

Original research

# The outcomes of aflibercept therapy in patients with age-related macular degeneration resistant to bevacizumab or ranibizumab

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## Abstract

**Purpose:** This study was designed to assess the functional and anatomic outcomes of intravitreal aflibercept injection in patients with wet age-related macular degeneration (AMD) refractory to intravitreal bevacizumab or ranibizumab therapy.

**Methods:** This retrospective study included 43 eyes of 43 patients resistant to treatment with at least 6 injections of bevacizumab or ranibizumab. Persistent intraretinal and subretinal fluid (IRF and SRF) on optical coherence tomography (OCT), no improvement in best corrected visual acuity (BCVA), and a central macular thickness (CMT) increase of more than 100  $\mu\text{m}$  due to SRF and/or IRF compared to baseline for at least 6 monthly intravitreal bevacizumab or ranibizumab injections were defined as resistant to bevacizumab/ranibizumab therapy. BCVA, intraocular pressure (IOP), CMT, maximum retinal thickness (MRT), and maximum pigment epithelial detachment (PED) height (MPEDH) were evaluated before and after aflibercept injections.

**Result:** After initiating aflibercept treatment, the mean final BCVA logarithm of the minimum angle of resolution or recognition (logMAR) improved to  $0.84 \pm 0.59$  which was statistically significant compared to baseline ( $1.14 \pm 0.51$ ), ( $P < 0.001$ ). After aflibercept injection, statistically significant reduction was noted in mean CMT ( $402.6 \pm 196.7 \mu\text{m}$  vs  $264.2 \pm 52.85 \mu\text{m}$ ,  $P < 0.05$ ), MRT ( $435.3 \pm 195.2 \mu\text{m}$  vs  $282.2 \pm 31.8 \mu\text{m}$ ,  $P < 0.05$ ), and MPEDH ( $154.2 \pm 86.0 \mu\text{m}$  vs  $68.3 \pm 70.6 \mu\text{m}$ ,  $P < 0.05$ ). There was no correlation between the total number of previous injections and the increase of BCVA ( $r = -0.10$ ,  $P = 0.265$ ). The decrease of mean IOP was statistically significant under aflibercept treatment ( $P < 0.001$ ).

**Conclusions:** The present study showed the efficacy of aflibercept treatment in eyes with persistent retinal or SRF under bevacizumab or ranibizumab therapy. A significant anatomical and functional improvement was noted.

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**Keywords:** Age related macular degeneration; Aflibercept; Anti-vascular endothelial growth factor; Bevacizumab; Ranibizumab

## Introduction

Age-related macular degeneration (AMD) is the most important cause of vision loss in developed countries in populations over 65 years of age.<sup>1,2</sup> The prevalence of AMD in

individuals over 40 years old is estimated at 6.5%.<sup>3</sup> AMD is a chronic, degenerative condition characterised by the presence of choroidal neovascularization (CNV), retinal fluid accumulation, hemorrhage, and, eventually, retinal scarring.<sup>2</sup> CNV is the main cause of vision loss due to its rapidly progressive and destructive course.<sup>2</sup>

It was well known that intravitreal anti-vascular endothelial growth factor (VEGF) agents are the mainstay of the therapy for AMD in the last decade and have had a significant beneficial impact on patients with neovascular AMD.<sup>3–5</sup> On the other hand, some patients may have persistent SRF or IRF under anti-VEGF therapy. The Comparison of Age-Related

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Macular Degeneration Treatments Trial (CATT) showed that 51.5% of eyes treated with monthly ranibizumab and 67.4% of eyes treated with monthly bevacizumab injections had persistent fluid after 2 years.<sup>4</sup>

Aflibercept (Eylea; Regeneron, Tarrytown, New York, USA, and Bayer, Berlin, Germany) is a fusion protein with binding domains consisting of native VEGF receptors, approved for the treatment of CNV. Unlike other known anti-VEGF agents, aflibercept binds with high affinity to all VEGF-A and VEGF-B isoforms, as well as to placental growth factors 1 and 2.<sup>3</sup> Additionally, it is able to penetrate through all the retinal layers and under the retina pigment epithelium.<sup>6</sup> On the basis of a mathematical model, aflibercept maintains significant intravitreal VEGF-binding activity for 10–12 weeks after a single injection.<sup>7</sup> It was shown that intravitreal aflibercept dosed monthly or every 2 months after 3 initial monthly doses had similar efficacy and safety outcomes as monthly 0.5 mg ranibizumab.<sup>7</sup>

