S H O R T R E P O R T

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Visual acuity and anatomical outcomes of intravitreal aflibercept treatment in patients with center-involved diabetic macular edema – a retrospective longitudinal cohort study

Oštrina vida i anatomski ishodi lečenja intravitrealnim afliberceptom kod bolesnika koji imaju centralni dijabetični edem makule – retrospektivna longitudinalna kohortna studija

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Abstract

Background/Aim. Center-involved diabetic macular edema (CI-DME) is a major cause of vision loss in diabetes mellitus, characterized by retinal thickening (1 mm) in the central foveal zone. Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents, such as aflibercept, are widely used to treat retinal edema and improve visual outcomes. The aim of the study was to evaluate anatomical and functional changes of the retina following intravitreal administration of aflibercept in patients with CI-DME. **Methods.** This retrospective longitudinal cohort study included 70 eyes in 50 patients with optical coherence tomography (OCT)-confirmed CI-DME [with central foveal thickness (CFT) ≥ 350 μm and best-corrected visual acuity (BCVA) ≥ 0.6 Snellen], treated with three monthly aflibercept injections. BCVA, CFT, and macular volume (MV) were measured using the Optovue RTVue XR OCT device at baseline and after 1, 3, and 6 months of treatment. **Results.** Mean patient age was 64.63 ± 7.79 years. Hypertension was the most prevalent comorbidity (72.0%). Over the six-month follow-up period, significant reductions were observed in mean CFT (459.00 μm to 379.92 μm, $p < 0.001$) and MV (9.05 mm³ to 8.44 mm³, $p < 0.001$) values. Although BCVA showed modest improvement, it did not reach statistical significance. Anatomical improvements align with aflibercept's inhibition of VEGF-A and placental growth factor, which reduced vascular permeability. **Conclusion.** Intravitreal aflibercept significantly decreases retinal thickness and MV in patients with CI-DME, confirming its anatomical efficacy. Functional visual improvement was limited, possibly due to chronic retinal damage. In order to clarify the effect of intravitreal aflibercept on visual outcomes, longer-term studies with larger patient cohorts are required.

Keywords:
aflibercept; diabetic retinopathy; intravitreal injections; macular edema; ophthalmologic surgical procedures; tomography, optical coherence; treatment outcome; vascular endothelial growth factors.

Apstrakt

Uvod/Cilj. Dijabetični edem makule koji zahvata centar makule (*center-involved diabetic macular edema* – CI-DME) jedan je od glavnih uzroka gubitka vida kod obolelih od dijabetesa melitusa, a karakteriše ga zadebljanje mrežnjače (1 mm) u centralnoj zoni fovee. Intravitrealni lekovi koji inhibiraju faktor rasta vaskularnog endotela (*anti-vascular endothelial growth factor* – anti-VEGF), kao što je aflibercept, široko se koriste za lečenje edema mrežnjače i poboljšanje ishoda vidnih funkcija. Cilj rada bio je da se procene anatomske i funkcionalne promene mrežnjače nakon intravitrealne primene aflibercepta kod obolelih od CI-DME. **Metode.** Retrospektivnom longitudinalnom kohortnom studijom obuhvaćeno je 70 očiju kod 50 bolesnika koji su imali CI-DME, potvrđen pomoću *optical coherence tomography* – OCT [sa centralnom debljinom fovee (*central foveal thickness* – CFT) ≥ 350 μm i najbolje korigovanom vidnom oštrinom (*best-corrected visual acuity* – BCVA) ≥ 0,6 po Snellen-u], lečenih primenom tri mesečne injekcije aflibercepta. BCVA, CFT i makularni volumen (MV) mereni su na početku tretmana i nakon 1, 3 i 6 meseci pomoću Optovue RTVue XR OCT uređaja.

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Rezultati. Prosečna starost bolesnika iznosila je 64,63 ± 7,79 godina. Hipertenzija je bila najčešća pridružena bolest (72,0%). Tokom šestomesečnog praćenja zabeleženo je značajno smanjenje prosečne vrednosti CFT (sa 459,00 μm na 379,92 μm, $p < 0,001$) i MV (sa 9,05 mm³ na 8,44 mm³, $p < 0,001$). Iako je pokazano blago poboljšanje rezultata BCVA, ono nije dostiglo statističku značajnost. Anatomska poboljšanja bila su u skladu sa inhibicijom VEGF-A i faktora rasta posteljice dejstvom aflibercepta, čime je smanjena vaskularna permeabilnost. **Zaključak.** Intravitrealna primena aflibercepta značajno smanjuje debljinu i MV mrežnjače kod obolelih od CI-DME, potvrđujući njegovu anatomsku efikasnost. Funkcionalno poboljšanje vida bilo je ograničeno, verovatno zbog hroničnog oštećenja mrežnjače. Da bi se razjasnio uticaj intravitrealno primenjenog aflibercepta na ishode vidnih funkcija, potrebne su dugotrajnije studije koje uključuju veći broj bolesnika.

