).

Table 1 presents the mean values and standard deviations for BCVA, CMT, and PED height, and their respective *p*-values. Additionally, it provides the number of eyes exhibiting or not exhibiting IRF, SRF, hemorrhage, and macular scar at each time points.

Table 1. *Longitudinal analysis of clinical and anatomical parameters across the three examination time points.*

Parameter	Baseline (E1)	Post-Bevacizumab (E2)	Post-Aflibercept (E3)	Overall p-value*	E1 vs E2 p-value†	E2 vs E3 p-value†	E1 vs E3 p-value†
BCVA (logMAR), (mean ±SD)	0.84±0.63	0.93 ±0.76	0.80 ±0.71	0.204[a]	0.512	0.384	0.615
CMT (µm, mean ±SD)	538.7±166.6	559.7 ± 248.6	465.0±202.4	0.007[a]*	1.000	0.007*	0.075
PED Height (µm, mean±SD)	295.5±252.3	253.4 ± 246.2	230.4±194.3	0.439[a]	0.910	0.620	0.312
SRF Presence, n(%)	18(54.5%)	14 (42.4%)	7 (21.2%)	0.004[b*]	0.508	0.180	0.016*
IRF Presence, n (%)	9 (27.3%)	9 (27.3%)	6 (18.2%)	0.453[b]	1.000	0.500	0.424
SRH Presence, n (%)	12 (36.4%)	4 (12.1%)	3(9.1%)	0.001[b*]	0.008*	1.000	0.004*
IOP (mmHg), (mean ±SD)	15.8 ±2.8	15.5 ±2.6	15.6 ±2.4	0.78[a]	0.890	0.920	0.910

E1: Baseline; E2: One month after three consecutive intravitreal bevacizumab injections; E3: One month after switching to the single dose of intravitreal aflibercept. BCVA: Best-Corrected Visual Acuity; CMT: Central Macular Thickness; PED: Pigment Epithelium Detachment; SRF: Subretinal Fluid; IRF: Intraretinal Fluid; SRH: Subretinal hemorrhage, IOP: Intraocular Pressure

*** Statistically significant at p < 0.05.**

[a] Calculated using Repeated Measures ANOVA with Greenhouse–Geisser correction for sphericity validation.

[b] Calculated using Cochran's Q test for multi-visit global categorical comparisons.

† Pairwise longitudinal post hoc comparisons are strictly Bonferroni-adjusted (paired t-test for continuous data and McNemar exact test for categorical variables).