One of the most commonly used methods for patients with persistent fluid under bevacizumab or ranibizumab treatment is to switch anti-VEGF agents.<sup>8–11</sup> The aim of this study was to assess the functional and anatomic outcomes of intravitreal aflibercept injection in patients with wet AMD that was refractory to intravitreal bevacizumab or ranibizumab therapy.

## Methods

A retrospective non-comparative study was designed to evaluate the functional and anatomic outcomes of intravitreal aflibercept injection in patients with subfoveal CNV secondary to AMD refractory to intravitreal bevacizumab or ranibizumab therapy. We retrospectively reviewed the medical charts of patients treated with intravitreal anti-VEGF (bevacizumab-ranibizumab-aflibercept) for AMD from January 2014 to January 2017.

The study protocol was approved by the local ethics committee. The study was designed in accordance with the Declaration of Helsinki. Before administration of an intravitreal anti-VEGF injection, informed patient consent was taken from all patients about the side effects of the drug and its application.

Bevacizumab or ranibizumab treatment were performed in three monthly loading doses until complete resolution of fluid. After complete retinal dryness was achieved, therapy was applied in an as-needed algorithm, and patients were followed up with optic coherence tomography every 4 weeks. Recurrent activity was defined as the re-appearance of fluid on optic coherence tomography (in the intraretinal or subretinal compartments) 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.

Patients who had insufficient response to bevacizumab or ranibizumab and were switched to aflibercept treatment were included in this study. Persistent IRF and/or SRF on optical coherence tomography (OCT), deterioration of best corrected visual acuity (BCVA), or a central macular thickness (CMT)

increase of more than 100  $\mu\text{m}$  due to SRF and/or IRF compared to baseline for at least 6 monthly intravitreal bevacizumab or ranibizumab injections were defined as the insufficient response to bevacizumab/ranibizumab therapy.

Four inclusion criteria were defined for the study: 1) age 50 years or older and a wet AMD diagnosis; 2) application of at least 6 intravitreal bevacizumab or ranibizumab injections as a previous treatment; 3) at least 6 months of follow-up after switching to aflibercept therapy, and 4) absence of any other pathology which may cause macular edema or atrophy including uveitis, glaucoma, advanced diabetic retinopathy, and diabetic macular edema. Six exclusion criteria were defined for the study: 1) treatment with ocular procedures other than uncomplicated cataract surgery or Nd:YAG laser posterior capsulotomy; 2) history of photodynamic therapy; 3) presence of the other pathologies which may cause macular edema or CNV; 4) inadequate information about previous injections; 5) treatment with an anti-VEGF therapy other than aflibercept elsewhere during the study period; and 6) an entity of peripapillary CNV.

Aflibercept treatment (2 mg/0.05 cc) were applied every 8 weeks after three monthly loading doses until complete resolution of fluid. Patients with dry retina after aflibercept therapy were treated in an as-needed algorithm and were followed up with optic coherence tomography every 4 weeks. Retreatments were applied if patients experienced more than one line loss in the BCVA, registered an increase of more than 100  $\mu\text{m}$  in CMT or developed a new-onset macular hemorrhage. Patients with a follow-up shorter than 6 months under aflibercept treatment were excluded from the study.

Basic demographic information, data obtained by full ophthalmic examination at each visit including BCVA, slit-lamp examination, dilated fundus biomicroscopy examination, and applanation tonometry and the total number of bevacizumab, ranibizumab, and aflibercept injections were recorded from the medical charts of the patients. OCT and fundus fluorescein angiography (FA) data were also reviewed. Monthly analysis of BCVA, CMT, and intraocular pressure (IOP) was performed. The post aflibercept final values (post-Afli Final) refer to the final data obtained for each patient.

