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Intravitreal Aflibercept Therapy in Intravitreal Bevacizumab/Ranibizumab Treatment-resistant Exudative Age-related Macular Degeneration

İntravitreal Bevacizumab/Ranibizumab Tedavisine Dirençli Eksüdatif Yaşa Bağlı Maküla Dejenerasyonunda İntravitreal Aflibercept Tedavisi

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ABSTRACT

Objectives: The objective of the study was to evaluate the functional and anatomical results of intravitreal aflibercept (IVA) in cases resistant to intravitreal bevacizumab (IVB)/ intravitreal ranibizumab (IVR) for exudative age-related macular degeneration (AMD).

Methods: Patients who did not have an increase in best-corrected visual acuity (BCVA) or intraretinal fluid (IRF)/ subretinal fluid (SRF) fluid regression despite at least three doses of IVB/IVR. The files of the patients were scanned and central macular thickness (CMT), presence of IRF/SRF, and height of pigment epithelial detachment (PED) were recorded before IVA, after 3 months of loading IVA, and 1 year after IVA and compared.

Results: A total of 31 patients with a mean age of 74.2±10.53 were included in the study. The mean BCVA, CMT, and PED heights before IVA were 0.52±0.31 LogMAR, 301.10±76.27 µm, and 130.81±73.72 µm, respectively. After three doses of IVA loading, mean BCVA, CMT, and PED heights were 0.51±0.28 LogMAR, 262.86±69.74 µm, and 96.00±57.66 µm, respectively. A significant decrease was found in CMT and PED height values compared to the results obtained before IVA (p=0.001 and p=0.006). In the 1- year of IVA, mean BCVA, CMT, and PED heights were 0.53±0.33 LogMAR, 257.61±92.05 µm and 95.61±66.67 µm, respectively. There was a significant decrease in CMT and PED values compared to the values obtained before IVA treatment (p=0.004 and p=0.04).

Conclusion: In exudative AMD patients resistant to IVB/IVR treatment, improvement in anatomical results is observed in the short and long term, while functional success is not affected by switch therapy.

Keywords: Aflibercept; age-related macular degeneration; bevacizumab; ranibizumab.

ÖZET

Amaç: Çalışmanın amacı, yaşa bağlı maküla dejenerasyonu nedeniyle uygulanan intravitreal bevacizumab/ranibizumab tedavisine dirençli olgularda intravitreal aflibercept uygulamasının fonksiyonel ve anatomik sonuçlarını değerlendirmektir.

Yöntem: En az üç doz intravitreal bevacizumab/ranibizumaba rağmen en iyi düzeltilmiş görme keskinliğinde (EİDGK) artış olmayan veya intraretinal/subretinal sıvıda gerileme olmayan hastalar çalışmaya alındı. Hastaların dosyaları tarandı ve santral maküla kalınlığı (SMK), intraretinal/subretinal varlığı ve pigment epitel dekolmanı (PED) yüksekliği intravitreal aflibercept öncesi, intravitreal aflibercept yüklemesinin üçüncü ayı ve intravitreal aflibercept sonrası birinci yıl kaydedildi ve sonuçlar karşılaştırıldı.

Bulgular: Yaş ortalaması 74,2±10,53 yıl olan toplam 31 hasta çalışmaya dahil edildi. İntravitreal aflibercept öncesi ortalama EİDGK, SMK ve PED yükseklikleri sırasıyla 0,52±0,31 LogMAR, 301,10±76,27 µm ve 130,81±73,72 µm idi. Üç doz in-

travitreal aflibercept yüklemesinden sonra ortalama EİDGK, SMK ve PED yükseklikleri sırasıyla 0,51±0,28 LogMAR, 262,86±69,74 µm ve 96,00±57,66 µm idi. İntravitreal aflibercept öncesi elde edilen sonuçlara göre SMK ve PED yükseklik değerlerinde anlamlı azalma tespit edildi (p=0,001 ve p=0,006). İntravitreal afliberceptin ilk yılında ortalama EİDGK, SMK ve PED yükseklikleri sırasıyla 0,53±0,33 LogMAR, 257,61±92,05 µm ve 95,61±66,67 µm idi. İntravitreal aflibercept tedavisi öncesi elde edilen değerlere göre SMK ve PED değerlerinde anlamlı azalma oldu (p=0,004 ve p=0,04).

