Switch to Aflibercept for Refractory Diabetic Macular Edema from Previous Ranibizumab/Bevacizumab Injections

Ranibizumab/Bevacizumab Tedavisine Dirençli Diabetik Maküler Ödem Tedavisinde Aflibercept Tedavisi

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ABSTRACT

Purpose: To evaluate the results of switching from ranibizumab/bevacizumab (R/B) to aflibercept therapy in patients with persistent diabetic macular edema (DME).

Method: A retrospective study was designed to assess the functional and anatomic outcomes of switching therapy from R/B to aflibercept in patients with persistent DME. The patients included in this study had persistent DME and received at least 3 previous anti-VEGF intravitreal injections in the last 6 months prior to baseline (pre-switch) examination. After applying 3 monthly loading doses of aflibercept treatment, all the patients were evaluated every 4 weeks and put on an as-needed regimen in case of recurrence. Best-corrected visual acuity (BCVA) and central macular thickness (CMT) were evaluated between pre-switch and the last examination after administering aflibercept therapy.

Results: Fifty eyes of 33 patients were included in the present study. The mean follow-up time before aflibercept and mean follow-up time after aflibercept were 25.2±19.7 and 10.7 ± 4.5 months, respectively. The mean final BCVA (logMAR) increased to 0.69±0.44, which was statistically significant compared to the baseline (0.81±0.37), (p= 0.007). The final BCVA showed a positive correlation to the baseline BCVA (p=0.001, r=0.720). The mean final CMT decreased to 373.9±146.1µm, which was statistically significant compared to baseline (475±140), (p=0.00,1). . The final CMT showed a weak positive correlation to baseline CMT (p=0.003, r=0.430).

Conclusion: Conversion to aflibercept in patients showing poor response to other anti-VEGF agents could result in significant functional and anatomical improvements. Although the present study could not suggest an exact time to switch the therapy, clinicians should not wait for a significant decrease in the BCVA.

Keywords: Diabetic macular edema, aflibercept, switch anti-vascular endothelial agents, central macular thickness.

ÖZ

Amaç: Dirençli diyabetik maküla ödemi (DMÖ) olan hastalarda ranibizumab/bevacizumab (R/B) tedavisinden aflibercept tedavisine geçişin sonuçlarını değerlendirmek.

Yöntem: Dirençli DMÖ tedavisinde R/B uygulamasından aflibercept tedavisine geçişin fonksiyonel ve anatomik sonuçlarını değerlendirmek amacıyla retrospektif bir çalışma planlandı. Aflibercept tedavisi öncesi, son 6 ay içinde en az 3 anti-VEGF intravitreal enjeksiyonuna rağmen dirençli diabetic makula ödemi olan olgular çalışmaya dahil edildi. Üç aylık yükleme dozunda aflibercept tedavisi uygulandıktan sonra, hastalar 4 haftada bir değerlendirildi ve nüks olduğu takdirde ek enjeksiyon uygulandı. Aflibercept tedavisine geçmeden önceki son muayene ile aflibercept tedavisini takip eden son muayenede belirlenen en iyi üzeltilmiş görme keskinliği (EİDGK) ve santral makula kalınlığı (SMK) değişimi istatiksel olarak analiz edildi.

Bulgular: Çalışmaya 33 hastanın 50 gözü dahil edildi. Aflibercept öncesi ortalama takip süresi ve aflibercept sonrası ortalama takip süresi sırasıyla 25.2 ± 19.7 ve 10.7 ± 4.5 ay idi. Aflibercept öncesi 0.81 ± 0.37 (logMAR) olan EİDGK, aflibercept sonrası son kontrolde 0.69 ± 0.44

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(logMAR) a yükseldiği görüldü, değişim istatistiksel olarak anlamlı idi, (p = 0.007). Son EİDGK'nin aflibercept öncesi EİDGK ile pozitif korelasyon gösterdiği belirlendi (r = 0.720, p = 0.001). Ortalama son SMK' nın (373.9 ± 146.1, µm), başlangıç değerine (475 ± 140, µm) göre istatistiksel olarak anlamlı derecede azaldığı saptandı, (p = 0.001). Son SMK nin aflibercept öncesi SMK ile zayıf bir korelasyon gösterdiği belirlendi (r = 0.430, p = 0.003).