Ključne reči:
aflibercept; dijabetesna retinopatija; injekcije, intravitrealne; žuta mrlja, edem; hirurgija, oftalmološka, procedure; tomografija, optička, koherentna; lečenje, ishod; faktori rasta endotela krvnih sudova.

Introduction

Diabetic macular edema (DME) is characterized by retinal thickening and accumulation of extracellular fluid in the macula. This fluid typically accumulates in retinal layers, including the inner nuclear layer, outer plexiform layer, Henle's fiber layer, and subretinal space. Accurate assessment of DME requires a comprehensive three-dimensional evaluation, traditionally achieved through dilated fundus examination using slit-lamp biomicroscope and/or stereo fundus photography [1, 2].

Current clinical guidelines recommend multiple treatment modalities for DME, including intravitreal anti-vascular endothelial growth factor (VEGF) therapy, laser photocoagulation, and corticosteroid administration. Anti-VEGF agents target VEGF to reduce retinal vascular permeability, thereby decreasing macular edema and improving visual acuity (VA). Laser photocoagulation is primarily employed in non-center-involved DME (CI-DME) to stabilize or reduce edema, whereas corticosteroids are applied to mitigate inflammation and swelling in refractory cases [3].

CI-DME is clinically significant due to retinal thickening affecting the central subfield zone–a 1-mm diameter area centered on the fovea–which is strongly associated with visual impairment [4]. CI-DME necessitates more aggressive treatment, predominantly anti-VEGF therapy, as it represents the leading cause of vision loss among diabetic patients [5]. The global prevalence of DME is estimated at approximately 5.5% among individuals with diabetes mellitus, with no statistically significant difference observed between high-income and low-to-middle-income countries [6].

Diagnosis of DME integrates clinical fundus examination with advanced imaging modalities, including fluorescein angiography (FA), fundus autofluorescence, and optical coherence tomography (OCT). OCT is a non-invasive, non-contact imaging technique that provides high-resolution, cross-sectional retinal images. By analyzing the intensity and depth of reflected light, OCT enables precise localization of pathology within specific retinal layers. This capability facilitates both quantitative assessment of retinal thickness (RT) and qualitative evaluation of individual retinal layer integrity, which holds significant prognostic value for treatment response. Baseline disorganization of retinal inner layers (DRIL), hyperreflective foci, and the disruption of the external limiting membrane, ellipsoid zone, and cone outer segment tip have been associated with poorer VA, whereas post-treatment restoration correlates with VA improvement. In contrast, cystoid edema and serous detachment are predictive of significant thickness reduction [7].

Aflibercept (2 mg; Eylea®), a recombinant fusion protein that inhibits VEGF-A, VEGF-B, and placental growth factor (PlGF), has been approved by the United States Food and Drug Administration – FDA [8] and the European Medicines Agency – EMA [9] since 2012 for DME treatment.

The present study aims to evaluate functional outcomes, specifically best-corrected VA (BCVA) and morphological changes assessed by OCT parameters – central foveal thickness (CFT) and macular volume (MV) in patients with CI-DME treated with intravitreal aflibercept.

Methods

This retrospective longitudinal cohort study was conducted at the Clinic for Eye Diseases, Clinical Hospital Center "Zvezdara", Belgrade, Serbia, from April 2022 to February 2025. This study adhered to the tenets of the Declaration of Helsinki and Good Clinical Practice guidelines. The study was approved by the Ethics Committee of the Clinical Hospital Center "Zvezdara" (No. 02/10/2025, from October 06, 2025).

The study included 70 eyes in 50 patients diagnosed with CI-DME who were treated with intravitreal aflibercept. The unit of observation in this study was the eye, so when a patient received intravitreal treatment in both eyes, this was analyzed as two separate units of observation.

The eligibility criteria were defined by the Republic Health Insurance Fund, which covered treatment costs for patients meeting the following criteria: FA-confirmed macular leakage, OCT-measured CFT ≥ 350 μm, BCVA ≥ 0.6 (Snellen chart), and glycated hemoglobin (HbA1c) ≤ 8%. Exclusion criteria included: BCVA < 0.6, CFT < 350 μm, HbA1c > 8%, concomitant ocular pathologies (such as exudative age-related macular degeneration, retinal vascular occlusions, or retinal detachment), myocardial infarction or stroke within the previous 6 months, ocular or periocular inflammation, pregnancy, and age < 18 years.

