The Results of Aflibercept Treatment in Patients With Naive Diabetic Macular Edema: A Real World Study

Tedavi Olmamış Diabetik Makula Ödemi Olan Hastalarda Aflibercept Tedavisi: Gerçek Yaşam Verileri

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ABSTRACT

Purpose: To present the long-term results of aflibercept treatment in patients with no previous treatment for diabetic macular edema (DME) in daily clinical practice.

Method: A retrospective, single-center study designed to evaluate the functional and anatomic outcomes of intravitreal aflibercept treatment in patients with no previous treatment for DME. The patients included in this study had DME defined by the loss of the foveal pit and central macular thickness (CMT) greater than 300 µm on OCT. Only patients who received at least the first 3 monthly (4 weeks) aflibercept (2 mg/0.05 cc) injections were included in the study. Retreatment was performed if a loss of best corrected visual acuity (BCVA) ≥5 letters were defined between 2 consecutive visits or CMT worsened which CMT of >300 micron, or increase in CMT by > 10 %.

Results: The mean BCVA (Logarithm of the minimum angle of resolution or recognition -logMAR) increased to 0.55±0.40 (0.1-2.0) after applying a mean of 3.2±0.53 aflibercept injections (p= 0.001). At the final examination, mean letter gain was 13.5±15.7 letters. At the final examination, gains in Early Treatment Diabetic Retinopathy Study (ETDRS) letters were documented in 44 eyes (69.8%), and visual acuity remained stable in 19 eyes (30%). The mean CMT was 430.8±135.39 µm (242-806) before initiating treatment with aflibercept and decreased to 303.6±57.7 µm (210-529) at the final examination (p= 0.0001).

Conclusion: Aflibercept could be used as a first-line therapy in patients with treatment-naive DME. Clinicians could decrease the number of injections with using as-needed treatment regimen, with a comparable improvement of visual acuity..

Key Words: Diabetic macular edema, aflibercept, anti-VEGF.

ÖZ

Amaç: Diyabetik maküla ödemi (DMÖ) nedeniyle daha önce tedavi almamış hastalarda günlük klinik şartlarda uygulanan aflibercept tedavisinin uzun dönem sonuçlarını sunmak.

Yöntem: Çalışma DMÖ tedavisi uygulanmamış olgularda intravitreal aflibercept tedavisinin anatomik ve fonksiyonel sonuçlarını araştırmak amacıyla tek merkezde retrospektif olarak dizayn edildi. Çalışmaya dahil edilen hastalarda optik koherens tomografide (OKT) 300 µm dan yüksek santral makula kalınlığı (SMK) ve foveal çukurluğun silinmesi ile tanımlanan diabetik makular ödem mevcuttu. En az ilk 3 yükleme dozu (4 hafta aralıklı) aflibercept (2 mg/0.05 cc) tedavisi uygulanmış olan hastalar çalışmaya dahil edildi. Ardışık iki vizite en iyi düzeltilmiş görme keskinliğinde (EİDGK) ≥5 harf kayıp olması, santral makula kalınlığının 300 µm dan yüksek olması veya santral makula kalınlığının %10 dan fazla artması durumunda ek tedavi uygulandı.

Bulgular: Ortalama 3.2 ± 0.53 aflibercept enjeksiyonu uygulanmasını takiben ortalama EİDGK (logMAR), 0.55 ± 0.40'a (0.1-2.0) yükseldiği saptandı (p = 0.001). Son vizitte, ortalama harf kazanımının 13.5 ± 15.7 harf olduğu belirlendi. 44 gözde (% 69,8) görme keskinliğin artış olduğu ve görme keskinliğinin 19 gözde (% 30) stabil kaldığı belirlendi. Ortalama SMK nin, aflibercept ile tedavisini takiben son muayenede 430.8 ± 135.39 µm (242-806) dan 303.6 ± 57.7 µm'ye (210-529) düştüğü izlendi. (p = 0.0001).

Sonuç: Bu çalışma aflibercept tedavisinin diabetik makular ödemi olan hastalarda birinci basamak tedavi olarak kullanılabileceğini desteklemektedir. Klinisyenler, gerektiğinde ek enjeksiyonlar uygulayarak, görme keskinliğinde karşılaştırılabilir bir iyileşme sağlayıp, enjeksiyon sayısını azaltmaları mümkündür.

