

ORIGINAL RESEARCH

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Efficacy and safety of intravitreal aflibercept therapy in diabetic macular edema**Ali Cihat Aslan, Serkan Erdenoz, Akin Cakir, Burak Erden, Cetin Akpolat, Mustafa Nuri Elcioglu***Okmeydani Training and Research Hospital, Department of Ophthalmology, Istanbul, Turkey*

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To conduct a retrospective evaluation of the efficacy and safety of intravitreal aflibercept treatment in diabetic macular edema. Patients treated with intravitreal aflibercept for diabetic macular edema participated in this study. Three injections were administered to the previously untreated 76 eyes of 50 patients for 3 consecutive months with one-month interval. The results were evaluated retrospectively by analyzing the patients' medical records. The patients' values of "best corrected visual acuity" inverted according to Snellen chart, and their central macular thickness and intraocular pressure were compared before and after treatment. The average age of the patients was 57.2 ± 10.1 . Of the cases, 77.6% were phakic, and 22.4 % were pseudophakic. The increases in "best corrected visual acuity" in the first month after each injection and at the end of the third month were statistically significant ($p < 0.001$). The mean central macular thickness was $405.63 \pm 106.93 \mu\text{m}$ before treatment and $288.83 \pm 62.49 \mu\text{m}$ after the third injection. This reduction in the mean central macular thickness was statistically significant ($p < 0.05$). During and after the three-month follow-up of the injection application process, the most common observed ocular side effect was subconjunctival hemorrhage (34.2%). During or after the applications, no systemic side effects, such as sudden death, thromboembolic events, or myocardial infarction, were seen. Functionally and anatomically, intravitreal aflibercept injection therapy in diabetic macular edema is an effective treatment option because it improves visual acuity and decreases central macular thickness.

Keywords: Central retinal thickness, diabetic retinopathy, vascular endothelial growth factor, aflibercept**Introduction**

Depending on the reduced synthesis of the insulin hormone or the resistance of the peripheral tissues to the insulin hormone, diabetes mellitus (DM) is a multisystemic disease characterized by chronic hyperglycemia; changes in carbohydrate, fat, and protein metabolism; impaired capillary membranes; and subsequent accelerated atherosclerosis [1-3].

Besides the prevalence of DM varies among different populations, it is 1–2% [3]. The most important risk factor for the development of diabetic retinopathy (DR) is the total duration of the disease [4]. The incidence of retinopathy is very low in individuals who have had Type I DM (insulin-dependent DM) for less than five years.

It is present in 27% of those who have had Type I DM for 5–10 years and 71–90% of those who have had Type I DM longer than 10 years. The incidence increases to 95% after 20–30 years, with proliferative diabetic retinopathy (PDR) developing in 30–50% of

these patients. In patients with non-insulin dependent diabetes, the incidence of DR is 23% at 11–12 years, 60% at 16 and more years. After 16 years, the incidence of PDR has been found to be 3% [5,6].

DR is divided into non-proliferative diabetic retinopathy (NPDR) and PDR. In NPDR, the lesions manifest only as local pathologies in retinas whereas the lesions in PDR also spread to the vitreous [7].

Diabetic macular edema (DME) can develop at any stage of DR, and it is one of the most important causes of vision loss from DR. The frequency of macular edema increases with the severity of DR. DME was reported in 3% of mild NPDR cases, 38% of moderate or severe NPDR cases, and 71% of PDR cases [8,9].

DME is caused by retinal microangiopathy, which is treated by laser photocoagulation, anti-vascular endothelial growth hormone (anti-VEGF), intravitreal corticosteroids, and combinations of these treatments.

In this study, following the administration of repeated intravitreal injections, the effects of the anti-VEGF agent aflibercept on visual acuity, intraocular pressure (IOP), and central macular thickness (CMT) were investigated.

*Corresponding Author: Ali Cihat Aslan, Okmeydani Training and Research Hospital, Department of Ophthalmology, Istanbul, Turke
E-mail: alicihataskan@gmail.com

Material and Methods

Prior to the study, approval was obtained from the local Ethics Committee. The study included patients who received intravitreal aflibercept (IVA) treatment for DME. In this retrospective study, 76 eyes of 50 patients with Type 1 and Type 2 diabetes were evaluated.