Patients received intravitreal injections (IVIs) of aflibercept 2 mg (Eylea®, Bayer AG, Germany), approved by the National Health Fund for DME. The treatment protocol consisted of three consecutive monthly injections. Primary outcome measures included BCVA, CFT, and MV, recorded at baseline and 1, 3, and 6 months after the treatment.

All patients underwent a comprehensive ophthalmologic evaluation, including OCT and FA. OCT imaging was performed using the RTVue XR Avanti (Optovue Inc., Fremont, CA, USA) to measure MV and CFT. FA was conducted with the VisuCam 500 (Carl Zeiss, Germany) according to standard protocols.

Statistical analyses were performed using IBM SPSS Statistics 26.0. Categorical variables were summarized as frequencies and analyzed using the Chi-square test. Continuous variables were expressed as mean ± standard deviation. Normality was assessed using the Kolmogorov-Smirnov test. Repeated measures analysis of variance with Bonferroni correction was applied for longitudinal comparisons. A p-value < 0.05 was considered statistically significant.

Results

A total of 70 eyes in 50 patients with confirmed type 2 diabetes mellitus were included in the analysis. The study population comprised 27 men (54.0%) and 23 women (46.0%), with a mean age of 64.63 ± 7.79 years. All 70 eyes received intravitreal aflibercept treatment, including 31 right eyes (44.3%) and 39 left eyes (55.7%). IVIs were administered in both eyes in 20 (40.0%) patients, accounting for 40 (57.1%) of all treated eyes. IVIs were administered in one eye in 30 (60.0%) patients. Hypertension was the most prevalent comorbidity, present in 36 (72.0%) patients, followed by hyperlipidemia in 7 (14.0%) patients. Other comorbidities, recorded in 7 separate cases, included hypothyroidism (n = 2), deep vein thrombosis (n = 2), cerebrovascular insult (n = 1), epilepsy (n = 1), and chronic kidney disease (n = 1). All participants had at least one comorbidity (Table 1).

The mean CFT showed a statistically significant reduction over time, decreasing from 459.00 µm at baseline to 351.33 µm at 3 months, and remaining stable at 379.92 µm at 6 months ($p < 0.001$). Similarly, mean MV decreased significantly from 9.05 mm³ at baseline to 8.44 mm³ at 6 months ($p < 0.001$). BCVA demonstrated a slight but non-significant improvement compared to baseline (0.66 vs. 0.70; $p = 0.688$), with minor fluctuations across follow-up visits. After aflibercept treatment, CFT and MV decreased significantly ($p < 0.001$), indicating sustained anatomical improvement, while BCVA showed mild, non-significant fluctuations over 6 months ($p = 0.688$) (Table 2).

Table 1

Baseline characteristics of study patients

Characteristic	Value
Participants	50
Eyes included	70
Sex	
men	27 (54.00)
women	23 (46.00)
Age, years	64.63 ± 7.79
Treated eyes	
right	31 (44.30)
left	39 (55.70)
Patients receiving injections in both eyes (all patients)	20 (40.00)
Eyes treated bilaterally (all treated eyes)	40 (57.10)
Comorbidities	
hypertension	36 (72.00)
hyperlipidaemia	7 (14.00)
other comorbidities	7 (14.00)

All values are given as numbers (percentages) or mean ± standard deviation.

Table 2

Anatomical and functional outcome in patients with center-involved diabetic macular edema treated by aflibercept

Reference point	CFT, µm	MV, mm³	BCVA
Baseline	459.00 (436.29–451.74)	9.05 (8.74–9.37)	0.66 (0.62–0.70)
After the loading dose			
at 1 month	344.17 (325.24–363.10)	7.99 (7.76–8.21)	0.72 (0.66–0.78)
at 3 months	351.33 (322.91–379.76)	8.10 (7.81–8.38)	0.71 (0.64–0.79)
at 6 months	379.92 (344.77–414.87)	8.44 (8.09–8.79)	0.70 (0.64–0.77)
p-value	< 0.001	< 0.001	0.688

CFT – central foveal thickness; MV – macular volume; BCVA – best-corrected visual acuity.
All values are given as mean (95% confidence interval).