Anahtar Kelimeler: Diyabetik makula ödemi, aflibercept, anti-VEGF.

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INTRODUCTION

Diabetic macular edema (DME) is the leading cause of visual loss in patients with diabetic retinopathy and is characterized by exudation and accumulation of extracellular fluid in the macula secondary to an increase in vascular permeability.[1] The prevalence of DME is reported about 5%.[2,3] It is already known that the pathogenesis of DME is multifactorial, including capillary endothelial vascular dysfunction, local inflammatory activity, cellular hypoxia, oxidative stress, breakdown of the blood-retinal barrier, however the overexpression of vascular endothelial growth factor (VEGF) has been identified as the most important cause for the development of DME.[4,5] The most relevant members of the VEGF family for the ocular disease are VEGF-A, VEGF-B, and the placental growth factor (PIGF).[6]

Awareness of the role of VEGF and inflammatory mediators for abnormal vascular permeability in DME has encouraged the development and widespread use of anti-VEGF agents and several clinical trials have reported improvement of visual acuity after the use of anti-VEGF agents as first-line therapy for DME.[7]

Today, the most commonly used anti-VEGF agents are bevacizumab, ranibizumab and aflibercept.[7] Bevacizumab (Avastin, Genentech, Inc., San Francisco, CA) is a full-length VEGF-A monoclonal antibody, ranibizumab is a VEGF-A monoclonal antibody fragment (Lucentis, Genentech, Inc., San Francisco, CA), and aflibercept (Eylea, Regeneron, Tarrytown, NY), is a fusion protein that acts as a trap receptor binding all isoforms of VEGF-A, VEGF-B and PlGF.[7]

Twenty four-month results of Diabetic Retinopathy Clinical Research Network (DRCR.net) reported that all three agents are effective in improving visual acuity and reducing central macular thickness (CMT).[8] Additionally, they show that aflibercept is significantly superior to ranibizumab and bevacizumab in the subset of patients with worse vision Early Treatment Diabetic Retinopathy Study [ETDRS] letter score <69, equivalent to 20/50 or worse at baseline.[8] Although, the clinical trials reports the effectiveness of aflibercept in DME therapy, there is limited information of real world. Several studies showed that patients with an incomplete response to bevacizumab and ranibizumab can benefit from aflibercept,[8,9] but data in patients with treatment-naive DME are limited.

We aim to present our long-term results of aflibercept treatment in patients with no previous treatment for DME and suggest a suitable treatment algorithm.

METHOD

This is a retrospective, single-center study to evaluate the functional and anatomic outcomes of intravitreal aflibercept treatment in patients with no previous treatment for DME. The medical charts of patients treated with intravitreal aflibercept for diabetic macular edema from January 2013 to January 2018 are reviewed retrospectively.

The study protocol was approved by the Local Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki for the protection of human subjects. An informed patient consent was taken from all patients about the side effects of the drug and the injection procedure, before the applications of an intravitreal anti-VEGF injection.

Patients older than 18 years of age with clinically significant DME due to type 1 or type 2 diabetes mellitus were included in the study. All patients included in this study were treatment-naïve of anti-VEGF agents. Clinically significant DME was diagnosed on clinical examination and confirmed by spectral-domain optical coherence tomography (Optovue OCT V 5.1, RTVue 100-2; Optovue, Fremont, CA, USA). The patients included in this study had DME defined by the loss of the foveal pit and CMT greater than 300 μm on optical coherence tomography (OCT).

Only patients who received at least the first 3 monthly (4 weeks) aflibercept (2 mg/0.05 cc) injections were included in the study. Patients previously treated with intravitreal steroid, vitrectomy surgery, cataract surgery or macular laser within 3 months of baseline were excluded. Additionally, patients with active proliferative diabetic retinopathy and uncontrolled diabetes mellitus (HbA1c $\geq$ 9%) were also excluded from the study.

After applying three monthly loading doses of aflibercept treatment (2 mg/0.05 cc), all patients were evaluated every 4 weeks and treated on an as-needed regimen in case of recurrence based on functional and anatomical parameters. Aflibercept was reinjected if the macular edema was persistent or the visual acuity decreased which best corrected visual acuity (BCVA) loss of $\geq$5 letters between 2 consecutive visits or central macular thickness worsened which CMT of >300 micron, or increase in CMT by > 10 %.