For the measurement of BCVA, the Early Treatment Diabetic Retinopathy Study (ETDRS) chart was used and converted to logMAR values. Biomicroscopic anterior segment examination was performed in all cases. IOP was measured with Goldmann applanation tonometer. Dilated fundus examination was performed with a 90 Diopter (D) lens after pupil dilation using 2.5% phenylephrine and 1% tropicamide.

OCT imaging was done the same OCT device (Optovue OCT, V 5.1, RTVue 100-2; Optovue, Fremont, CA, USA) after pupillary mydriasis. Low quality images were repeated. Only measurements that had a reliability index (signal strength) of 60 or higher were included. CMT, maximum retinal thickness (MRT), and maximum pigment epithelial detachment (PED) height (MPEDH) were evaluated by an experienced retina specialist (E.U.) before the first aflibercept injection and during each visit. CMT was defined as the distance between the internal limiting membrane (ILM) and Bruch membrane in the

1 mm central fovea. The maximum vertical distance between the ILM and Bruch membrane within an area 2000  $\mu\text{m}$  from the fovea was measured and named as the MRT. The distance between the outer border of the retinal pigment epithelium (RPE) and the inner border of the Bruch membrane in the area of CNV was named as the maximum height of the PED. The localization of PED was defined as foveal (within 500  $\mu\text{m}$  from the center of the fovea) and/or extrafoveal (CNV located within 501–2000  $\mu\text{m}$  from the fovea center). The evaluation of fluid was done by recording the location of the fluid (intra or subretinal). The other pathologic events such as vitreomacular traction (VMT), anomalous posterior vitreous detachment accompanied by anatomic distortion of the fovea, was also assessed on OCT scans. Any increased reflectivity of the choroid on OCT due to loss of outer retinal layers and pigment epithelium within 2000  $\mu\text{m}$  of the fovea was defined as atrophy. One horizontal and one vertical scan in addition to raster scans cutting through the fovea were used to determine all anatomic parameters. Fundus FA was also conducted at the time of the treatment switch, and repeated when needed during the aflibercept treatment.

All injections were applied in an operating room under topical anesthesia obtained by 0.5% proparacaine hydrochloride (Alcaine; Alcon). After povidone-iodine solution (5%) was used for irrigation of conjunctiva, anti-VEGF agent (repackaged 1.25 mg/0.05 ml bevacizumab- 0.5 mg/0.05 ml ranibizumab- 2 mg/0.05 ml aflibercept) injection was performed via the pars plana, 3, 4–5 mm posterior to limbus using a syringe with 30 gauge needle. After the procedure, moxifloxacin eye drop (Vigamox; Alcon, USA) was used 4 times daily for 5 days. IOP measurement was performed by the same person (E.U.) with Goldmann applanation tonometer before injection, the first day after injection, and at first week and first month visit. Baseline IOP was defined as the pre-aflibercept injection mean IOP for two consecutive visits before the first injection of aflibercept and the final IOP was defined as the mean IOP for two consecutive visits measured at first week and at first month after the last injection of aflibercept.

Statistical Package for the Social Sciences (SPSS) version 20.0 software (IBM, New York, USA) was used for all statistical analyses. Descriptive statistics are presented as minimum, maximum, and mean  $\pm$  standard deviation. The normality was checked using the Kolmogorov-Smirnov test. Wilcoxon signed rank test and paired samples *t*-test were used for paired samples. Pearson correlation analysis was used to show the linear correlation between to variables.  $P < 0.05$  was considered statistically significant.

## Results

One thousand three hundred medical charts of patients who were diagnosed with AMD were reviewed. There were 2 eyes involved in 4 patients. One random eye of these patients was taken into the study. Nine patients treated with aflibercept were excluded from the study because their follow-up period was shorter than 6 months. Forty-three eyes of 43 patients

fulfilled the inclusion criteria and were analyzed in this study. The demographic characteristics of patients at the time of switching to aflibercept treatment and the mean follow-up time before and after aflibercept of patients are shown in Table 1. Forty-three eyes of 43 patients were analyzed in the first 6 months, 38 eyes of 38 patients in nine months, and 23 eyes of 23 patients in 12 months.