Sonuç: R/B tedavisine yetersiz yanıt veren hastalarda, aflibercept tedavisine geçiş, başarılı fonksiyonel ve anatomik sonuçlar sağlayabilmektedir. Bu çalışma, tedavi değişimi için kesin bir zamanlama öneremiş olmakla birlikte, görme düzeyinde belirgin bir azalmayı beklemenin gereksiz olduğunu göstermektedir.

Anahtar Sözcükler: Diyabetik maküler ödem, aflibercept, anti-vasküler endotelyal faktör tedavisinde ilaç değişimi, santral makular kalınlık.

INTRODUCTION

Diabetic macular edema (DME) is the leading cause of vision loss in patients with diabetic retinopathy.[1] The prevalence of DME is reported to be about 5%. [2,3] Vascular endothelial growth factor (VEGF) is the most important mediator responsible for abnormal vascular permeability in DME, and several clinical trials have reported improvements in best corrected visual acuity (BCVA) after the use of anti-VEGF agents as first-line therapy for DME.[4] The full-length VEGF-A monoclonal antibody bevacizumab (Avastin; Genentech, Inc., San Francisco, CA); VEGF-A monoclonal antibody fragment ranibizumab (Lucentis; Genentech, Inc., San Francisco, CA); and aflibercept (Eylea; Regeneron, Tarrytown, NY), which is a fusion protein that acts as a trap receptor binding all isoforms of VEGF-A, VEGF-B, and placental growth factor (PlGF), are the most important anti-VEGF agents that have been the mainstay of therapy.[4] According to the 24-month results of the Diabetic Retinopathy Clinical Research Network (DRCR.net), all three agents were effective in improving BCVA and reducing central macular thickness (CMT).[5]

Despite undergoing regular anti-VEGF therapy, some patients respond incompletely to the treatment and may be considered resistant to treatment.[6] In 2015, DRCR.net defined treatment failure as persistent CMT detected by optic coherence tomography (OCT) and/or a BCVA loss of 10 Early Treatment Diabetic Retinopathy Study (ETDRS) letters despite the administration of 4 weekly intravitreal injections.[4] Persistent and chronic macular edema may cause ultrastructural changes and neuronal damage, leading to visual impairment and limiting potential for vision recovery.[7] It has been suggested that patients with incomplete response to bevacizumab and ranibizumab can benefit from aflibercept since it binds to all isoforms of VEGF-A, VEGF-B, and PlGF;[8, 9] however, the ideal time for the therapeutic switch is still unclear.[10]

The purpose of this study was to assess the long-term results of aflibercept treatment in switching therapy from ranibizumab/bevacizumab to aflibercept in patients with persistent DME.

METHOD

A retrospective study was designed to assess the functional and anatomic outcomes of intravitreal aflibercept treatment in patients with DME refractory to intravitreal bevacizumab or ranibizumab therapy. The medical charts of patients treated with intravitreal aflibercept for DME previously treated with other anti-VEGF agents (ranibizumab-bevacizumab) from January 2013 to January 2017 were reviewed retrospectively.

Ethical approval was obtained from the Local Ethics Committee. The study was designed in accordance with the Declaration of Helsinki. The consent form outlining the adverse effects of the drug and its application was provided to all patients. Informed consent was obtained from all patients on the side effects of the drug and the injection procedure before going ahead with the application of intravitreal anti-VEGF injections.

Patients older than 18 years of age with DME due to type-1 or type-2 diabetes mellitus were included in the study. The patients included in this study had persistent DME defined by the loss of the foveal pit and CMT greater than 300 µm on OCT (Optovue OCT V 5.1, RTVue 100-2; Optovue, Fremont, CA, USA) and treated with at least 3 previous anti-VEGF (ranibizumab-bevacizumab) intravitreal injections in the last 6 months prior to baseline (pre-switch) examination. Only the patients who received at least 3 monthly aflibercept injections were included in the study.

Patients previously treated with intravitreal steroid therapy and those who underwent vitrectomy surgery, cataract surgery, or macular laser surgery within 3 months of the baseline were excluded. Additionally, patients with active proliferative diabetic retinopathy and uncontrolled diabetes mellitus (HbA1c ≥9 %) were also excluded from the study.

After receiving 3 monthly loading doses of aflibercept (2 mg/0.05 cc), all patients were evaluated every 4 weeks and were treated on an as-needed regimen in case of recurrence as per functional and anatomical parameters. Recurrence was defined as BCVA loss of ≥5 letters between 2 consecutive visits, CMT of >300 µm, or increase in CMT by >10%. 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 best-corrected visual acuity (BCVA), slit-lamp examination, dilated fundus biomicroscopy, applanation tonometry; and total number of bevacizumab, ranibizumab, and aflibercept injections were recorded on the medical charts of the patients. The ETDRS chart was used to measure the BCVA. ETDRS letter scores were converted to Snellen and LogMAR (logarithm of the minimum angle of resolution or recognition) for statistical analysis.