Inclusion criteria:

- Macular edema associated with DM
- CMT values of $>260 \mu\text{m}$
- Three injections over 3 consecutive months

Exclusion criteria:

- Macular edema other than DR (uveitis, retinal vein occlusion, etc.)
- History of glaucoma
- Cataract or vitreoretinal surgery interventions in the previous 6 months
- Focal or grid laser treatments in the previous 3 months

The patients' files were analyzed to obtain the recorded visual acuity, CMT, and IOP parameters required for the study. Before the IVA injection was administered to the patients and four weeks after each application, the best corrected visual acuity (BCVA) was determined in converted logMAR unit according to the Snellen chart. The CMT values were measured with optical coherence tomography (OCT) (Cirrus SD-OCT Model 4000, Carl Zeiss Meditec, Dublin), and the IOP values were measured by Goldmann applanation tonometry.

Optical Coherence Tomography Measurement Method

The measurement was performed using the fast-macular thickness protocol of the Cirrus SD-OCT Model 4000 device. The pupil diameter of $\geq 5 \text{ mm}$ required for optimum measurement was obtained in all patients because detailed biomicroscopic and fundoscopic examinations were performed at the beginning of the study. The fundus was imaged by Cirrus SD-OCT with a modified ETDRS grille ($6 \times 6 \text{ mm}$), and values such as the retinal thickness and macular volume (MV) between the inner limiting membrane (ILM) and retinal pigment epithelium (RPE) were obtained. Images with artefacts resulting from unintentional eye movements and images with signal levels of 0.22 logMAR or worse were not included. These image captures were repeated.

The modified ETDRS grid (Figure 1) was divided into nine independent sectors. These circular maps consist of three interlaced circles with diameters of 1 mm, 3 mm, and 6 mm. From the center of the fovea are a central sector (Cen) with a radius of $500 \mu\text{m}$, an inner sector $500 \mu\text{m}$ – $1,500 \mu\text{m}$ from the foveal center divided into four quadrants (Sin, Tin, Iin, and Nin) and an outer sector $1500 \mu\text{m}$ – $3,000 \mu\text{m}$ from the foveal center also divided into four quadrants (Sout, Tout, Iout, and Nout). These are all represented in the grid [10].

The central subfield thickness and the volume cube parameters were subtracted from the data obtained by Cirrus SD-OCT. The parameter measured as the central subfield thickness corresponds to the 1 mm area of the modified ETDRS grid. This is indicated in the current study as the CMT. The volume cube represents the retinal volume in the 6 mm diameter central portion of the macula. This value was defined as the MV.

Method for Intravitreal Injections

An IVA injection was administered by an experienced physician under sterile conditions following pupillary dilatation. After the periocular skin was cleaned with 10% povidone iodide, the patient was dressed with a sterile drape, and a sterile retractor was fixated. Prior to receiving the injections, the patients were given proparaine drops as a topical anesthetic. In addition, 2 mg aflibercept was injected into the vitreous with a 30-gauge needle 3.5 mm behind the limbus in patients who had undergone cataract surgeries, and 4 mm was injected behind the limbus in patients who had not undergone cataract surgery. Immediately after the needle was pulled back following injection, short-term pressure was gently applied with a cotton tipped applicator to the injection point to prevent the backflow of the drug or vitreous and to prevent conjunctival hemorrhage. After injection, the patients were prescribed moxifloxacin drops 8 times per day for 7 days. The patients were told to be on the alert for symptoms such as sudden and unexpected vision loss, pain, and redness. They were checked for infection and other complications on the first day of follow-up.

From the first month, the patients were examined after the administration of each injection. At each visit, detailed ophthalmologic examinations were performed, the same parameters were studied, and the OCT measurements were repeated. The fundus examination findings were recorded following the dilatation of the pupils. The patients with IOP higher than 21 mmHg were planned to be started on anti-glaucomatous treatment. Complications were also noted.

