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COMPARISON OF BEVACIZUMAB AND AFLIBERCEPT IN TREATMENT OF DIABETIC MACULAR EDEMA

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ABSTRACT

Objective: To compare change in visual acuity letter score and central subfield thickness on optical coherence tomography between aflibercept and bevacizumab in DME.

Methods: A randomized controlled trial was conducted in the Department of Ophthalmology, Combined Military Hospital, Multan, Pakistan, from August 2025 to November 2025. Using consecutive sampling, 116 patients were randomized (1:1) to intravitreal aflibercept or bevacizumab. Adults aged 30 to 60 years with diabetes for at least 5 years, visual acuity 20/50 or worse, and OCT central macular thickness at least 300 µm were enrolled. Two aflibercept and four bevacizumab patients were lost to follow-up.

Results: Complete analysis included 110 eyes (aflibercept, n = 56; bevacizumab, n = 54). Baseline visual acuity did not differ (56.83 ± 10.17 vs 57.66 ± 9.72; p = 0.662). At month 2, mean visual acuity was 70.24 ± 10.17 versus 67.65 ± 11.78 letters (p = 0.220), while letter-score gain was greater with aflibercept (13.41 ± 5.92 vs 9.71 ± 5.93; p = 0.001). Baseline central subfield thickness was similar (p = 0.448). Month-2 central subfield thickness was lower with aflibercept (295.84 ± 98.15 vs 337.59 ± 102.30 µm; p = 0.031), with a larger reduction (p = 0.011).

Conclusion: Aflibercept produced greater visual acuity gain and larger central subfield thickness reduction than bevacizumab in center-involving DME.

KEYWORDS: Diabetic macular edema, intravitreal aflibercept, intravitreal bevacizumab, optical coherence tomography, visual acuity.

INTRODUCTION

Diabetes mellitus remains a major global public health challenge, with rising microvascular complications that impair vision and quality of life. In 2022, an estimated 828 million adults had diabetes, with steepest rises in low and middle income regions including South Asia.[1] In Pakistan, approximately 34.5 million adults were living with diabetes in 2024.[2] Diabetic macular edema (DME) represents one of most clinically consequential manifestations of diabetic retinopathy.[3] Recent epidemiological Optical coherence tomography based estimates indicate a global DME prevalence of 5.47% among individuals with diabetes, rising to 5.81% in low- and middle-income settings.[4] Population-based registry data suggest that, despite improved screening, overall treatment demand continues to increase with the expanding diabetic population and greater use of intravitreal therapy.[5]

Diabetic macular edema results from diabetes-related microvascular damage, capillary leakage, and blood retinal barrier failure, leading to intraretinal fluid and macular thickening. Vascular endothelial growth factor increases vascular permeability and inflammation, supporting anti-vascular endothelial growth factor (anti-VEGF) therapy in center-involving disease.[6] Aflibercept is a fusion protein that binds VEGF A and B and placental growth factor and is

approved for diabetic macular edema. [7] Bevacizumab is a full-length monoclonal antibody originally developed for cancer therapy and is used off label for diabetic macular edema and other retinal vascular diseases.[8] A study of 18 randomized trials found no difference in change in visual acuity at 12 months, although aflibercept showed a some extent greater reduction in central subfield thickness.[9]

Despite extensive use of both drugs, uncertainty persists regarding their comparative short term effectiveness. Recent comparative studies and meta-analyses have reported variable findings, with some showing greater early anatomical and functional response with aflibercept while others have shown smaller or non significant differences. Therefore, present trial was conducted to compare intravitreal aflibercept and bevacizumab in patients with DME. The purpose of study was to determine whether aflibercept provides greater improvement in visual acuity and central subfield thickness than bevacizumab.

METHODS

A randomized open label controlled trial (NCT07338097) was executed in Department of Ophthalmology, Combined Military Hospital, Multan, Pakistan, from August 2025 to November 2025. Recruitment was performed from the outpatient department and referral clinics using non-probability consecutive sampling. A sample size of 116 (58 each group) was calculated based on comparative change in visual acuity letter score, where mean improvement was 17.1 ± 9.7 for aflibercept and 12.1 ± 9.4 for bevacizumab. With 80% power and 95% confidence interval.[10] Two participants in aflibercept and 4 participants in bevacizumab group were lost follow up and were therefore not included in final analysis.

Patients of either gender aged between 30 to 60 years, had type 1 or type 2 diabetes mellitus for at least 5 years, had baseline visual acuity of 20/50 or worse and demonstrated central macular thickness of at least 300 µm on optical coherence tomography were included. Patients were excluded if prior treatment for diabetic macular edema had been received, including intravitreal anti-VEGF therapy, intravitreal corticosteroids or laser photocoagulation or if active ocular infection was present. Exclusion also applied in the presence of documented cardiac disease or stroke, pregnancy or breastfeeding, hypersensitivity to aflibercept or bevacizumab, or refusal to provide consent.