Sonuç: İntravitreal bevacizumab/ranibizumab tedavisine dirençli eksüdatif yaşa bağlı maküla dejenerasyonu hastalarında kısa ve uzun dönemde anatomik sonuçlarda düzelme gözlenirken fonksiyonel başarı değişim tedavisinden etkilenmez.

Anahtar sözcükler: Aflibercept; yaşa bağlı maküla dejenerasyonu; bevacizumab; ranibizumab.

Age-related macular degeneration (AMD), the leading cause of blindness among older people, is a progressive and degenerative disease of the retina. Dry type AMD is characterized by drusen, pigment changes, or atrophy of the retinal pigment epithelium (RPE) and is treated with antioxidants.[1] Exudative type (neovascular) AMD is neovascularization originating from the choroidal vasculature and extending into the pigment epithelium or subretinal space.[2] Excessive secretion of vascular endothelial growth factor (VEGF), a proangiogenic cytokine, has been shown to be the main cause of choroidal neovascularization (CNV). In the case of ischemia, VEGF is released by astrocytes and Müller cells, initiating the neovascular process by stimulating endothelial cell proliferation and migration. With neovascularization, retinal and subretinal anatomy is disrupted; and bleeding, fluid accumulation, or fibrovascular tissue formation occurs.[2] CNV is the leading cause of vision loss due to its rapid progression and destructiveness.[3] The mainstay of treatment for exudative AMD is Intravitreal anti-VEGF agents. Bevacizumab (Avastin; Genentech, South San Francisco, CA) and Ranibizumab (Lucentis; Genentech, South San Francisco, CA) are the most commonly used anti-VEGFs in the treatment of exudative AMD and inhibit all isoforms of VEGF-A. Aflibercept (Eylea; Regeneron, Tarrytown, New York, USA, and Bayer, Berlin, Germany) binds to VEGF more potently, longer, and with higher affinity. Aflibercept exhibits lower antigenicity; can inhibit VEGF-A, VEGF-B and placental growth factor (PIGF); and shows higher penetration into all retinal layers.[3] VIEW 1 and VIEW 2 studies have shown that the efficacy of intravitreal aflibercept (IVA) injections every 2 months after a 3-month IVA loading phase in preserving visual function in patients with exudative AMD over 1 year is not inferior to monthly intravitreal ranibizumab (IVR).[4,5]

Some patients respond poorly or not at all to anti-VEGF injections, while others show a gradually diminishing response to treatment after repeated injections.[5,6] The CATT study showed that 51.5–67.4% of patients with exudative AMD who received monthly injections of IVR or intravitreal Bevacizumab (IVB) still had fluid on optical coherence tomography (OCT) at the end of 2 years.[6] Various treatment strategies have been proposed to overcome this resistance, such as switching to other anti-VEGF therapies, or increasing the concentration of the drug, or the frequency of injections.[5] It has been shown that IVA may be effective in patients with exudative AMD resistant to IVB or IVR injections. A decrease in intraretinal fluid (IRF) or subretinal fluid (SRF) and an increase in visual acuity were observed with the transition to IVA injection.[1]

In this study, we aimed to evaluate the anatomical and functional results of switching to IVA therapy in exudative AMD patients resistant to IVR and Bevacizumab therapy.

Methods

This observational study was approved by the Research Ethics Committee (E-17073117-050.06) and was conducted in accordance with the Helsinki Declaration. All patients have been provided with information and their written consents were obtained.

Patients who were refractory to IVB/IVR for exudative AMD and treated with IVA injection between 2016 and 2022 were included in the study. Patients were evaluated with OCT every 4 weeks and IVB/IVR injection was applied to the patients when fluid was seen in the macula after 3 months of loading dose. Persistent IRF or SRF on OCT or worsening best-corrected visual acuity (BCVA) compared to baseline was defined as unresponsiveness. Upon obtaining the consent of the patient, the decision was taken to change to IVA therapy. Changes in BCVA, central macular thickness (CMT) and pigment epithelial detachment (PED) values and the existence of SRF and IRF on OCT after 3 loading IVA doses and after 1 year of IVA therapy were recorded and compared with pre-injection values. Patients who had previously undergone photodynamic therapy or had macular fluid for other reasons were not included in the study. Patients were administered 3 monthly loading doses of IVA followed by OCT every 4 weeks and treated with pro re nata (PRN) protocol as needed. Demographic data, monthly analysis of BCVA, IOP, slit-lamp examination, and the number of IVA,