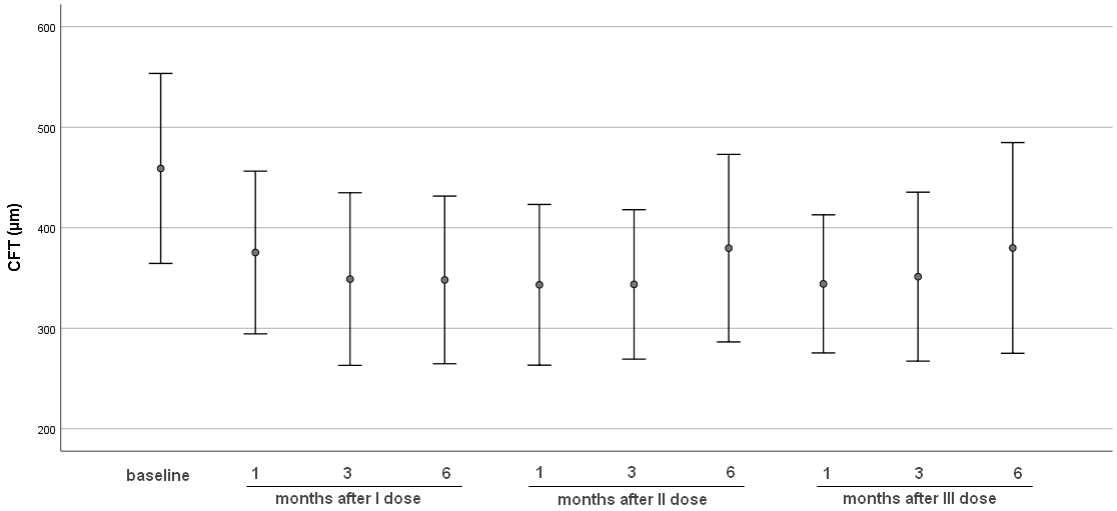

Fig. 1 – Mean values of central foveal thickness (CFT) before and after treatment administration. All values are given as mean ± standard deviation.

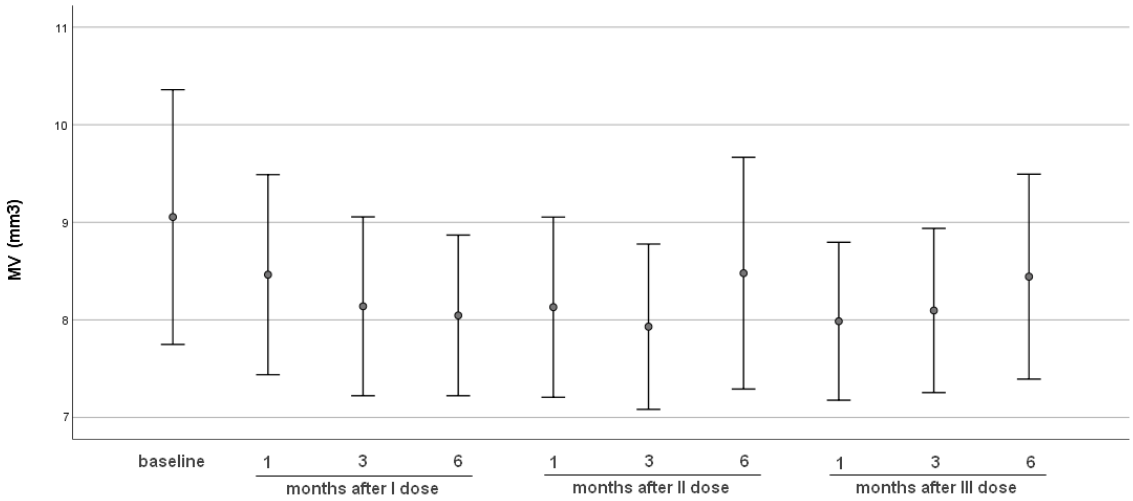

Fig. 2 – Mean values of macular volume (MV) before and after treatment administration. All values are given as mean ± standard deviation.

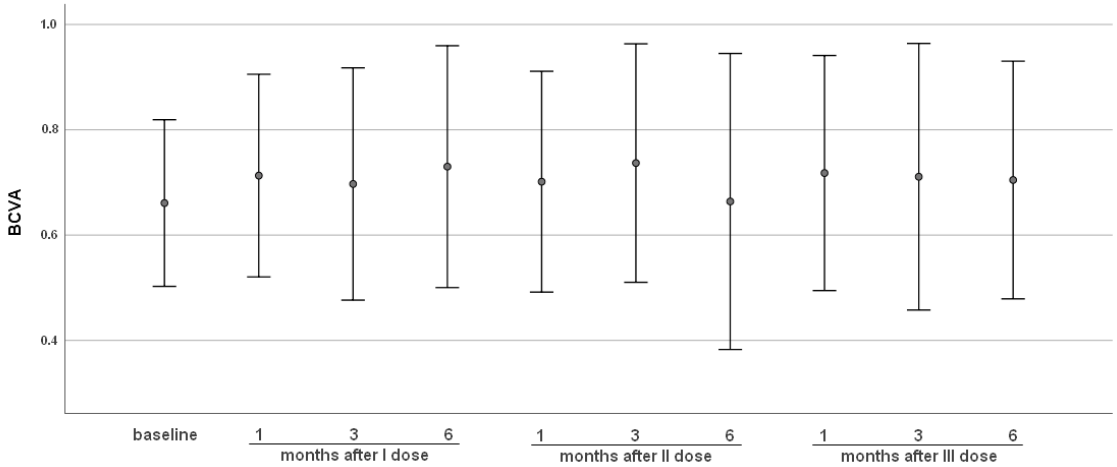

Fig. 3 – Mean values of best-corrected visual acuity (BCVA) before and after treatment administration. All values are given as mean ± standard deviation.