Patients with a follow-up shorter than 6 months under aflibercept treatment were excluded from the study.

Injection of intravitreal aflibercept was performed by the same retina specialist (E.U) as an outpatient procedure using topical anesthesia with 0,5% proparacaine hydrochloride (Alcaine; Alcon) and strict sterile conditions. After the ocular surface and the lid were disinfected with povidone-iodine, the anti-VEGF agent (2 mg/0.05 ml aflibercept) was performed via the pars plana, 3,5-4 mm posterior to limbus using a syringe with 30 gauge needle. The injection site was compressed by cotton swab to avoid reflux, and the fundus was examined to assess any complication and to check perfusion of the retinal artery.

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 a total number of aflibercept injections were recorded from the medical charts of the patients. The BCVA was measured by using ETDRS chart. ETDRS letter score was converted into a Snellen and Logarithm of the minimum angle of resolution or recognition (LogMAR) for statistical analysis.

The same specialist performed the measurements by using the same OCT device (Optovue OCT V 5.1, RTVue 100-2; Optovue, Fremont, CA, USA) after pupillary mydriasis by using 2.5% phenylephrine and 1% tropicamide.

The mean changes in BCVA from baseline to the final study visit were the primary endpoint of the study. Secondary endpoint was changes in central macular thickness from baseline to the final study. Additionally monthly analyzes of BCVA and CMT were performed. Serum hemoglobin A1c (HbA1c) levels were also measured at the baseline and at the 6 months.

Statistical Package for the Social Sciences (SPSS) version 20.0 software was used for all statistical analyses. Descriptive statistics are presented as 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

Sixty-three of 44 patients fulfilled the inclusion criteria and are included in the current study. The demographic characteristics of patients and the mean follow up time are shown in Table 1.

Table 1. *Demographic Characteristics.*

Parameters	Values	Range
Mean Age(y)	58.5±8,8	22-77
Patients/eye	44/63	
Female/male	24/39	
Mean Follow-up Time After Aflibercept	8.74±3.49	6-16
Mean number of aflibercept injections	3.2±0.53	3-5
Phakia/pseudophakia	49/14	
History of glaucoma (E)	2	
Type of DM Tip1/Tip2	1/44	
HbA1C *(Mean± SD)	**8.1±0.9**	
HbA1C ° (Mean± SD)	**8.0 ±1.0**	

y: year, m: month E: eye, *; at the beginning of aflibercept therapy, °; at the 6 month

The mean BCVA (logMAR) is 0.79±0.47 (0.1-2.0) before beginning the treatment of aflibercept. In the final examination of all our patients, the mean final BCVA (logMAR) increases to 0.55±0.40 (0.1-2.0) after applying a mean of 3.2±0.53 aflibercept injections which is statistically significant compared to baseline (Table 2), (Fig 1A), (p= 0.001). The monthly follow-up of BCVA (logMAR) is shown in Table 2. At the final examination, mean letter gain is 13.5±15.7 letters. At the final examination, gains in ETDRS letters are documented in 44 eyes (69.8%), with gains ≥10 letters in 40 eyes (63.9%), ≥15 letters in 36 eyes (57.1%), and ≥20 letters in 18 eyes (28.5%). VA remains stable in 19 eyes (30%). However, the mean CMT decreases in 8 of these 19 eyes.

The mean CMT is 430.8±135.39 µm (242-806) before initiating treatment with aflibercept. In the final examination of all our patients following aflibercept therapy, the mean final CMT decreases to 303.6±57.7 µm (210-529) which are statistically significant compared to baseline (p= 0.0001),