A 90-diopter (D) lens was used to perform the fundus examination after applying 2.5% phenylephrine and 1% tropicamide.

The same retina specialist (E.U.) administered all injections in an operating room under topical anesthesia with 0.5% proparacaine hydrochloride (Alcaine®; Alcon Laboratories, Inc., USA). After irrigation of the conjunctiva with povidone-iodine, the anti-VEGF agent (repackaged 1.25 mg/0.05 mL bevacizumab-0.5 mg/0.05 mL ranibizumab-2 mg/0.05 mL aflibercept) was injected via the pars plana, 3.5-4 mm posterior to the limbus using a syringe with a 30-gauge needle. Moxifloxacin eye drops (Vigamox®; Alcon, USA) were administered 4 times daily for 5 days after all intravitreal injections.

OCT was performed by the same specialist for all patients with the same OCT device (Optovue OCT V 5.1, RTVue 100-2; Optovue, Fremont, CA, USA) after achieving pupillary mydriasis with the use of 2.5% phenylephrine and 1% tropicamide.

We defined 2 BCVA values for the endpoints of our study. The pre-switch BCVA was the BCVA measured before the first aflibercept injection and the final BCVA was the BCVA measured 3-4 weeks after the last aflibercept injection.

The first endpoint of the study was the mean alteration in BCVA between the pre-switch and final BCVA according to our definition. The second endpoint was the mean alteration in CMT between the pre-switch examination and last examination after aflibercept therapy. Additionally, the BCVA and CMT were recorded on a monthly basis. Serum hemoglobin A1c (HbA1c) levels were also measured at the beginning of aflibercept treatment and at the 6 months.

Statistical Package for the Social Sciences (SPSS) version 20.0 software was used for all statistical analyses. Descriptive statistics were presented as the minimum, maximum, and mean ± 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. P values <0.05 were accepted as statistically significant.

RESULTS

Fifty eyes of 33 patients fulfilled the inclusion criteria and were included in the present study. The demographic characteristics of the patients and mean follow-up time are presented in Table 1.

Table 1. *Demographic Characteristics*

Parameters	Values	Range
Mean Age(y)	61.04±8.8	47-81
Patients/eye	33/50	
Female/male	13/20	
Mean Follow-up Time Before Aflibercept	25.2±19.7	4-69
Mean Follow-up Time After Aflibercept(m)	10.7 ± 4.5	3-24
Mean number of previous injections	5.8±4.1	3-22
Mean number of aflibercept injections	4.2±1.6	3-8
Phakia/pseudophakia	37/13	
History of glaucoma (E)	2	
Type of DM Tip1/Tip2	0/33	
HbA1C (Mean± SD)	**8.2±1.0**	

The mean BCVA (logMAR) was 0.81 ± 0.37 (0.1-1.6) before switching to aflibercept. In the final examination of all our patients after they received aflibercept injections, the mean final BCVA (logMAR) increased to 0.69 ± 0.44 (0.1-1.3), which was statistically significant compared to the baseline value (p = 0.007) (Table 2, Fig. 1A). The BCVA (logMAR) values recorded at the monthly follow-up are shown in Table 2. The mean letter gain was 6.3 ± 15.0 letters. Twenty-six eyes of 50 (52%) patients gained 1 or more line at the last follow-up. The BCVA remained stable in 12 eyes (24%) and deteriorated in 10 eyes (20%). However, the mean CMT decreased in 11 of these 22 eyes. There was no correlation between the total number of previous injections and the increase in BCVA, (r = -0.09, p = 0.490). Additionally, sex and age did not influence the increase in BCVA (r = -0.19, p = 0.140; r = -0.03, p = 0.82 respectively). The final BCVA showed a positive correlation to baseline BCVA (r = 0.720, p = 0.001).