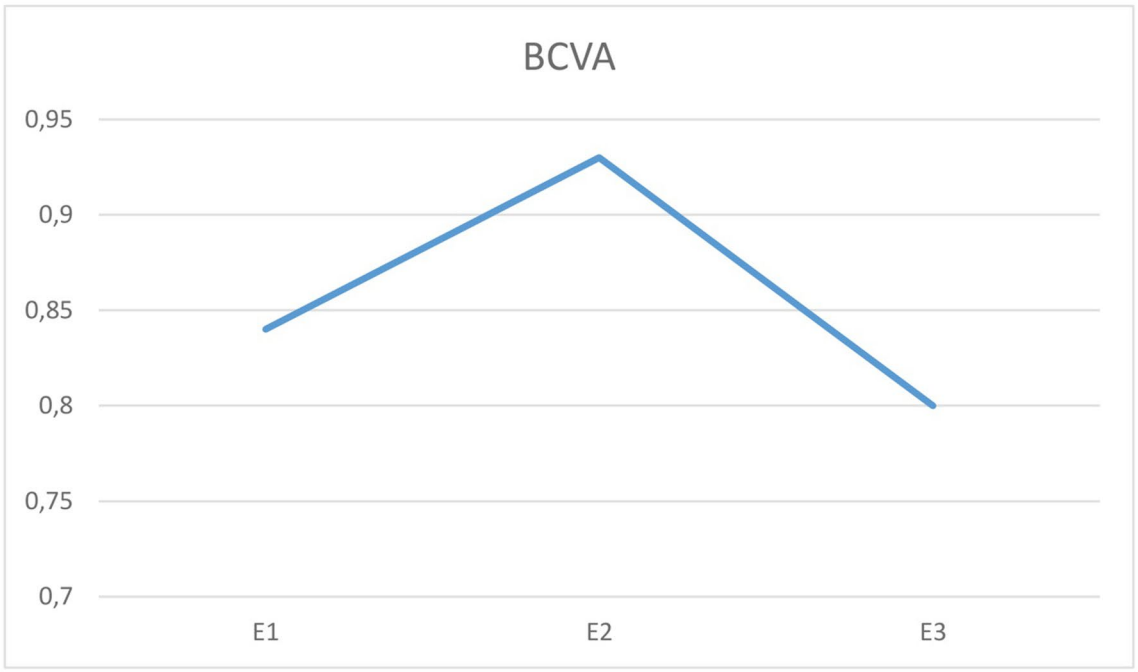

Figure 1: *Change in BCVA after anti-VEGF agents. E1: Baseline ; E2: One month after three consecutive bevacizumab injections; E3: One month after switch to aflibercept in bevacizumab-resistant cases. The change in BCVA was not significant (p = 0.204).*

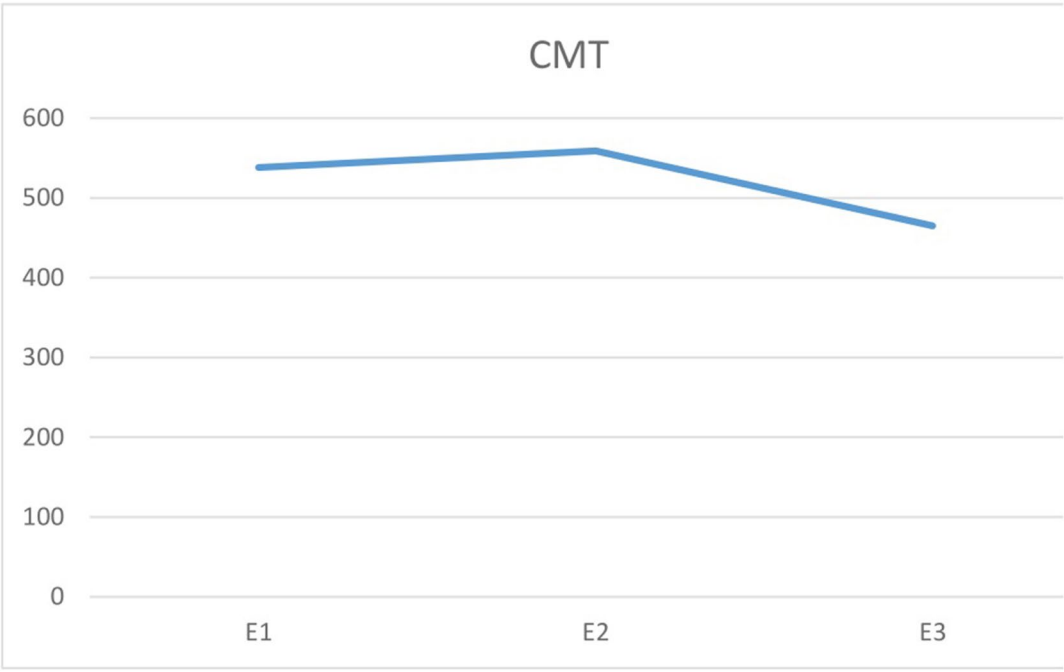

Figure 2: *Change in mean central macular thickness after intravitreal anti-VEGF agents. E1: Baseline ; E2: One month after three consecutive bevacizumab injections; E3: One month after switch to aflibercept in bevacizumab-resistant cases. A significant decrease in central macular thickness was observed after switching to aflibercept (p = 0.007).*

DISCUSSION

AMD leads to visual morbidity and blindness and has a significant impact on public health and economy. Presently, there is no cure, so the focus of pharmacological treatments is to slow down the disease's progression. Current approaches are relatively costly and require ongoing treatment. Bevacizumab is a potential treatment option, and the advantage of bevacizumab's cost–benefit profile compared to other treatment molecules benefits both the healthcare system and patients.