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	0.79±0.47	0.80±0.41	0.67±0.36	0.60±0.35	0.59±0.41	0.50±0.29	0.54±0.40	0.57±0.43	0.57±0.48	0.60±0.43	0.67±0.44	0.57±0.31	0.47±0.37	0.55±0.40
(Min-Max)	(0.1-2.0)	(0.15-2.0)	(0.1-2.0)	(0.1-2.0)	(0.15-2.0)	(0.15-1.3)	(0.1-2.0)	(0.15-1.3)	(0.1-2.0)	(0.1-2.0)	(0.15-1.3)	(0.3-1.0)	(0.1-2.0)	(0.1-2.0)
	n=63	p*=0.10 n=63	p*=0.002 n=63	p*=0.001 n=63	p*=0.001 n=53	p*=0.001 n=40	p*=0.001 n=40	p*=0.024 n=23	p*=0.028 n=23	p*=0.019 n=21	p**=0.017 n=16	p**=0.7 n=10	p**=0.035 n=16	p*=0.001 n=63
CMT, µm Mean±SD	430.8±135.39	343.7±92.2	312.0±75.1	289.8±53.7	299.2±67.9	279.2±50.5	281.2±32.4	290.6±50.9	385.7±158.9	337.5±117.5	341.3±75.4	294.0±69.4	280.2±73.3	303.6±57.7
(Min-Max)	(242-806)	(202-769)	(242-425)	(241-523)	(225-522)	(179-380)	(241-336)	(203-389)	(210-532)	(256-679)	(271-343)	(237-394)	(210-496)	(210-529)
	n=63	p*=0.001 n=63	p*=0.0001 n=63	p*=0.0001 n=63	p*=0.0001 n=53	p*=0.0001 n=40	p*=0.0001 n=40	p*=0.004 n=23	p*=0.31 n=23	p*=0.15 n=21	p**=0.12 n=16	p**=0.124 n=10	p**=0.001 n=16	p*=0.0001 n=63
IOP,mmHg Mean ±SD	16.18±2.11	16.15±2.31	16.09±2.33	16.21±2.36	16.39±2.29	16.38±2.28	16.29±2.38	16.01±2.27	16.29±2.26	16.49±2.11	16.53±2.45	16.59±2.18	16.41±2.12	16.01±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=63	P*=0.1 n=63	p*=0.09 n=63	p*=0.04 n=53	p*=0.034 n=40	p*=0.01 n=40	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=16	p*= 0.28 n=63

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).

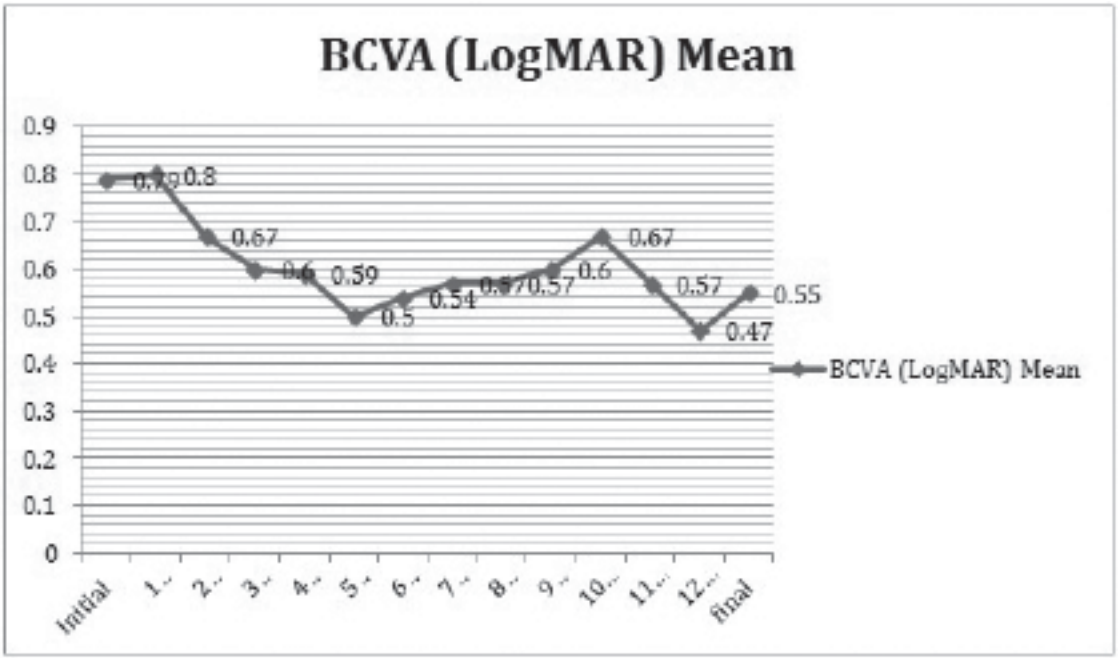

Figure 1A. *Mean BCVA at the onset of aflibercept treatment and follow-up months.*