Comparing pre- and post-treatment metrics revealed a significant reduction in both CFT and MV, whereas BCVA remained statistically unchanged (Figures 1–3).

Baseline CFT was significantly higher than at all subsequent time points, decreasing from 459.00 µm to 379.92 µm at 6 months after the third dose (Table 3). It is

Table 3

The values of monitored parameters

Parameter/Time point	Mean (SD)	*p*-value
CFT, μm		
BL	459.00 (94.53)	
I1	375.38 (80.97)	
I3	348.94 (85.87)	
I6	348.12 (83.42)	
II1	343.24 (79.97)	
II3	343.65 (74.34)	< 0.001
II6	379.68 (93.30)	
III1	344.17 (68.69)	
III3	351.33 (84.01)	
III6	379.92 (104.82)	
Total	369.50 (92.26)	
MV, mm³		
BL	9.05 (1.30)	
I1	8.46 (1.03)	
I3	8.14 (0.92)	
I6	8.05 (0.82)	
II1	8.13 (0.92)	
II3	7.93 (0.85)	< 0.001
II6	8.48 (1.19)	
III1	7.99 (0.81)	
III3	8.10 (0.84)	
III6	8.44 (1.05)	
Total	8.30 (1.04)	
BCVA		
BL	0.66 (0.16)	
I1	0.71 (0.19)	
I3	0.70 (0.22)	
I6	0.73 (0.23)	
II1	0.70 (0.21)	
II3	0.74 (0.23)	0.688
II6	0.66 (0.28)	
III1	0.72 (0.22)	
III3	0.71 (0.25)	
III6	0.70 (0.23)	
Total	0.70 (0.22)	

SD – standard deviation; CFT – central foveal thickness; BL – baseline; MV – macular volume; BCVA – best-corrected visual acuity.
All values are given as mean (SD).
***Note*: Roman numerals indicate the first (I), second (II), and third (III) dose, and Arabic numerals indicate months (1, 3, 6) after each dose.**

noteworthy that 6 months after the second dose, there was another increase in CFT, although the value remained lower than before treatment (459.00 vs. 379.68). Following the third dose, CFT decreased again, with a slight rise 6 months after the third dose. A similar trend was observed in MV, decreasing from 9.05 mm³ to 8.44 mm³, with minor increases recorded at the same intervals as CFT – 6 months after the second and third doses.

Tables 4 and 5 present the results after the Bonferroni correction, showing that differences in CFT and MV were