Statistics

IBM SPSS Statistics version 18.0 for Windows was used to evaluate the data obtained in the study. In addition to descriptive statistical methods, the paired sample t-test was used for the intra-group comparison of the normal distributed parameters, the Wilcoxon sign test was used for the intra-group comparison of the non-normal distributed parameters, and the Friedman test was used for comparing two or more interrelated distributions. Multivariate linear regression analysis was used to investigate the predictive factors affecting CMT reduction and BCVA gain. A p value of <0.05 was considered statistically significant.

Results

This study assessed 76 eyes of 50 patients: both eyes of 26 patients and a single eye of 24 patients. Of these patients, 26 (34.22%) eyes belonged to females, and 50 (65.78%) belonged to males. In the study, 59 (77.63%) of the eyes were phakic, and 17 (22.37%) eyes were pseudophakic. In addition, 56 (73.7%) of the eyes had NPDR, and 20 (26.4%) had PDR. The mean duration of DM in these 50 patients was 11.83 years.

The mean BCVA at baseline was $0.38 \pm 0.26 \text{ logMAR}$. It was $0.53 \pm 0.32 \text{ logMAR}$ 4 weeks after the first injection, $0.57 \pm 0.34 \text{ logMAR}$ 4 weeks after the second injection, and 0.64 ± 0.33 4 weeks after the third injection (Figure 1). The mean CMT was $405.63 \pm 106.93 \mu\text{m}$ at baseline, $328.58 \pm 77.824 \mu\text{m}$ after the first injection, $299.96 \pm 66.25 \mu\text{m}$ after the second, and $288.53 \pm 62.49 \mu\text{m}$ after the third (Figure 2). The mean MV values were as follows: $12.55 \pm 1.91 \text{ mm}^3$ at baseline, $11.83 \pm 1.54 \text{ mm}^3$ after the first injection, $11.36 \pm 1.19 \text{ mm}^3$ after the second injection,

and 11.23 ± 1.10 mm³ after the third injection (Figure 4.3). The mean IOP was 15.53 ± 3.44 mmHg before treatment, 15.21 ± 3.25 mmHg after the first injection, 15.21 ± 3.25 mmHg after the second injection, and 15.14 ± 3.20 mmHg after the third injection.

The statistical analysis revealed significant alterations in the BCVA, CMT, and MV values at all visits ($p < 0.001$); however, there were no statistical changes in the mean IOP values ($p = 0.724$). (Table 1)

Table 1. The alteration of the data during follow up

	Baseline	Month1	Month 2	Month 3	P value
BCVA (logMAR)	0.38±0.26	0.53±0.32	0.57±0.34	0.64±0.33	<0.001
CMT (µm)	405.63±106.93	328.57±77.82	299.96±66.25	288.57±62.49	<0.001
MV (mm3)	12.55±1.91	11.83±1.54	11.36±1.19	11.23±1.10	<0.001
IOP (mmHg)	15.53±3.44	15.21±3.25	15.21±3.25	15.14±3.20	0.724

BCVA: Best corrected visual acuity, CMT: Central macular thickness, MV: Macular volume, IOP: Intraocular pressure

There was a statistically significant difference in the monthly evaluation of the CMT and MV mean values ($p < 0.05$). Other than the insignificant difference between the first and second months ($p = 0.053$), there was a significant difference ($p < 0.05$) in the mean values of the BCVA. (Table 2)

When the correlation of the BCVA gain with the other parameters was assessed, the baseline BCVA ($R = -0.228$, $p = 0.024$) was found to be statistically significant but slightly correlated with the baseline CMT ($R = 0.242$, $p = 0.018$) and the baseline MV ($R = 0.304$, $p = 0.004$). (Table 3)

Table 2. Evaluation of differences using binary comparison (Wilcoxon Test)