Table 1. Demographic characteristics and the number of injections of patients undergoing IVA injections resistant to IVB/IVR treatment

Parameters	Values	Range
Mean age (year)	75.44±10.80	56–95
Female/male	15/16	
Right eye/left eye	14/17	
Mean number of previous IVB* injections	1.57±1.88	1–6
Mean number of previous IVR** injections	5.57±5.53	4–17
Mean number of IVA*** injections 1 year after the loading dose	2.57±1.56	0–6

*: Intravitreal bevacizumab; **: Intravitreal ranibizumab; ***: Intravitreal aflibercept. IVA: Intravitreal aflibercept; IVB: İntravitreal bevacizumab; IVR: Intravitreal ranibizumab.

IVB, and IVR injections were recorded from the medical files of the patients. The Early Treatment Diabetic Retinopathy Study chart was used for BCVA and converted to logarithm of the minimum angle of resolution (logMAR). Images were obtained using an enhanced depth imaging OCT (Nidek RS-3000 Advance, Gamagori, Japan). The distance between the inner limiting membrane at 1 mm circumference of the fovea and Bruch's membrane was defined as CMT. The maximum height of the PED was defined as the distance between the outer border of the RPE and the inner border of Bruch's membrane in the CNV area. IRF/SRF was determined by looking at the localization of the fluid. All injections were applied in an operating room under topical anesthesia obtained by 0.5% proparacaine hydrochloride (Alcaine; Alcon, Texas, USA). 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 through the pars plana, 3–4.5 mm posterior to limbus using a syringe with a 30-gauge needle.

Statistical analyses were performed using the SPSS Statistics for Mac version 26 (IBM Corp., Armonk, NY). Numbers and percentages are used to define categorical variables. The normal distribution of the data was evaluated by performing the Shapiro–Wilk test. Paired samples t-test was used for in-group comparisons. P<0.05 was considered statistically significant.

The primary outcome of the study was the change from baseline in BCVA and CMT values after 3 loading doses and after 1 year of IVA therapy. The secondary outcome measures of the study were the existence of SRF/IRF or PED.

Results

A total of 31 eyes of 31 patients with exudative AMD resistant to IVB/IVR received IVA injections. The patients' ages ranged from 56 to 95, with a mean of 75.44±10.80 years. Fifteen patients were female, 16 male. Fourteen eyes were right, and 17 were left. Twelve patients received IVR injection, 18 patients received IVB injection and 1 patient received both injections. Before IVA therapy, the mean number of total injections was 7.14±4.66 (range, 3–20), and the mean number of IVA injection at 1 year after the loading dose was 2.57±1.56 (0–6). Demographic characteristics and the number of injections of the patients are shown in Table 1. Patients with 1-year results after IVA treatment had at least 2 years of follow-up before IVA injections.

No significant change was detected in BCVA values. A significant decrease was found in CMT values at the end of 3 months (p=0.001) and at the end of 1 year compared to values obtained before IVA (p=0.004). A significant decrease was found in PED height values at the end of 3 months (p=0.006) and at the end of 1 year compared to values obtained before IVA (p=0.04). Changes in BCVA, CMT, and PED heights at each time point following the transition to IVA injection are shown in Table 2.

While SRF/IRF was present in 14 (45.1%) eyes before IVA, SRF/IRF was detected in 8 (25.8%) eyes at the end of the three loading doses (p=0.05) and in 14 (45.16%) eyes at the end of 1 year (p=1). At the end of 1 year, pigment epithelial rupture developed in one patient, while BCVA and IOP remained stable. No serious systemic adverse events were observed due to intravitreal injections during follow-up.

There was no significant change in IOP values before and after IVA.