The mean CMT was 475.8 ± 140.3 μm (309-862 μm) before initiating treatment with aflibercept. In the final examination of all our patients after they received aflibercept therapy, the mean final CMT decreased to 373.9 ± 146.1 μm (141-776 μm), which was statistically significant compared to the baseline value (p = 0.001), (Table 2, Fig 1B). The CMT values recorded at the monthly follow-up are shown in Table 2. The CMT increased in 11 eyes after a mean of 5.9 ± 1.9 aflibercept injections. The BCVA did not improve in these patients. There is no correlation between the total number of previous injections and the decrease in CMT, (r =

Table 2. *Comparison of the Mean BCVA(logMAR), CMT (μm), and IOP (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**	**PostAfli Final**
BCVA (logMAR), Mean±SD	0.81±0.37	0.78±0.40	0.76±0.40	0.72±0.40	0.70±0.44	0.67±0.43	0.71±0.44	0.73±0.37	0.67±0.40	0.60±0.40	0.60±0.33	0.78±0.37	0.71±0.45	0.69±0.44
(Min-Max)	(0.1-1.6)	(0.15-1.7)	(0.1-1.7)	(0.1-1.7)	(0.1-1.7)	(0.1-1.7)	(0.15-2.0)	(0.15-1.5)	(0.1-1.3)	(0.1-2.0)	(0.15-1.3)	(0.3-1.7)	(0.1-2.0)	(0.1-1.3)
	n=50	p*=0.71 n=50	p*=0.22 n=50	p*=0.044 n=50	p*=0.005 n=48	p*=0.062 n=34	p*=0.046 n=30	p*=0.57 n=23	p*=0.25 n=23	p*=0.048 n=21	p**=0.55 n=16	p**=0.51 n=10	p**=0.42 n=10	p*=0.007 n=50
CMT, μm Mean±SD	475.8±140.3	347.3±93.1	374.0±115.1	354.9±112.3	353.3±139.5	383.6±150.5	381.5±117.4	416.5±173.2	372.0±127.1	373.5±108.0	383.6±122.9	361.4±124.3	379.1±137.6	373.9±146.1
(Min-Max)	(309-862)	(157-561)	(138-596)	(141-543)	(150-746)	(152-676)	(222-676)	(173-976)	(188-707)	(200-571)	(242-715)	(222-776)	(222-776)	(141-776)
	n=50	p*=0.001 n=50	p*=0.001 n=50	p*=0.004 n=50	p*=0.001 n=48	p*=0.062 n=34	p*=0.001 n=30	p*=0.61 n=23	p*=0.08 n=23	p*=0.01 n=21	p**=0.12 n=16	p**=0.07 n=10	p**=0.064 n=10	p*=0.001 n=50
IOP,mmHg Mean ±SD	16.08±2.11	16.15±2.31	16.16±2.33	16.18±2.36	16.39±2.29	16.28±2.28	16.25±2.38	16.19±2.27	16.31±2.26	16.47±2.11	16.43±2.45	16.56±2.18	16.51±2.12	16.03±2.37
(Min-Max)	(11-20)	(12-20)	(12-19)	(11-21)	(11-19)	(11-19)	(11-20)	(11-21)	(12-19)	(11-20)	(12-19)	(11-20)	(12-20)	(12-19)
	n=48	p*=0.1 n=48	P*=0.1 n=48	p*=0.09 n=48	p*=0.04 n=46	p*=0.034 n=34	p*=0.01 n=30	p*=0.003 n=23	p*=0.027 n=23	p*=0.01 n=21	p**=0.01 n=16	p**=0.016 n=10	p**= 0.018 n=10	p*= 0.28 n=50

BCVA: Best corrected visual acuity, CMT: Central macular thickness, IOP: Intraocular Pressure, Af: Aflibercept, M: month, n: number of eyes, p*: paired samples t test p**:Wilcoxon signed rank test, ($p<0.05$ indicates statistical significance according to Bonferroni adjustment).

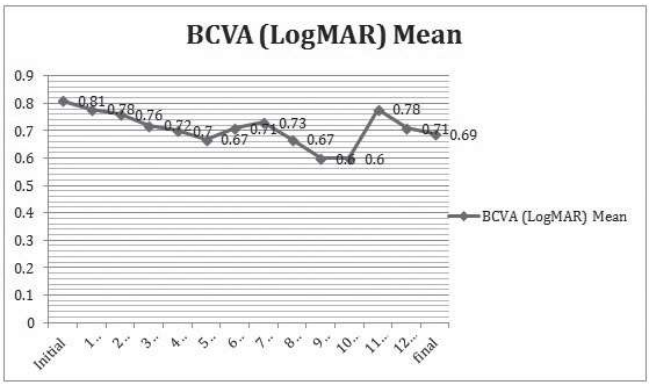

Figure 1A. *Mean BCVA at the onset of aflibercept treatment and follow-up months*