Before enrolment, the study purpose was explained and written informed consent was obtained. Baseline data included age, gender, BMI, diabetes duration, hypertension, smoking, and glycated hemoglobin. The treated eye was recorded as right or left, and one eye was selected when both met eligibility. Participants were randomized 1:1 by a computer-generated sequence to intravitreal aflibercept 2.0 mg or bevacizumab 1.25 mg. The trial was open label and no participant, injector or treating ophthalmologist masking was performed. Injections were administered under topical proparacaine 0.5% after povidone iodine preparation, via pars plana using a 30G needle 3.5 to 4.0 mm from the limbus. Patients were observed for 1 hour for any adverse reaction and topical antibiotics were prescribed for 5 days. Injections were given at baseline, month 1 and month 2, with assessments at months 1 and 2.

The primary outcome was the mean change in visual acuity from baseline to month 2, expressed as Early Treatment Diabetic Retinopathy Study letter score. Visual acuity was measured on a Snellen chart at 6 m under standard lighting using current correction or pinhole, then converted to Early Treatment Diabetic Retinopathy Study letter score. The secondary outcome was the mean change in central subfield thickness from baseline to month 2, measured in micrometers on spectral-domain optical coherence tomography. Central subfield thickness was measured in micrometers on spectral domain optical coherence tomography after dilation with tropicamide 1%, using the central 1 mm foveal zone, and diabetic macular edema was confirmed at 300 micrometers or more, with slit lamp examination excluding other pathology.

Statistical Analysis

Data were entered and analyzed by SPSS version 26. Continuous data were summarized as mean ± SD and grouped data as frequency and percentage. Continuous variables were compared using the independent t test and grouped variables were compared using chi square. Between-group differences in change scores were tested using the independent t test, with $p \leq 0.05$ considered significant. Effect estimates were reported as mean differences with 95% CI.

RESULTS

Baseline variables were analogous between groups (Table 1). Mean age was 52.13 ± 5.94 years in the aflibercept group and 53.14 ± 5.82 years in bevacizumab group ($p = 0.373$). Mean body mass index was 28.72 ± 4.35 kg/m² versus 27.59 ± 4.41 kg/m² ($p = 0.179$). Mean duration of diabetes was 10.20 ± 3.22 years versus 10.99 ± 3.56 years ($p = 0.224$), and mean glycated hemoglobin was 8.37 ± 1.30% versus 8.22 ± 1.53% ($p = 0.571$). Distribution of categorical variables did not differ significantly by treatment allocation, including age group ($p = 0.360$), gender ($p =$

0.808), treated eye laterality (p = 0.835), hypertension status (p = 0.287), smoking history (p = 0.344) and ASA status (p = 0.822).

Table 1. Baseline demographic and clinical characteristics (complete-case analysis, N = 110)

Variable	Aflibercept (n = 56)	Bevacizumab (n = 54)	p-value
Age group, n (%)			0.360
○ 30 to 45 years	19 (33.9)	14 (25.9)	
○ 46 to 60 years	37 (61.1)	40 (74.1)	
Gender, n (%)			0.808
○ Male	34 (60.7)	34 (63.0)	
○ Female	22 (39.3)	20 (37.0)	
Eye treated, n (%)			0.835
○ Right	30 (53.6)	30 (55.6)	
○ Left	26 (46.4)	24 (44.4)	
Hypertension, n (%)	34 (60.7)	38 (70.4)	0.287
Smoking history, n (%)	16 (28.6)	20 (37.0)	0.344
ASA physical status, n (%)			0.822
○ I	24 (42.9)	22 (40.7)	
○ II	32 (57.1)	32 (59.3)	

ASA, American Society of Anesthesiologists; SD, standard deviation.

Baseline visual acuity was similar between groups (56.83 ± 10.17 versus 57.66 ± 9.72 ETDRS letters, p = 0.662). At month 2, mean visual acuity was 70.24 ± 10.17 letters versus 67.65 ± 11.78 letters (p = 0.220). Mean change was 13.41 ± 5.92 letters in aflibercept group compared with 9.71 ± 5.93 letters in bevacizumab group, (MD 3.69, 95% CI 1.45 to 5.93, p = 0.001) (Table 2).

Table 2. Visual acuity outcomes and primary endpoint (ETDRS letters)

Outcome	Aflibercept (n = 56) mean ± SD	Bevacizumab (n = 54) mean ± SD	Mean difference (95% CI)	p-value
Baseline visual acuity	56.83 ± 10.17	57.66 ± 9.72	−0.83 (−4.59 to 2.93)	0.662
Month 1 visual acuity	64.33 ± 11.23	63.59 ± 10.82	0.74 (−3.43 to 4.91)	0.727
Month 2 visual acuity	70.24 ± 10.17	67.65 ± 11.78	2.59 (−1.57 to 6.74)	0.220
Primary endpoint: change baseline to month 2	13.41 ± 5.92	9.71 ± 5.93	3.69 (1.45 to 5.93)	0.001
Within-group p-value, baseline vs month 2*	<0.001	<0.001	N/A	N/A

ETDRS, Early Treatment Diabetic Retinopathy Study.
** Paired t-test within each treatment group.*

Baseline central subfield thickness was similar between groups (470.63 ± 84.10 µm versus 483.50 ± 93.21 µm, p = 0.448). At month 2, central subfield thickness was 295.84 ± 98.15 µm versus 337.59 ± 102.30 µm (p = 0.031). For the prespecified secondary endpoint, defined as change in CST from baseline to month 2, a greater reduction was observed with aflibercept (−147.04 ± 66.03 µm) than with bevacizumab (−114.72 ± 65.69 µm) (Table 3).