The mean BCVA (logMAR) was  $1.14 \pm 0.51$  prior to the treatment switch to aflibercept. At the final examination after initiation of aflibercept treatment, the mean final BCVA (logMAR) increased to  $0.84 \pm 0.59$ , which was statistically significant when compared to the baseline values (Table 2), ( $P < 0.0001$ ). The monthly follow-up of BCVA is shown in Table 2. The mean BCVA significantly improved over the baseline values at all visits except for the first-month visit.

In total, 21 eyes of 43 (48.8%) patients gained 1 or more line at the last follow-up. Six eyes of 43 (13.9%) patients gained 3 or more lines at the last follow-up. By contrast, 14 (32.5%) eyes showed no improvement in visual acuity although the mean CMT decreased in 12 of these 14 eyes with stable visual acuity. The remaining 8 (16.6%) eyes lost one line. There is no correlation between the total number of previous injections and the increase of BCVA, ( $r = -0.10$ ,  $P = 0.265$ ).

At final examination 37 (86%) eyes were without any SRF or IRF. The mean CMT was  $402.6 \pm 196.7 \mu\text{m}$  (142–861  $\mu\text{m}$ ) before initiating treatment with aflibercept. In the final examination following aflibercept therapy, the mean final CMT decreased to  $264.2 \pm 52.85 \mu\text{m}$  (165–400  $\mu\text{m}$ ), which was statistically significant when compared to the baseline CMT ( $P < 0.0001$ ) (Table 2). Monthly follow-up CMT measurements are shown in Table 2, and the analysis of CMT values belonging to different follow-up periods are summarized in Fig. 1. The CMT decreased in 39 of 43 eyes (90.6%) and increased in 2 eyes after 5 aflibercept injections. The BCVA did not improve in patients with increased CMT.

There is no correlation between the total number of previous injections and the decrease of CMT, ( $r = 0.009$ ,  $P = 0.962$ ). The monthly follow-up of MRT and MPEDH are shown in Table 2. Both were decreased significantly after the aflibercept treatment had started. The analysis of both is summarized in Fig. 1.

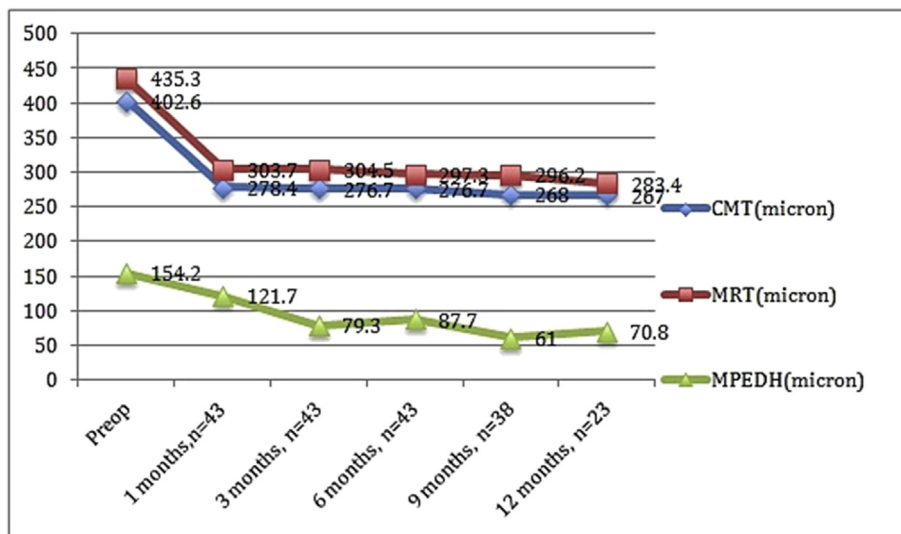
Table 1  
Demographic characteristics.