Abbreviations: LogMAR; Logarithm of the minimum angle of resolution or recognition

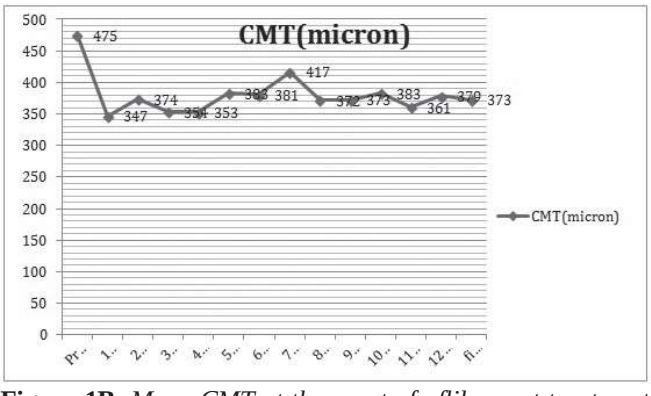

Figure 1B. *Mean CMT at the onset of aflibercept treatment and follow-up months*

Abbreviations: CMT, Central foveal retinal thickness

0.9, p = 0.180). Additionally, sex and age did not influence the decrease in CMT (r = -0.022, p = 0.84; r = -0.27, p = 0.06, respectively). The final CMT showed a weak positive correlation to baseline CMT (r = 0.430, p = 0.003).

After excluding patients with glaucoma, while the mean baseline IOP value was 16.08 ± 2.11 (11-21 mmHg), the final mean IOP value was 16.03 ± 2.37 (12-19 mmHg). The decrease in the mean IOP was not statistically significant under aflibercept treatment (p = 0.28) (Table 2, Fig. 1C).

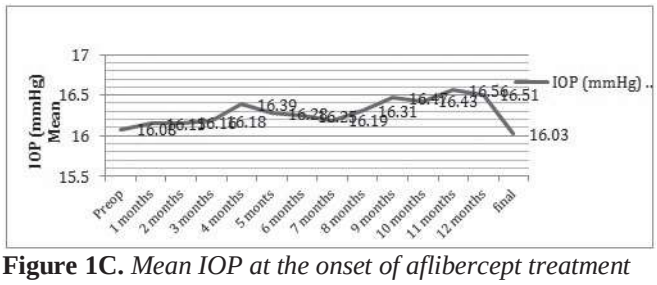

Figure 1C. *Mean IOP at the onset of aflibercept treatment and follow-up months*

Abbreviations: IOP; Intraocular pressure

The mean hemoglobin A1c (HbA1c) level was 8.2 ± 1.0 at the beginning of aflibercept treatment and 8.1±0.9 at the 6 months (p=0,342).No ocular or systemic side effect was observed from intravitreal injections during the follow-up period.

DISCUSSION

The present study showed the efficacy of aflibercept in patients with DME who are refractory to other anti-VEGF agents (bevacizumab and/or ranibizumab).

It is known that anti-VEGF agents are the most important treatment choice for center-involved DME. [4, 5] Several large studies have shown anti-VEGF treatment with bevacizumab or ranibizumab to be superior to laser alone.[11, 12] Both bevacizumab and ranibizumab are widely used owing to their effectiveness.[4, 5] Despite the effectiveness of anti-VEGF agents, some patients do not respond at all to ranibizumab or bevacizumab or demonstrate an initial response to treatment followed by subsequent non-response to further treatment.[8-10] DRCR.net reported that laser photocoagulation (focal, grid, or both) was performed at least once between 24 and 48 weeks in 115 of 206 bevacizumab-treated eyes (56%), and 95 of 206 ranibizumab-treated eyes (46%) for persistent diabetic macular edema .[4]

Increased VEGF expression from inflammatory cells, upregulation of VEGF receptors, and immune response to the anti-VEGF antibodies may cause this loss of therapeutic effect.[13] In this situation, a different agent could be used to suppress VEGF.