Discussion

In this study, we analyzed how switching to aflibercept injection altered functional and morphological outcomes

Table 2. Changes in BCVA*, CMT**, and PED*** heights at each time point following transition to IVA injection

Parameters	Before IVA* injection	After three loading doses of IVA injection	1 year of IVA* injection
BCVA* (logMAR), mean±SD (min-max)	0.52±0.31 (0.2–1.3)	0.51±0.28 (0.2–1)	0.53±0.33 (0.1–1.3)
CMT**, µm mean±SD (min-max)	301.10±76.27 µm (166–546)	262.86±69.74 µm (131–433) (P=0.001)	257.61±92.05 µm (156-504) (p=0.004)
PED***, µm mean±SD (min-max)	130.81±73.72 µm (0–271)	96.00±57.66 µm (0–208) (p=0.006)	95.61±66.67 µm (0–244) (p=0.04)

*: Best-corrected visual acuity, **: Central macular thickness, ***: Pigment epithelial detachment, *: Intravitreal aflibercept. BCVA: Best-corrected visual acuity; CMT: Central macular thickness; PED: Pigment epithelial detachment; IVA: Intravitreal aflibercept.

in patients with exudative AMD who did not respond to ranibizumab and bevacizumab. In our results, it was observed that functional results remained stable, while significant improvement was observed in anatomical results as reducing CMT and PED heights.

Some patients initially respond poorly or at all to anti-VEGF therapy or respond with a slow decline in the efficacy of anti-VEGF agents over time after repeated administration. Patients with low or no response to initial anti-VEGF therapy, or patients who have a successful initial dose but experience a gradual decrease in this response are referred to as resistant to anti-VEGF therapy.[7] The effect that diminishes over time is called drug tolerance and requires more anti-VEGF therapy to be effective.[8] Another reason for resistance development may be tachyphylaxis induced by ranibizumab/bevacizumab therapy. Tachyphylaxis is defined as a rapid decrease in the response to the drug after repeated use of drugs. As a result of tachyphylaxis, there is no response to treatment even with the use of drugs in high concentrations in contrast to tolerance.[3]

On the other hand, since anti-VEGFs are antigenic, local or systemic immune reactions may occur due to the development of antibodies after intravitreal anti-VEGF treatment. Furthermore, chronic VEGF blockade by anti-VEGFs paradoxically leads to overexpression of VEGF by macrophages in the choroidal neovascular tissue.[2]

Ranibizumab and bevacizumab bind only to VEGF-A; aflibercept binds with high affinity to all VEGF-A and VEGF-B isoforms as well as PIGF. Furthermore, Aflibercept has a longer intravitreal half-life than ranibizumab and bevacizumab so it can be administered less frequently. For these reasons, the use of Aflibercept in patients with treatment resistance may be more potent as it can inhibit more angiogenic factors more potently.[5,8-10]

Most likely, both pharmacodynamics and the possibility of tachyphylaxis to previous anti-VEGFs lead to reductions in CMT and PED heights with switching to aflibercept therapy.[8]

The VIEW 1 and 2 trials reported that the use of every 2 months or every month IVA was not less effective than monthly IVR administration. The study showed that macular fluid resolved earlier in IVA-treated eyes than in IVR-treated eyes, but no clear visual improvement after 1 year. In the combined VIEW trials, 38% of the eyes in the IVR group had persistent fluid at 1 year, whereas this rate was 27.6% in the group administered 2 mg IVA every 4 weeks and 32.3% in the group administered 2 mg IVA every 8 weeks.[4]

Similar to the VIEW study, we did not find any visual gain after three loading doses or 1 year after switching to IVA in our study. The chronic nature of exudative AMD and repeated administration of anti-VEGF, recurrent exudation, worsening cataract, and progression of RPE damage such as geographic atrophy can lead to loss of photoreceptors, which may hinder visual acuity improvement after switching to IVA.[1] Some studies[1,3,9-13] reported significant visual gains after switching to aflibercept while others[2,8,11,12] have shown no improvement. There are also studies showing significant visual improvement in the short term after switching to IVA but decreased visual improvement after the second 6 months.[1,7,13]

We have found a significant decrease in CMT values at all visits after switching to IVA. Similar to our study, in several studies it has been reported that no significant increase or decrease in BCVA but a significant reduction in CMT values.[2,12,14,15]

In our study, SRF significantly decreased at the end of the three loading doses of IVA, but at the end of 1 year, it was back to the starting level without an increase in CMT and PED heights and any change in BCVA (Fig. 1). The 2-year re-