Parameters	Values	Range
Mean age (year)	$71.3 \pm 11.1$	47–84
Patients/eye (6 months)	43/43	
Patients/eye (9 months)	38/38	
Patients/eye (12 months)	23/23	
Female/male	13/30	
Mean follow-up time (months)	$41.6 \pm 25.4$	11–81
Mean follow-up after aflibercept	$13.2 \pm 2.03$	6–20
Mean number of previous injections	$9.14 \pm 5.07$	6–28
Mean number of aflibercept injections	$3.78 \pm 1.06$	3–6
Phakia/pseudophakia	32/15	
History of glaucoma	2	
Diabetic retinopathy	2	

**Table 2**  
Comparison of the Mean best corrected visual acuity (BCVA) (logMAR), central macular thickness (CMT), maximum retinal thickness (MRT), maximum pigment epithelial detachment height (MPEDH), and intraocular pressure (IOP) (mmHg) values at the beginning of the aflibercept therapy and follow-up months.

Parameters	PreAfli	PostAfli 1. M	PostAfli 3. M	PostAfli 6. M	PostAfli 9. M	PostAfli 12. M	PostAfli Final
BCVA (logMAR), Mean ± SD (Min–Max) n:43	1.15 ± 0.51 (0.3–2.0)	1.06 ± 0.41 (0.2–2.0)	0.87 ± 0.51 (0.2–1.3)	0.85 ± 0.43 (0.0–1.3)	0.91 ± 0.52 (0.0–2.0)	0.85 ± 0.50 (0.0–2.0)	0.84 ± 0.59 (0.0–2.0)
CMT, µm Mean ± SD (Min–Max) n:43	402.6 ± 196.7 (142–861)	278.4 ± 43.2 (225–378)	276.7 ± 47.9 (202–400)	263.0 ± 34.3 (201–322)	268.1 ± 30.6 (209–321)	267.6 ± 30.7 (202–322)	264.2 ± 52.85 (165–400)
MRT, µm Mean ± SD (Min–Max) n:43	435.3 ± 195.2 (256–831)	303.7 ± 49.6 (234–433)	304.5 ± 44.8 (232–407)	297.3 ± 45.9 (211–398)	296.2 ± 32.9 (242–345)	283.4 ± 32.7 (231–328)	282.2 ± 31.8 (231–318)
MPEDH, µm Mean ± SD (Min–Max) n:28	154.2 ± 86.0 (45–313)	121.7 ± 96.8 (0–308)	79.3 ± 89.8 (0–250)	87.7 ± 89.5 (0–232)	61.0 ± 70.9 (0–148)	70.8 ± 71.3 (0–122)	68.3 ± 70.6 (0–122)
IOP, mmHg Mean ± SD (Min–Max) n:43	16.35 ± 2.55 (11–20)	16.33 ± 2.42 (11–20)	16.28 ± 2.36 (11–20)	16.25 ± 2.31 (11–20)	16.10 ± 2.31 (11–20)	16.18 ± 2.22 (11–20)	16.08 ± 2.12 (12–19)
		<i>P</i> *:0.09 n:43	<i>P</i> *:0.005 n:43	<i>P</i> *:0.001 n:43	<i>P</i> *:0.001 n:38	<i>P</i> *:0.001 n:23	<i>P</i> *:0.001 n:43
		<i>P</i> *:0.008 n:43	<i>P</i> *:0.023 n:43	<i>P</i> *:0.021 n:43	<i>P</i> *:0.031 n:38	<i>P</i> *:0.023 n:23	<i>P</i> *:0.001 n:43
		<i>P</i> *:0.001 n:43	<i>P</i> *:0.001 n:43	<i>P</i> *:0.001 n:43	<i>P</i> *:0.001 n:38	<i>P</i> *: 0.001 n:23	<i>P</i> *: 0.001 n:43
		<i>P</i> *:0.038 n:28	<i>P</i> *:0.012 n:23	<i>P</i> *:0.044 n:22	<i>P</i> *:0.043 n:18	<i>P</i> *:0.041 n:8	<i>P</i> *:0.009 n:18
		<i>P</i> **:.01 n:43	<i>P</i> **:.01 n:43	<i>P</i> **:.006 n:43	<i>P</i> **:.001 n:38	<i>P</i> **:. 0.003 n:23	<i>P</i> **:. 0.001 n:43