	CMT1- Baseline CMT	CMT2- Baseline CMT	CMT3- Baseline CMT	CMT2-CMT1	CMT3-CMT1	CMT3-CMT2
P value	0.000	0.000	0.000	0.000	0.000	0.020
	BCVA1-Baseline BCVA	BCVA2- Baseline BCVA	BCVA3- Baseline BCVA	BCVA2-BCVA1	BCVA3-BCVA1	BCVA3-BCVA2
P value	0.000	0.000	0.000	0.053	0.001	0.015
	MV1-Baseline MV	MV2- Baseline MV	MV3- Baseline MV	MV2-MV1	MV3-MV1	MV3-MV2
P value	0.000	0.000	0.000	0.000	0.000	0.008

BCVA: Best corrected visual acuity, CMT: Central macular thickness, MV: Macular volume, 1: First month, 2: Second month, 3: Third month

Table 3. Parameters related to visual acuity gain (pearson correlation analysis)

Parameters	R value	P value
Age	-0.092	0.216
Gender	-0.130	0.132
Baseline BCVA	-0.228	0.024
Baseline CMT	0.242	0.018
Baseline MV	0.304	0.004
Edema Type	-0.092	0.216
Diabetes Type	-0.078	0.251

BCVA: Best corrected visual acuity, CMT: Central macular thickness, MV: Macular volume

When the predictive values, which were effective on the final BCVA were examined, the baseline BCVA was observed to be statistically significant (B coefficient=0.766, $p < 0.001$). Thus, when the baseline BCVA increased by 1 unit, the final BCVA increased by 0.766 units. In addition, another parameter that was observed to be closest to statistical significance was the baseline

MV (coefficient B=0.044, $p = 0.082$). When the baseline MV increased by 1 unit, the final BCVA increased by 0.044 units.

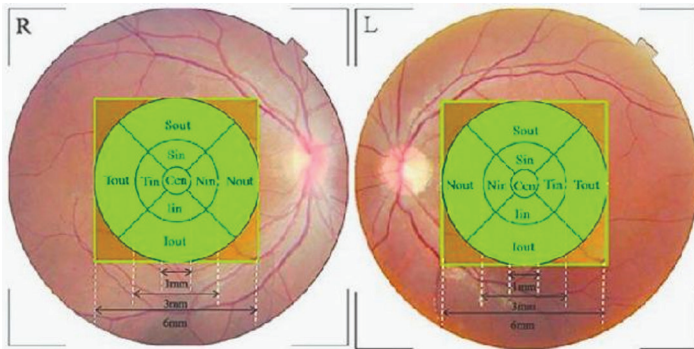
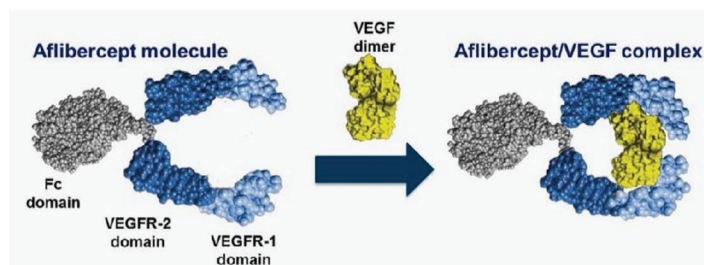
When the predictive values that could affect BCVA gain were examined, the baseline BCVA was observed to be the closest value to statistical significance (B coefficient=-0.234, $p = 0.072$). When the baseline BCVA increased by 1 unit, the BCVA gain decreased by 0.234 units. Thus, a higher BCVA gain was achieved in the cases with a lower baseline BCVA. Another parameter that was observed to be close to statistical significance was the initial MV (coefficient B=0.044, $p = 0.082$). When the baseline MV increased by 1 unit, the gain of the BCVA increased by 0.044 units. When the predictive values that could be effective on the final CMT were examined, only the baseline CMT was found to be statistically significant (B coefficient=0.274, $p = 0.007$). When the baseline CMT increased by 1 unit, the final CMT increased by 0.274 units. Thus, the higher the baseline CMT, the higher the final CMT.