Table 4

***Post hoc* comparison of central foveal thickness**

Comparison	Mean (95% CI)	*p*-value
BL vs. I1	83.621 (34.05–133.19)	< 0.001
BL vs. I3	110.061 (62.15–157.97)	< 0.001
BL vs. I6	110.881 (56.42–165.34)	< 0.001
BL vs. II1	115.762 (67.27–164.26)	< 0.001
BL vs. II3	115.346 (64.24–166.45)	< 0.001
BL vs. II6	79.324 (21.01–137.63)	< 0.001
BL vs. III1	114.830 (64.00–165.66)	< 0.001
BL vs. III3	107.667 (50.45–164.88)	< 0.001
BL vs. III6	79.081 (22.38–135.79)	< 0.001
I1 vs. I3	26.440 (-23.65–76.53)	1.000
I1 vs. I6	27.260 (-29.12–83.64)	1.000
I1 vs. II1	32.141 (-18.50–82.78)	1.000
I1 vs. II3	31.725 (-21.42–84.87)	1.000
I1 vs. II6	-4.297 (-64.40–55.81)	1.000
I1 vs. III1	31.209 (-21.67–84.09)	1.000
I1 vs. III3	24.046 (-35.00–83.09)	1.000
I1 vs. III6	-4.540 (-63.09–54.01)	1.000
I3 vs. I6	0.820 (-54.11–55.75)	1.000
I3 vs. II1	5.701 (-43.32–54.72)	1.000
I3 vs. II3	5.286 (-46.32–56.89)	1.000
I3 vs. II6	-30.737 (-89.48–28.01)	1.000
I3 vs. III1	4.770 (-46.56–56.10)	1.000
I3 vs. III3	-2.394 (-60.05–55.26)	1.000
I3 vs. III6	-30.980 (-88.13–26.17)	1.000
I6 vs. II1	4.881 (-50.55–60.32)	1.000
I6 vs. II3	4.465 (-53.27–62.20)	1.000
I6 vs. II6	-31.557 (-95.76–32.64)	1.000
I6 vs. III1	3.949 (-53.54–61.44)	1.000
I6 vs. III3	-3.214 (-66.42–59.99)	1.000
I6 vs. III6	-31.800 (-94.54–30.94)	1.000
II1 vs. II3	-0.416 (-52.56–51.72)	1.000
II1 vs. II6	-36.438 (-95.66–22.78)	1.000
II1 vs. III1	-0.932 (-52.80–50.94)	1.000
II1 vs. III3	-8.095 (-66.24–50.05)	1.000
II1 vs. III6	-36.681 (-94.32–20.96)	1.000
II3 vs. II6	-36.023 (-97.40–25.35)	1.000
II3 vs. III1	-0.516 (-54.83–53.80)	1.000
II3 vs. III3	-7.679 (-68.02–52.66)	1.000
II3 vs. III6	-36.265 (-96.12–23.59)	1.000
II6 vs. III1	35.507 (-25.64–96.65)	1.000
II6 vs. III3	28.343 (-38.21–94.89)	1.000
II6 vs. III6	-0.242 (-66.35–65.87)	1.000
III1 vs. III3	-7.164 (-67.27–52.94)	1.000
III1 vs. III6	-35.749 (-95.37–23.87)	1.000
III3 vs. III6	-28.586 (-93.73–36.56)	1.000

BL – baseline; CI – confidence interval. All values are given as mean (95% CI).

***Note*: Results of the Bonferroni-corrected correlation analysis. Roman numerals indicate the first (I), second (II), and third (III) dose, and Arabic numerals indicate months (1, 3, 6) after each dose.**

Table 5

***Post hoc* comparison of macular volume**

Comparison	Mean (95% CI)	*p*-value
BL vs. I1	0.59064 (0.0108–1.1705)	0.040
BL vs. I3	0.91437 (0.3539–1.4748)	< 0.001
BL vs. I6	1.00820 (0.3712–1.6452)	< 0.001
BL vs. II1	0.92328 (0.3561–1.4905)	< 0.001
BL vs. II3	1.12334 (0.5256–1.7211)	< 0.001
BL vs. II6	0.57538 (-0.1066–1.2574)	0.264
BL vs. III1	1.06788 (0.4734–1.6624)	< 0.001
BL vs. III3	0.95780 (0.2886–1.6270)	< 0.001
BL vs. III6	0.61067 (-0.0526–1.2739)	0.120
I1 vs. I3	0.32373 (-0.2621–0.9096)	1.000
I1 vs. I6	0.41756 (-0.2419–1.0771)	1.000
I1 vs. II1	0.33264 (-0.2597–0.9250)	1.000
I1 vs. II3	0.53270 (-0.0889–1.1543)	0.231
I1 vs. II6	-0.01525 (-0.7183–0.6878)	1.000
I1 vs. III1	0.47724 (-0.1413–1.0958)	0.526
I1 vs. III3	0.36716 (-0.3235–1.0578)	1.000
I1 vs. III6	0.02003 (-0.6648–0.7049)	1.000
I3 vs. I6	0.09383 (-0.5487–0.7363)	1.000
I3 vs. II1	0.00891 (-0.5644–0.5822)	1.000
I3 vs. II3	0.20897 (-0.3946–0.8125)	1.000
I3 vs. II6	-0.33898 (-1.0261–0.3481)	1.000
I3 vs. III1	0.15351 (-0.4469–0.7539)	1.000
I3 vs. III3	0.04343 (-0.6310–0.7178)	1.000
I3 vs. III6	-0.30370 (-0.9722–0.3648)	1.000
I6 vs. II1	-0.08492 (-0.7333–0.5635)	1.000
I6 vs. II3	0.11514 (-0.5601–0.7904)	1.000
I6 vs. II6	-0.43282 (-1.1837–0.3181)	1.000
I6 vs. III1	0.05968 (-0.6128–0.7321)	1.000
I6 vs. III3	-0.05040 (-0.7897–0.6889)	1.000
I6 vs. III6	-0.39753 (-1.1314–0.3364)	1.000
II1 vs. II3	0.20006 (-0.4098–0.8099)	1.000
II1 vs. II6	-0.34789 (-1.0406–0.3448)	1.000
II1 vs. III1	0.14460 (-0.4621–0.7513)	1.000
II1 vs. III3	0.03452 (-0.6455–0.7146)	1.000
II1 vs. III6	-0.31261 (-0.9868–0.3616)	1.000
II3 vs. II6	-0.54795 (-1.2658–0.1699)	0.568
II3 vs. III1	-0.05546 (-0.6908–0.5799)	1.000
II3 vs. III3	-0.16553 (-0.8713–0.5402)	1.000
II3 vs. III6	-0.51267 (-1.2127–0.1874)	0.750
II6 vs. III1	0.49249 (-0.2227–1.2077)	1.000
II6 vs. III3	0.38242 (-0.3960–1.1608)	1.000
II6 vs. III6	0.03529 (-0.7380–0.8086)	1.000
III1 vs. III3	-0.11007 (-0.8131–0.5929)	1.000
III1 vs. III6	-0.45721 (-1.1545–0.2401)	1.000
III3 vs. III6	-0.34713 (-1.1091–0.4149)	1.000