BCVA: Best corrected visual acuity, CMT: Central macular thickness, MRT: Maximum retinal thickness, MPEDH: Maximum pigment epithelial detachment height, IOP: Intraocular pressure, Afli: Aflibercept, M: Month, n: Number of eyes, PostAfli Final: The post aflibercept final values, SD: Standard deviation. *P*\*: Wilcoxon signed rank test. *P*\*\*:. Paired samples *t*-test, (*P* < 0.05 indicates statistical significance according to Bonferroni adjustment).



**Fig. 1.** Mean central macular thickness (CMT), maximum retinal thickness (MRT), and maximum pigment epithelial detachment height (MPEDH) at the onset of switching to aflibercept treatment and follow-up.

At the beginning of aflibercept treatment, 15 (34.8%) of 43 eyes had no PED. In total, 21 of the 28 PED were foveal (71.4%), and 8 were extrafoveal (28.6%). Of the 28 PED, 8 (28.5%) were serous, 8 (28.5%) were fibrovascular, and 12 (42.8%) were fibrous. At final examination (*postAfli Final*), 7 of 8 serous PED (87.5%) and 3 of 8 fibrovascular PED (37.5%) were completely dry, and PEDs were not associated with CME and or SRF. Though the height of 12 fibrotic PED decreased, it did not disappear. Twelve of the 18 PED were foveal (66.6%), and 6 were extrafoveal (33.3%). None of the

PEDs had any displacement. Twenty-five eyes (58.1%) were detected as dry and without PED. A disciform scar was determined by fundus examination in 16 eyes and foveal atrophy in 4 eyes. Four eyes with foveal scar also had epiretinal membrane, and 2 also had VMT.

After excluding patients with glaucoma, the mean baseline IOP of 16.35 ± 2.55 decreased to 16.08 ± 2.12 (12–19 mmHg). The decrease of mean IOP was statistically significant under aflibercept treatment (*P* = 0.001) (Table 2).



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

## Discussion

Intravitreal anti-VEGF therapy typically requires chronic and repeated administration to maintain its effect.<sup>12</sup> The chronic activity of the pathologic process may be an important cause that necessitates repeated injections. However, drug tachyphylaxis and the development of tolerance or an immune reaction to a component of the anti-VEGF solution have also been viewed as reasons for recurrent injections. Tachyphylaxis is defined as a rapidly decreasing response when drugs are used repeatedly. It eventually leads to no response to treatment even at high drug concentrations.<sup>13</sup> Nevertheless, if the medication is stopped for a period of time, efficacy can be increased.<sup>13</sup> Unlike tachyphylaxis, tolerance is characterised by a slow loss of efficacy caused by long-term drug application. In tolerance, the drug efficacy can be improved by using a higher dosage or applying shorter time intervals.<sup>13</sup> Keane et al.<sup>14</sup> first suggested a possible tachyphylactic response to ranibizumab in the treatment of neovascular AMD after investigating retinal morphology by OCT. Additionally, a possible tachyphylactic response to bevacizumab was presented after observing the decreased standardized OCT volumetric change index over time.<sup>15</sup> Gasperini et al. suggests that the majority of patients (81%) who develop tachyphylaxis to ranibizumab or bevacizumab may respond favorably to a change in the treatment regimen to another anti-VEGF drug.<sup>16</sup>

Aflibercept is a new agent that contains binding domains from native VEGF receptors. Unlike other anti-VEGF agents, aflibercept binds with high affinity to all VEGF-A and VEGF-B isoforms, as well as to placental growth factors 1 and 2.<sup>3</sup> In our study, after the first aflibercept treatment, the mean CMT, MRT, and MPEDH in the entire group decreased, and after the third aflibercept treatment, the mean BCVA improved. The improvement of BCVA continued throughout the mean 13-month follow-up.