Various studies have reported that when comparing the effectiveness of bevacizumab with ranibizumab and aflibercept in this context, bevacizumab is not inferior to them, and all of these drugs have shown comparable effects on efficacy-related outcomes.[6–7] However, some patients exhibit a poor or no response to bevacizumab treatment.[8] The Comparison of Age-Related Macular Degeneration Treatments Trial (CATT) study found that 67.4% of eyes treated with monthly bevacizumab injections still had persistent fluid after two years.

Numerous studies have indicated that switching to aflibercept could offer potential advantages for patients who have shown an inadequate response to bevacizumab therapy. Cho et al. showed decreased central subfoveal thickness with a single dose of aflibercept treatment in patients with nAMD after an average of 20 regular injections of ranibizumab/bevacizumab.[3] The ASSESS study, a 12-month, prospective, interventional, single-arm study, showed a decrease in central subfoveal thickness and an improvement in visual acuity in patients who were unresponsive to three doses of anti-VEGF agents (ranibizumab/bevacizumab) and had been switched to aflibercept.[9]

In a recent meta-analysis of 28 studies, switching to aflibercept after inadequate response to bevacizumab/ranibizumab showed significant anatomical improvement. However, improvements in visual acuity were limited. The authors attributed this limitation to better baseline visual acuity and greater disease chronicity in the included patients.[5] In our study, we observed similar anatomical success rates; however, there was no significant improvement in BCVA. Disruption of the ellipsoid zone integrity may be one reason for the inadequate visual improvement.

In studies on AMD treatment with anti-VEGF therapy, better initial BCVA is associated with a better final BCVA.[10–13] In a study conducted in Sweden, patients with an initial BCVA > 20/63 had a 20% risk of having low BCVA after one or two years of treatment, compared to 60% in patients with low initial VA. The group with good initial BCVA was also younger than those with moderate or poor initial BCVA.[14] Clinical studies evaluating the predictors of visual acuity in the treatment of nAMD demonstrated that younger patients had better visual outcomes.[12,15,16]

In the ANCHOR study comparing ranibizumab and photodynamic therapy, younger patients had better final visual acuity.[12] According to the VIEW study, final BCVA was better than 20/40 in patients younger than 69.[15] Similarly, patients with better final BCVA were younger and had better initial vision in our study. Although previous studies have generally not demonstrated a significant relationship between AMD prognosis and gender, the CATT study showed a more significant letter gain (> 15 letters) in women.[14] There was no effect of gender on visual prognosis in our study.

Type 2 CNV may cause worse visual impairment than Type 1 CNV due to the lesion's location in the subretinal space and direct damage to the neurosensory retina.[17] The CATT study showed that patients with classic lesions had worse final BCVA at one year compared to those with occult lesions. Similarly, in the VIEW study, patients with Type 2 CNV had final VA worse than 20/200 at one year.[14] In our study, patients with Type 1 CNV demonstrated a clinically favorable final visual acuity trend (0.51 ± 0.19 logMAR) compared to those with Type 2 CNV (0.87 ± 0.77 logMAR); however, this cross-sectional variation did not reach the threshold of statistical significance ($p = 0.731$), likely due to our limited sample size.