A new agent, aflibercept, was found to be as effective as bevacizumab and ranibizumab.[4] Additionally, recent studies claim that aflibercept is the most potent anti-VEGF treatment for DME. [8-10, 14-17] Very few studies have presented the anatomic and functional improvements in conversion to aflibercept when initial treatment with ranibizumab and/or bevacizumab failed.[8-10, 14-17] The different pharmacodynamics of aflibercept such as high affinity to VEGF-A and ability to block PlGF and VEGF-B may be the reasons behind its strong effect. [4, 5,18]

The decision of switching to aflibercept is controversial.[19] The most crucial aspect of the switch is that of determining the correct time of the switch. It is known that persistent macular edema leads to deterioration of BCVA; hence, early switching is recommended. However, the possibility of late response could be a reason behind late switching. Previously, it was suggested that early switching does not warrant better long-term visual results because the number of previous anti-VEGF injections before the switch does not influence the outcome.[20] Similarly, we did not define a correlation between the increase in BCVA, the decrease in CMT, and the total number of previous injections. However,

we could not suggest an exact time to switch the therapy as we thought that early switching is not necessary.

The results of aflibercept treatment when switching therapy from ranibizumab/bevacizumab to aflibercept in patients with persistent DME have been previously presented.[8-10, 15-17, 20] Lim et al.[8] reported significant functional and anatomical improvements in 21 eyes that were administered aflibercept injections at a mean interval of 2.4 months. Another retrospective study presented a significant functional improvement at the fourth visit after the switch.[9]Additionally, in 2017, Bahrami et al.[15] reported that aflibercept was effective in improving anatomical and visual outcomes for patients with persistent DME after intravitreal bevacizumab therapy. They administered 5 monthly loading doses of intravitreal aflibercept and the 4-week treatment interval was extended to 8 weeks during the 48 weeks of follow-up. They reported that eyes with a gain of 5 or more letters at 4 weeks after the first aflibercept injection had significantly better vision outcomes at 24 weeks (6.8 ± 7.1 letters).[15]

In the current study, after applying 3 monthly loading doses of aflibercept (2 mg/0.05 cc), all patients were evaluated every 4 weeks and treated on an as-needed regimen in the case of recurrence as per functional and anatomical parameters. Consistent with the literature,[8-10, 15-17, 20] significant anatomical and functional improvements were detected after switching the therapy. After administering aflibercept injections, the mean final BCVA (logMAR) increased to 0.69 ± 0.44 (baseline BCVA, 0.81±0.37), which was statistically significant compared to the baseline values (Table 2), and the mean final CMT significantly decreased to 373.9 ± 146.1 μm (baseline CMT, 475±140 μm). The mean letter gain was 6.3 ± 15.0 letters. Twenty-six eyes of 50 (52%) patients gained 1 or more line at the last follow-up. The significant improvement in BCVA started after the second injection. The mean value of aflibercept injections administered was 4.2 ± 1.6. We thought that 3 monthly loading doses of aflibercept followed by a rigid as-needed regimen was necessary to improve the BCVA. However, no improvement in BCVA was determined in 22 eyes (44%). Additionally, 11 of those 22 eyes showed no anatomical improvement. Similarly, Laiginhas et al.[20] reported that the BCVA remained stable in 51% and deteriorated in 12% of their patients. The presence of inflammatory cytokines other than VEGF could explain these results.

The most important findings of our study come from the correlation analysis. It was already known that baseline BCVA is an important predictive factor in DME treatment: the higher the baseline BCVA the better the final BCVA.[21] We reported that this knowledge was also true for the switch therapy. Hence, clinicians should not wait for a significant decrease in the BCVA to switch the therapy.

The most important limiting factor of the current study was its retrospective design. The lack of masking for BCVA and OCT measures and lack of a control group may also affect the reliability of our results. Prospective and comparative studies with a higher number of patients would give more information and answer the most important question on this topic: When?

In conclusion, for patients with poor response to other anti-VEGF agents, conversion to aflibercept could lead to significant functional and anatomical improvements. The most crucial aspect of this topic is when the therapy should be switched. Although the present study could not suggest the exact time to make the switch, clinicians should not wait for a significant decrease in the BCVA. Additionally, clinicians should note that the total number of previous injections does not influence the final CMT and BCVA values. Hence, early switching is not always necessary.

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Ethical approval: 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.

Informed consent: Informed consent was obtained from all individual participants included in the study.

Author Contributions ; EU: Research concept and design. **EU, MOC, FC**: Collection of data. **EU, MOC:** Data analysis and interpretation. **EU, MOC:** made the figures. **EU, MOC:** made the table. **EU, MOC:** Writing the manuscript. **EU, MOC:** Critical revision and Final approval of the manuscript. **EÜ, MOC**: supervised the study

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