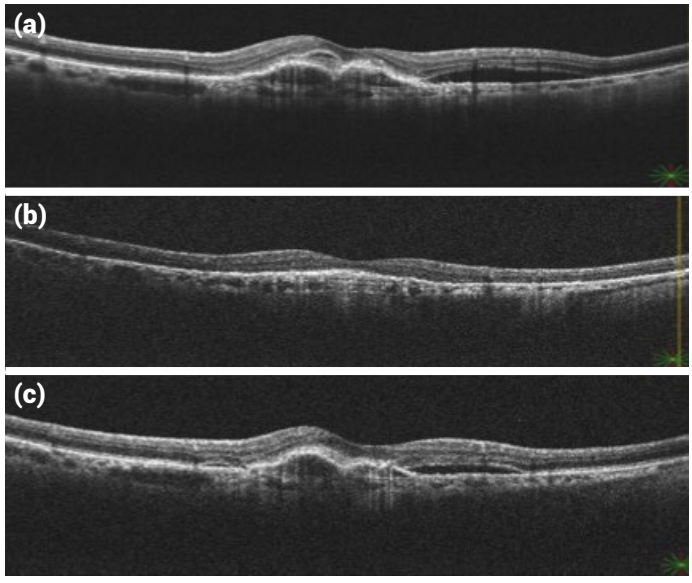

Figure 1. **(a)** Optical coherence tomography horizontal sections from 1 patient showed subretinal fluid and pigment epithelial detachment (PED) before intravitreal aflibercept (IVA) treatment. **(b)** Following 3 months of loading IVA injection, SRS, and PED resolved completely. **(c)** At the end of 1 year, it was back to the starting level without an increase in central macular thickness and PED heights and any change in best-corrected visual acuity.

sults of the CATT study showed that the presence of residual SRF may be associated with lower rates of macular atrophy and better visual acuity suggesting that some residual SRF may be tolerated.[16] Similarly, Arcinue et al.[15] reported that eyes with SRF had a greater tendency to gain vision.

On the contrary long-term advanced photoreceptor damage resulting from chronic fluid accumulation due to persistent IRF/SRF prevented significant improvement in BCVA.[2]

Various types of PED have been shown to occur in 62% of exudative AMD.[17] We have not separated the PEDs according to their characteristics like serous or fibrinous PED. One study has shown that PEDs responded poorly to anti-VEGF therapy. This is because the PED is located deeper within the RPE layer and the RPE acts as a barrier against the penetration of anti-VEGF under the RPE.[18] In our analysis, PED heights decreased significantly at the end of the loading doses (26%) and the 1st year (26%). Similar to our study, a significant reduction has been reported in PED heights after aflibercept therapy.[11,17,19] Patel et al.[17] showed that PED height decreased by 12–33% after aflibercept treatment. Bakall et al.[14] reported a significant decrease in both CMT and PED heights at the visit after three doses of aflibercept loading injection, but a significant decrease in only CMT after 6 months.

In one study, both an improvement in BCVA and a decrease in CMT were observed after switch therapy.[7]

While Unsal et al.[3] reported a significant decrease in mean IOP with IVA injection, we did not find any change in IOP values.

We applied the PRN protocol after three loading doses of aflibercept while treating our patients. Although the efficacy of the PRN regimen was confirmed in the CATT study,[20] the resulting treat and extend regimen is considered to be a more efficient regimen, requiring fewer patient visits.[7]

There are studies showing that the PRN protocol applied without three loading doses of IVA is also effective in cases resistant to IVB/IVR treatment.[2,15]

In this study, the mean number of IVA injection at 1 year after the three loading doses was 2.57±1.56 (0–6). In our study, it was observed that the number of intravitreal injections decreased compared to monthly IVB/IVR injections in addition to anatomical improvement.

There was no correlation between the number of IVB/IVR injections or the number of IVA injections administered and the anatomical results. In conclusion, aflibercept is anatomically beneficial in cases of exudative AMD unresponsive to ranibizumab and/or bevacizumab therapy.

Limitation

The limitations of this study are that it includes a small number of patients, was retrospective and no results obtained for longer than 1 year.

Disclosures

Ethics Committee Approval: The study was approved by Fatih Sultan Mehmet Training and Research Hospital Ethics Committee, Date: 30.03.2021, decision number: E-17073117-050.06.

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Conflict of Interest: None declared.

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