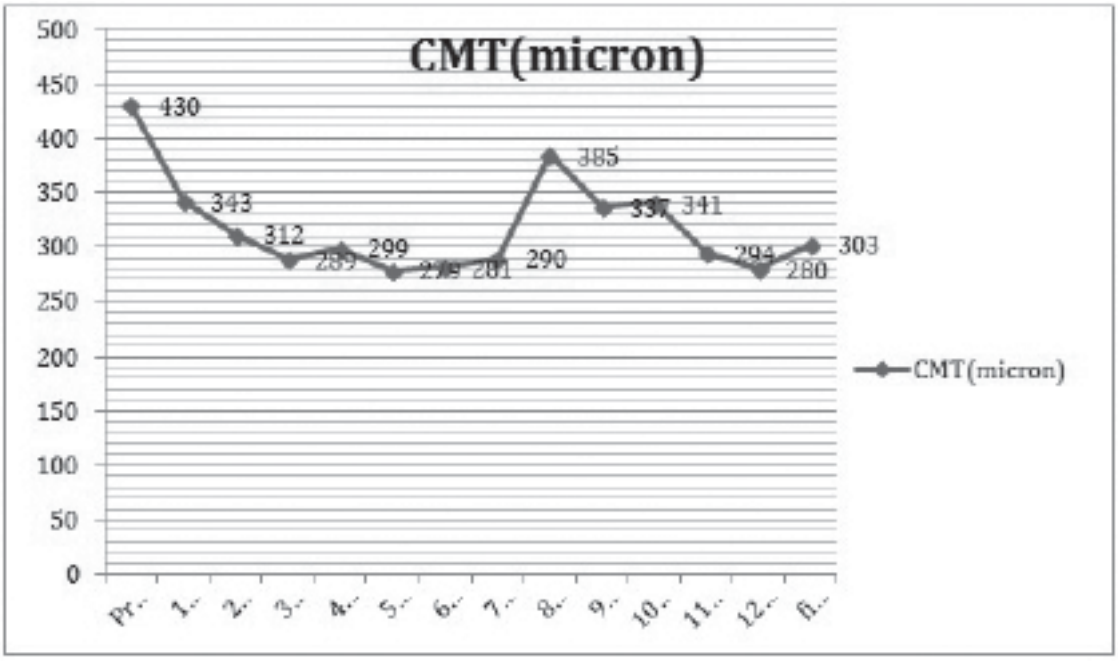

Figure 1B. *Mean CMT at the onset of aflibercept treatment and follow-up months.*

(Table 2), (Figure 1B). Monthly follow-up of CMT is shown in Table 2.

After excluding patients with glaucoma, while Baseline IOP value of all eyes is measured as 16.18±2.11 (11-20) mmHg, final IOP value of all eyes is 16.01±2.37 (12-19) mmHg. The decrease of mean IOP is statistically not significant under aflibercept treatment, (p=0.27), (Table 2), (Figure 1C).

The mean HbA1c level is 8.1 ± 0.9 at the beginning of aflibercept therapy and 8.0 ±1.0 at the 6 months (p=0.391).

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

DISCUSSION

The current retrospective study is designed in daily clinical practice to evaluate the effectiveness of intravitreal aflibercept for the treatment of patients with clinically significant DME and naive to anti-VEGF treatment. In randomized Phase III clinical trials VISTA-DME and VIVID-DME, patients are randomized to intravitreal aflibercept therapy 2 mg

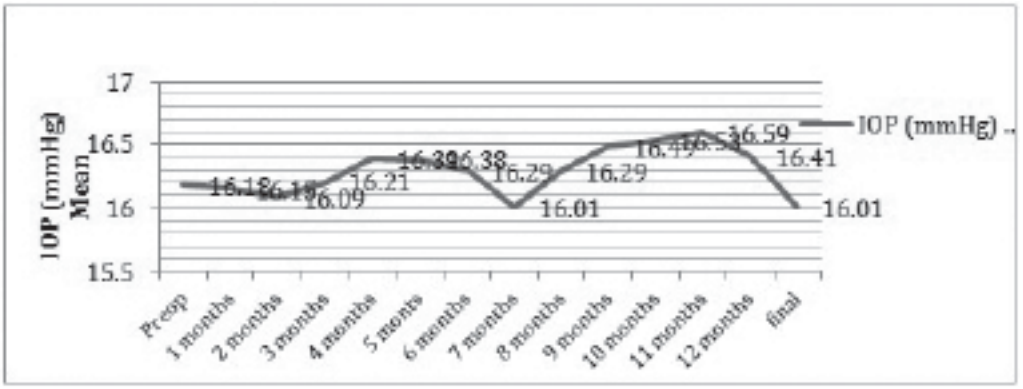

Figure 1C. *Mean IOP at the onset of aflibercept treatment and follow-up months.*