When the effective predictive values on CMT recovery were examined, only the baseline CMT was statistically significant (B coefficient: 0.726, $p < 0.001$). When the baseline CMT increased by 1 unit, the CMT gain was 0.726 units. Thus, higher CMT gains were observed in cases with higher CMT values. (Table 4)

Table 4. Predictive factors (multiple linear regression analysis table)

	Parameter	B coefficient	P value
Final BCVA	Baseline BCVA	0.766	0.000
	Baseline MV	0.044	0.082
BCVA Gain	Baseline BCVA	-0.234	0.072
	Baseline MV	0.044	0.082
Final CMT	Baseline CMT	0.274	0.007
	Baseline CMT	0.726	0.000

BCVA: Best corrected visual acuity, CMT: Central macular thickness, MV: Macular volume

**Figure 1.** The modified ETDRS grid**Figure 2.** Molecular structure of aflibercept

Discussion

Treatment approaches for DME vary because of the differences in the mechanisms of macular edema. They can be grouped into three main categories: laser photocoagulation, intravitreal steroid injection, and intravitreal anti-VEGF injection [11,12]. Treatment success is assessed through OCT, and the treatment options can be changed on the basis of the OCT results. Significant ocular problems can occur when DME is not treated. When untreated, 24% of eyes with clinically significant macular edema (CSME) and 33% of eyes with centralized CSME will have moderate vision loss within 3 years [13,14].

Aflibercept consists of an IgG backbone fused to extracellular VEGF receptor sequences of human VEGFR1 and VEGFR2 (Figure 2). As a soluble trap receptor, it binds to VEGF-A with greater affinity than its natural receptors. Aflibercept's high affinity to VEGF prevents the signaling and activation of the natural VEGF receptors. Reduced VEGF activity leads to decreased angiogenesis and decreased vascular permeability. In addition, the inhibition of PlGF and VEGF-B also contributes to antiangiogenesis [15-17].

Aflibercept has been used prospectively in some studies on DME as an anti-VEGF. And DA VINCI, VIVID, and VISTA studies

have been conducted. In the DA VINCI study, an average of 11.4 letters of visual acuity were gained with an average of 5.5 injections at week 24. The VISTA study in the United States and the VIVID study in Europe were conducted with a similar arrangement. The general information obtained from these studies is that approximately 2 lines of visual acuity gain were observed with 8–12 injections at week 52 [18].

An objective the DRCR.net Protocol T study was to compare the effect of three anti-VEGFs. Bevacizumab (1.25 mg), ranibizumab (0.3 mg), and aflibercept (2 mg) were randomly injected into 660 patients. In the first year, gains of 9.7 letters in the bevacizumab group, 11.2 in the ranibizumab group, and 13.3 in the aflibercept group were achieved. In the second year, the gains in letters were 10, 12.3, and 12.8 in the bevacizumab, ranibizumab, and aflibercept groups, respectively. The average number of injections performed in the first year was reported as 10 for each of bevacizumab and ranibizumab and 9 of aflibercept. The average number of injections in the second year was reported as 6 each of bevacizumab and ranibizumab and 5 of aflibercept [19,20].

Aflibercept and focal or grid laser therapy were compared in a study conducted by Do et al. [21] The randomized multicentered double-blind study comprised 221 patients. Depending on the administration of aflibercept at different doses and intervals, the gain in visual acuity for the aflibercept group was reported as 9.7–13.1 letters at the end of the first year. A reduction of 1.3 letters was reported for the laser group. The decrease in central retinal thickness was 127–194 μm in the aflibercept group, but it remained at 67.9 μm in the laser group.

This study, which included naive patients with DME, aimed to investigate the effects of 2 mg IVA injections on visual acuity, CMT, MV, and IOP. In addition, it assessed the possible complications.

A statistically significant decrease in CMT values was observed at all visits, and the mean decrease of 117 μm at the end of the third month was found to be statistically significant. These results were similar to those of previous studies.

Because the MV represents a wider area, 6 mm diameter, of the macula as opposed to a 1 mm diameter area of the central macula represented by the CMT, the MV might be an ancillary parameter to the CMT in treatment follow-up and planning. Although there was not a significant decrease in CMT in some of the cases, there was a significant decrease in MV. In contrast, in the current study, the analysis of the predictive factors affecting BCVA gain and final BCVA indicated that the most significant parameter after the baseline BCVA was the baseline MV.