BL – baseline; CI – confidence interval.
All values are given as mean (95% CI).
***Note*: Results of the Bonferroni-corrected correlation analysis. Roman numerals indicate the first (I), second (II), and third (III) dose, and Arabic numerals indicate months (1, 3, 6) after each dose.**

significant across all time points. BCVA remained consistently higher compared to baseline across all time points, with a minor decrease recorded 6 months after the second dose.

Discussion

This retrospective longitudinal cohort study demonstrated that intravitreal aflibercept effectively reduces CFT and MV in patients with CI-DME. These findings are consistent with prior clinical trials and real-world studies, which similarly report significant anatomical improvements following aflibercept therapy. Real-world studies and randomized clinical trials have shown comparable decreases in CFT, typically ranging from 150 to 250 μm after the initial loading phase, followed by sustained anatomical improvement during maintenance treatment [10, 11]. The observed mean CFT reduction of approximately 79 μm at 6 months is somewhat smaller than those reported in pivotal trials; the reported CFT range in literature was 100 μm – 250 μm with significant decreases after initial treatment phases. This effect is attributed to aflibercept's high binding affinity for VEGF-A and PlGF, leading to decreased vascular permeability and resolution of intraretinal and subretinal fluid [11].

A significant association between reductions in CFT and improvements in BCVA has been reported, although the relationship is not strictly proportional. Persistent structural changes, such as DRIL or photoreceptor damage, may limit functional recovery despite substantial anatomical improvement. Overall, the decrease in CFT observed with aflibercept therapy represents a reliable anatomical biomarker of treatment response in DME and reinforces its role as a first-line anti-VEGF agent in managing center-involved disease [12, 13].

In our daily clinical practice, as well as in the current study, mean baseline MV typically ranges between 10.0 mm³ and 11.5 mm³, ultimately decreasing to approximately 7.5–8.5 mm³ at 12 months post-treatment. Munayco-Guillén et al. [14] reported a mean reduction from 10.8 mm³ to 9.3 mm³, corresponding to about 14% decrease 12 months after treatment. Similarly, Lukic et al. [11] demonstrated a progressive decline in MV parallel to a decrease in CFT, with the most substantial anatomical response occurring after the initial administration phase, followed by stabilization during maintenance injections.

This anatomical improvement is attributed to aflibercept's dual inhibition of VEGF-A and PlGF, leading to decreased vascular permeability, reduced extracellular fluid accumulation, and restoration of macular architecture. The reduction in MV closely correlates with improved BCVA in most studies, although the relationship is not strictly linear. Chronic macular ischemia, DRIL, and photoreceptor loss may limit visual recovery despite significant anatomical resolution [13]. Meta-analyses indicate that switching refractory DME from bevacizumab or ranibizumab to aflibercept leads to significant improvement in VA and reductions in macular thickness, with sustained efficacy and acceptable safety up to 12 months [15].

The consistent reduction in MV observed across both randomized clinical trials and real-world cohorts underscores its value as a quantitative biomarker of treatment response. Regular OCT assessment of MV and CFT offers an objective approach to monitoring disease activity and tailoring dosing intervals [16]. Overall, the decrease in MV following aflibercept treatment confirms its strong efficacy in improving retinal structure and maintaining visual stability in patients with CI-DME. Some authors demonstrated aflibercept efficacy even in DME treatment in so-called nonresponders to bevacizumab [17]. Systematic review and correlation analyses suggest MV may serve as a surrogate biomarker for VA in DME, showing moderate endpoint correlation but no significant treatment-effect correlation, thereby requiring cautious interpretation [18].

Compared with the APOLLON study [19], which reported a moderate, yet statistically significant improvement in BCVA [+5–8 Early Treatment of Diabetic Retinopathy Study (ETDRS) letters] at 12 months, our findings show stable, non-significant BCVA changes over 6 months despite pronounced anatomical improvement. Differences in follow-up duration and in the methodology of VA assessment should be acknowledged, as BCVA in this study was measured using Snellen charts rather than ETDRS.