There are studies evaluating aflibercept in patients with wet AMD showing inadequate response to bevacizumab and ranibizumab.<sup>9–11,17–20</sup> Consistently, an anatomical improvement was presented; however, not all studies showed a functional success.<sup>11,21</sup> One such study by Yonekawa et al.<sup>9</sup> investigated BCVA and retinal thickness in 102 eyes of 96 patients treated with aflibercept after developing an insufficient response to ranibizumab. They found that although CRT significantly decreased, BCVA remained stable. A significant improvement of CRT was detected in 91% of the patients. On the other hand, CRT remained unchanged in 9% of their patients. No cases of increased CRT were observed. Muftuoglu et al.<sup>11</sup> presented significant anatomical improvement following aflibercept therapy; however, only 32% of eyes gained 1 or more line in BCVA, which was not statistically significant. Unlike our study, their mean previous anti-VEGF injection number was 14 compared to 9 in our study, and their previous BCVA was 0.5 (Snellen), which was 0.05 (Snellen) in our study.<sup>11</sup> Similar to our study, Singh et al.<sup>22</sup>

showed significant improvement of BCVA in patients previously treated with an average of 9 anti-VEGF injections. Singh et al.<sup>22</sup> found that 84.6% of patients gained visual acuity with aflibercept treatment. Heussen et al.<sup>17</sup> studied 71 eyes of 65 patients with wet AMD resistant to intravitreal bevacizumab or ranibizumab therapy who were switched to aflibercept, and presented a 33% improvement in BCVA.

Similar to the results reported in the literature, we found that 21 of 43 eyes (48.8%) gained 1 or more lines in BCVA. We also found a significant reduction in CMT, which was decreased in 39 of 43 eyes (90.6%) at the final examination (*postAflibercept Final*). However, 12 of these 43 eyes had a reduction in CMT but showed no improvement in BCVA. Our opinion is that the long-term retinal damage due to the persistent presence of retinal fluid prevented any improvement in BCVA. Muftuoglu et al. also reported a significant anatomical improvement, but stable visual acuity,<sup>11</sup> and they suggested that the persistent SRF or IRF may have prevented visual improvement.<sup>11</sup>

The association between the PED type and the anti-VEGF treatment response has also been evaluated by many researchers. For example, Hoerster et al.<sup>18</sup> reported that serous PED is responsive to ranibizumab therapy, whereas fibrovascular PED is resistant. Inoue et al.<sup>23</sup> showed improvement in 100% of patients with serous or mixed-type PED versus only 67% of patients with fibrovascular PED. In the present study, the symptoms in 87% of the patients with serous PED and in 33% of those with fibrovascular PED completely disappeared. Conversely, although the height of the fibrous PED decreased, this PED persisted. Taken together, the results of the present study suggest that aflibercept treatment is an effective option for decreasing the PED height in a subset of eyes. Further studies are needed to evaluate PED width, type, and angiographic pattern to establish the relationship between the characteristics of PED and the treatment response in these resistant cases.

An interesting result of this study was the change in IOP. After excluding patients with glaucoma, we found a significant decrease of the mean IOP under aflibercept treatment (paired samples *t*-test,  $P = 0.0001$ ). Similarly, Rusu et al.<sup>24</sup> presented a significantly lower IOP in patients switched to aflibercept. They suggested that aflibercept may be a safer agent in patients previously treated with other anti-VEGF molecules.

The retrospective design of our study is the most crucial limiting factor. A single retina specialist treated all patients using the same OCT-guided pro re nata treatment algorithm and protocol. Even though an experienced retina specialist (E.U.) analyzed the images without any information of visual acuity, the absence of a second observer may cause some bias in the measurement of anatomic outcomes in the present study. Additionally, excluding the patients with a follow-up shorter than 6 months under aflibercept treatment may lead to a bias because patients not content with their treatment might be more prone to terminate the treatment than patients experiencing a successful treatment.

In conclusion, the present study showed the efficacy of aflibercept treatment in eyes with persistent retinal or SRF under bevacizumab or ranibizumab therapy. A significant

anatomical and functional improvement was presented in our study. We also suggested that aflibercept may have a lesser impact on IOP than the other anti-VEGF agents.

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