every 4 weeks (2q4; n=290), 2 mg every 8 weeks (2q8; n=286) after five initial monthly doses, or macular laser photocoagulation (n=286).[10,11] Their primary endpoint is the change from baseline in BCVA in ETDRS letters at week 52. The mean gain in ETDRS letters are 12.5, 10.7, and 0.2 in the 2q4, 2q8, and laser groups, respectively after aflibercept treatment. Additionally, the mean reduction in CMT is reported as 185.9 and 195.0 µm, and 183.1 and 192.4 µm for the 2q4 and 2q8 regimens of aflibercept, respectively, in this two randomized trials.[10,11] Results obtained in our study are gain of 13.5±15.7 ETDRS letters which are consistent with these trials.[10,11] However, the mean reduction in central macular thickness of the present study is 127.7 ±152.1 µm after a mean number of 3.2±0.53 aflibercept injections. The real world settings and the lower number of intravitreal injections can cause the lower reduction of central macular thickness in the present study.

The data of the real-world setting on the effect of aflibercept for the management of DME is limited. Campos et al.[12] design a prospective study in the real-world setting, followed for 12 months, in whom aflibercept is indicated as a first-line therapy. Faudo and Bahgat[13] design a randomized prospective study conducted in daily practice which compares intravitreal aflibercept and ranibizumab after a follow-up of 12 months in 70 eyes with DME. The most important difference between this two study is the treatment regimen. Campos et al.[12] apply five loading doses of aflibercept injections every 4 weeks and then a fixed dose every 8 weeks, Fouda et al.[13] perform an as-needed treatment regimen after three loading doses of aflibercept every 4 weeks. Campos et al.[12] reports a mean gain of 13.0 ETDRS letters after aflibercept treatment. They present that gains in ETDRS letters are documented in all eyes at 12 months with gains ≥10 letters in 89.6% (n=26), ≥15 letters in 65.5% (n=19), and ≥20 letters in 6.9% (n=2). The mean reduction in central macular thickness is 231 µm in their study.[12] Additionally, Fouda et al.[13] report visual improvement in 22 eyes (62.9%) treated with aflibercept in an as-needed treatment. The visual acuity worsens in 7 eyes (20%) and remains stable in 6 eyes (17.1%) in their study. Fouda and Bahgat[13] also report the mean reduction in central macular thickness as 105 µm. In the present study gains in ETDRS letters are documented in 44 eyes (69.8%), with gains ≥10 letters in 40 eyes (63.9%), ≥15 letters in 36 eyes (57.1%), and ≥20 letters in 18 eyes (28.5%) however, visual acuity remains stable in 19 eyes (30%). We also find the mean reduction in central macular thickness as 127.7 ±152.1 µm after applying a mean number of 3.2±0.53 aflibercept injections in the present study. Because the same treatment regimen is used in both studies, our results are comparable with the results of Faudo and Bahgat[13]. However, the improvement of visual acuity and the decrease of CMT are not as successful as the study presented by Campos et al. due to the as-needed treatment regimen. But, the most important advantages of the as-needed treatment regimen are 1. lower economic cost, and 2. Applicability in daily life.

Limitations of the study include retrospective design and the small sample. The lack of masking for visual acuity and OCT measure and lack of a control group may also affect the reliability of our results. However, under real-life setting, the present study shows that aflibercept injections applying in an as needed treatment regimen are successfull as a first-line therapy in patients with treatment-naïve DME, with sustained BCVA improvement and reduction in central macular thickness.

In conclusion, we recommend that aflibercept could be used as a first-line therapy in patients with treatment-naïve DME. Clinicians could decrease the number of injections with using as-needed treatment regimen, with a comparable improvement of visual acuity.

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