SRF was observed in 18 patients (54.5%) at baseline, in 14 patients (42.4%) after three bevacizumab injections, and in seven patients (21.2%) after one aflibercept injection. In our study, there was a significant decrease in the percentage of eyes with SRF compared with baseline. While the detection of SRF on OCT has been a criterion for retreatment in nearly all major AMD studies, it has recently been hypothesized that a limited SRF leakage from the CNV complex may represent a mechanism to compensate for the reduced choriocapillaris perfusion of the outer retina

in advanced AMD.[18] Analysis of the two-year outcomes in the CATT study showed that the presence of residual SRF with a lower incidence of macular atrophy and better visual outcomes. [19] In the present study, while switching to aflibercept resulted in a highly significant anatomical reduction in SRF prevalence, presence or absence of residual SRF at 4 months showed no statistically significant association with the final visual acuity outcomes, indicating that short-term anatomical fluid resolution may precede functional visual recovery.

In the present study, at baseline, post-bevacizumab, and post-aflibercept examinations, the rates of IRF presence were 27.3% (nine patients), 27.3% (nine patients), and 18.2% (six patients), respectively. There were no significant differences among the groups. It is believed that damage to the outer retinal barrier and the tight connections of the outer limiting membrane contribute to the emergence of SRF.[20] Generally, the presence of IRF leads to a worse functional prognosis compared to SRF. In a study by Hamid et al., a significant decrease was observed in the percentage of eyes with IRF compared to baseline. Additionally, eyes with IRF were reported to have poorer vision compared to those without IRF.[21] In the current study, IRF had no significant effect on visual prognosis.

PED was observed in 62% of cases with neovascular AMD.[22] Its presence is known to result in a weaker response to anti-VEGF therapy.[23] This might be due to the deeper location of the RPE layer, impeding the drug's penetration into the subretinal space.[24–25] Previous studies have shown that aflibercept significantly reduces the height of PED by 12–33%.[22] Additionally, it has been shown to effectively reduce the dimensions of PEDs resistant to other anti-VEGF agents.[22,23,26,27] In their comperative study, Balaskas et al. concluded a more significant decrease in PED height with aflibercept treatment compared to ranibizumab treatment at month 3.[28] In the current study, there was also a reduction in PED height after switching to aflibercept, but the reduction was not significant. There was no correlation between PED height and final BCVA.

Although the prevalence of subretinal hemorrhage decreased significantly from baseline to the post-aflibercept visit, the presence of residual hemorrhage at the final visit demonstrated no independent statistical association with 4-month visual outcomes in our study. This is similar to the CATT study, which showed that the presence of clinical haemorrhage by itself is not associated with worse visual outcomes. However, the location (subfoveal), size (> 1 optic disc diameter), and duration of subretinal hemorrhage may be associated with poor visual outcomes.[29] The five-year CATT follow-up study showed that relatively larger subretinal haemorrhages over long-term observations also increased the risk of developing scarring. In subretinal hemorrhages, vision loss may occur due to scar formation and photoreceptor damage caused by iron toxicity.[30]

Our study's limitations include its retrospective, uncontrolled design. Our sample size was relatively small due to the Social Security Institution's strict treatment protocol. In cases of deviations from the scheduled injection timing, aflibercept is not reimbursed; furthermore, it could not be administered in some patients. Another important limitation of our study is the short total follow-up period of 4 months, which is insufficient to evaluate long-term visual acuity outcomes or definitive prognostic factors. Finally, the findings may not be fully representative of all CNVM subtypes and therefore may not be entirely generalizable to the broader neovascular AMD population.

Despite these limitations, our findings demonstrate the short-term effects of aflibercept use in nAMD patients who are non-responsive to bevacizumab treatment. Aflibercept resulted in a significant reduction in central macular thickness and a reduction in subretinal fluid in these patients. However, we did not observe a significant impact on visual acuity. These results suggest that even a single dose of aflibercept was associated with significant short-term anatomical improvement for nAMD patients who are non-responsive to bevacizumab therapy.

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Statistical analysis: Kübra Özata Gündoğdu

Obtaining funding: None

Supervision of administrative, technical, or material support: Özlem Bursalı, Kübra Özata Gündoğdu, Emine Doğan, İsa Yuvacı

Research group leadership: Özlem Bursalı

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