One study has shown modest improvements in VA within the first year of treatment [20], which was also confirmed in our cohort. However, this improvement is inconsistent and tends to diminish over time. In line with our findings, the same study reported a significant decrease in CFT [20]. In this study, some parameters that were observed in our study were not reported. In everyday clinical practice, compared to controlled trial settings, the treatment effects on VA are less pronounced [20, 21]. In general, similar observations were shown in a 2022 meta-analysis [22]. The slightly better outcomes reported in that study, compared to our results, may be explained by the higher number of injections administered. While our patients received three doses, their study reported up to eight doses [23]. As we similarly found, MV after the treatment showed a significant decrease in other studies [23, 24]. This can be attributed to the reduction of macular exudation and central RT under treatment. Therefore, this reduction in MV increased gradually from 15% at 6 months to 25% at 12 months [25].

Considering the significance of DME as a leading cause of irreversible visual impairment in the diabetic population, early detection and timely treatment, including anti-VEGF therapy, are key steps toward slowing disease progression and preserving functional vision. Clinical studies have shown that administration of aflibercept leads to improvement in VA within the first year of treatment. In a multicenter study, Korobelnik et al. [21] reported an average increase of 10–12 letters in BCVA at 52 weeks, with a significant reduction in central RT. Our results have also shown a morphological response, although without statistically significant functional improvement. After 100

weeks of follow-up, Brown et al. [26] confirmed the durability of the obtained functional improvement, with an emphasis on continuous treatment. By analyzing the results at 148 weeks, Heier et al. [27] confirmed that the effect of the treatment can be preserved long-term. However, they also observed that in certain patients, the effects decreased progressively. Our findings are partially consistent with theirs, as our study also showed a slight increase in morphological parameters after the second dose, which was corrected after the third aflibercept administration. In the AURIGA study, Donati et al. [20] recorded a clinically significant decrease in CFT and a slight improvement in BCVA in a 24-month real-world setting, while highlighting a high variability in treatment response. Similar observations were reported in the study by Santhakumaran et al. [22]. This meta-analysis found that the number of administrations and earlier initiation of treatment are key factors in anti-VEGF therapy success. The aforementioned studies achieved better results compared to our findings, most likely because their patients received up to eight doses within the first year, while ours were given only three. Korobelnik et al. [21] confirmed that more intensive treatment regimens yield more prominent and stable responses, especially in early-stage cases. Griffin et al. [23] state that secondary neurodegenerative retinal impairments, which are common in elderly patients with long-term DME, may limit the potential for full recovery of the visual function, despite anatomical improvement. This may explain the absence of a more significant functional improvement in our sample. In line with our findings, a significant reduction in MV has been widely reported in the literature. Donati et al. [20] observed a progressive decline in MV, reporting a 15% reduction at 6 months that extended to 25% at the 12-month follow-up. Tran et al. [25] additionally demonstrated that the treatment response remains positive even in vitrectomized eyes, although with a potentially different dynamic.

Most studies worldwide consider the eye, rather than the patient, as the unit of analysis when evaluating treatment effects [28–32].

Limitations of this study

Limitations of this study include the relatively short follow-up period (other studies track patients for up to 5 years), a fixed three-dose regimen (other studies include more doses), and the lack of stratification by prior treatment (i.e., naïve vs. previously treated with corticosteroids or other anti-VEGF agents). The study analyzed 70 eyes in 50 patients. The statistical approach did not account for interocular correlation, which may be a significant limitation of the study. However, treatment is administered individually to each eye. When both eyes are treated, the results can be quite different.

Conclusion

Intravitreal administration of aflibercept results in a significant reduction in retinal thickness and macular volume in patients with center-involved diabetic macular edema, thereby confirming its anatomical efficacy. This decrease in macular edema is critical for preventing further retinal damage and preserving retinal architecture. However, the observed functional improvement, as measured by best-corrected visual acuity, was limited in this cohort. This limited visual recovery may be attributed to chronic retinal changes and irreversible structural damage, such as photoreceptor loss and disruption of retinal layers, which likely predated treatment initiation.

Given the complex and progressive nature of center-involved diabetic macular edema, longer-term studies with larger patient populations are necessary to better elucidate the relationship between anatomical improvements and functional visual outcomes following aflibercept therapy. Future research should also investigate optimal dosing regimens, the timing of intervention, and potential combination therapies to enhance visual rehabilitation. Such data will be essential for developing personalized treatment protocols aimed at maximizing visual function in patients with center-involved diabetic macular edema.

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