Paracentral scotomas have an important role in the reading difficulty of patients with decreased visual acuity. It is likely that the decrease in MV is an indirect parameter indicating a decrease in paracentral scotomas. Thus, MV reduction might have a positive effect on the evaluation of patients' general reading activities (e.g., newspapers and magazines).

When the BCVA gain was correlated with the other parameters of the cases, it was found to be statistically significant but slightly associated with the baseline BCVA, baseline CMT, and baseline MV. The worse the baseline BCVA, the higher the BCVA gain.

The greater the baseline CMT and the baseline MV, the higher the BCVA gain. Age, sex, type of edema, and diabetes type had no significant effect on visual acuity outcomes.

In this study, the statistically significant parameter affecting the final BCVA was found to be the baseline BCVA, and the baseline MV parameter was the closest to statistical significance on the final BCVA. Thus, the better the baseline BCVA, the better the final BCVA; however, an opposite finding drew attention to BCVA gain. Patients with a worse baseline BCVA had a higher BCVA gain (peak effect), but they did not achieve the final BCVA values reached by patients with a higher baseline BCVA. The parameter closest to significance level on BCVA gain was the baseline MV, which had a positive correlation with BCVA gain.

The only statistically significant parameter on the final CMT was the baseline CMT: namely, the higher the baseline CMT, the higher the final CMT. In contrast, the patients with a higher baseline CMT had a greater CMT gain. However, these patients did not achieve the optimal CMT values reached by the patients with a lower baseline CMT.

In sum, early diagnosis in the treatment of DME and, therefore, early anti-VEGF treatment are very important. The final BCVA was at the highest levels and the final CMT was at the most optimal levels with intravitreal aflibercept treatment initiation when the BCVA was not yet greatly decreased and the CMT was not yet greatly increased. However, in patients with delayed admission or onset of symptoms, the baseline BCVA was much worse, and the baseline CMT was much higher. Despite the increased letter gain with late treatment, the final BCVA levels were never as good as those of the patients with a better baseline BCVA. Likewise, when the baseline CMT was higher, the CMT gain was greater than in patients with a lower baseline CMT. However, the higher baseline CMT values did not fall to the optimum levels like those of the patients with lower CMT.

Although a statistically significant decrease in CMT levels was observed each month, a correlated increase in CMT was not seen during this period. There might be a relationship between the reduction in CMT and the improvement in BCVA. Because anatomical correction does not always provide functional improvement, a significant change in BCVA was not observed between the first and second months. A lack of immediate improvement in BCVA in response to a decrease in CMT could lead a delay period, and this could result in a negative interpretation of patients' functional outcomes. Thus, according to the PRN treatment protocol, an anti-VEGF indication in patients with or without a loss in BCVA should be noted if an increase in CMT is observed at clinic visits.

In this study, subconjunctival hemorrhage (34.2%) was the most common complication from the injection technique. Although some side effects have been reported in the literature, no endophthalmitis, TRD, retinal tear, glaucoma, vitreous hemorrhage, or local or systemic side effects were observed in any of the patients [22,23].

Conclusion

In conclusion, IVA injection can be considered an effective and safe treatment option for DME. The absence of additional factors, such

as hypertension and lipid profile, that could increase the severity of macular edema, the relatively small number of patients, and the short duration of the follow-up are among the limitations of this study. Thus, prospectively designed studies should be conducted.

Competing interests

The authors declare that they have no competing interest

Financial Disclosure

All authors declare no financial support.

Ethical approval

Consent of Ethics was approved by local ethics committee.

Ali Cihat Aslan ORCID: 0000-0001-5889-0462

Serkan Erdenoz ORCID: 0000-0002-8673-6101

Akin Cakir ORCID: 0000-0001-5880-283X

Burak Erden ORCID: 0000-0003-0650-4552

Cetin Akpolat ORCID: 0000-0002-7443-6902

Mustafa Nuri Elcioglu ORCID: 0000-0002-8238-9106

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