Table 3. OCT central subfield thickness outcomes and secondary endpoint (µm)

Outcome	Aflibercept (n = 56) mean ± SD	Bevacizumab (n = 54) mean ± SD	Mean difference (95% CI)	p-value
Baseline CST	470.63 ± 84.10	483.50 ± 93.21	−12.88 (−46.40 to 20.65)	0.448
Month 1 CST	377.36 ± 94.22	407.98 ± 113.99	−30.62 (−70.09 to 8.84)	0.127
Month 2 CST	295.84 ± 98.15	337.59 ± 102.30	−41.75 (−79.64 to −3.87)	0.031
Secondary endpoint: change baseline to month 2	−147.04 ± 66.03	−114.72 ± 65.69	−32.31 (−57.21 to −7.42)	0.011
Within-group p-value, baseline vs month 2*	<0.001	<0.001	N/A	N/A

CST, central subfield thickness
** Paired t-test within each treatment group.*

DISCUSSION

The present randomized controlled trial compared the therapeutic efficacy of intravitreal aflibercept and bevacizumab in patients with DME over a two month follow-up. The principal finding was that aflibercept produced a statistically significant and clinically meaningful greater improvement in visual acuity compared with bevacizumab at 2 months, with a mean letter gain of 13.41 versus 9.71 ETDRS letters (MD 3.69 letters; 95% CI 1.45 to 5.93; p = 0.001). The secondary anatomical endpoint similarly favored aflibercept, with a greater reduction in central subfield thickness from baseline (−147.04 µm versus −114.72 µm; MD −32.31 µm; 95% CI −57.21 to −7.42; p = 0.011). These findings indicate that during early loading phase of anti-VEGF therapy, aflibercept offer a quicker and pronounced functional and anatomical response in the management of DME.[11]

In this study advantage of aflibercept is consistent with Protocol T trial reported by Wells et al. which showed that aflibercept produced greater visual acuity gains than bevacizumab at two years in patients with baseline visual acuity of 20/50 or less, with adjusted difference of +4.7 letters (95% CI 0.5 to 8.8; p = 0.02).[12] In current study, the baseline visual acuity was 57 ETDRS letters (20/70) in both groups, placing study population within the poorer baseline acuity population where Protocol T demonstrated most pronounced advantage of aflibercept. A study by Jampol et al. confirmed advantage of aflibercept over bevacizumab of +4.5 letters (95% CI 1.6 to 7.3; p < 0.001) in this visual acuity population.[10] The direction and magnitude of the between group difference observed in present trial at two months (3.69 letters) are therefore in agreement with these multicenter data although direct comparison must be interpreted cautiously given shorter follow up duration and smaller sample size.

The anatomical findings of this study validate the existing evidence. In Protocol T, the mean central subfield thickness reduction at two years was 171 µm with aflibercept compared with 126 µm with bevacizumab, showing a between group difference of 48.5 µm (p < 0.001) that preferred aflibercept [12]. The present study documented a between group difference of 32.31 µm at two months suggesting that anatomical advantage of aflibercept may manifest early during loading phase. Khaqan et al. comparing intravitreal aflibercept with bevacizumab in macular edema, reported similar results with aflibercept reaching central macular thickness reduction of 213µm compared with 170µm for bevacizumab at three months.[13] Erden et al. similarly noted that aflibercept produced meaningfully greater central macular thickness reduction than ranibizumab (p = 0.03) in treatment naive patients further supporting earlier anatomical resolution with aflibercept.[14]

However, not all previous literature supports superiority of aflibercept over bevacizumab across all clinical settings.[15] Knezović et al. noted no between group differences in either visual acuity improvement or macular thickness reduction.[16] The meta analysis by Santhakumaran et al. also found no statistically significant difference in visual acuity between aflibercept and bevacizumab at 12 months (MD 1.71 letters; p = 0.34) while possible anatomical advantage for aflibercept was noted.[17] The study by Sangroongruangsri et al., pooling data from 11 randomized trials involving 1,830 patients with macular edema, likewise concluded that no differences existed among anti-VEGF agents though between trial heterogeneity was recognized threat to inference.[18] These findings suggest that magnitude of aflibercept's advantage may differ depending on follow up duration, patient selection, baseline disease severity and treatment intensity.

The question of whether aflibercept should be used as first line agent or reserved as step up therapy after initial bevacizumab has central implications for clinical practice. Jhaveri et al., randomized 312 eyes to aflibercept versus bevacizumab first therapy. Notably, 70% of eyes in bevacizumab group required switching yet primary visual acuity outcome over two years did not differ significantly between groups (MD 0.8 letters; 95% CI −0.9 to 2.5; p = 0.37).[19] This suggests that despite early functional advantage of aflibercept confirmed in current trial, a sequential approach beginning with bevacizumab may yield equivalent long term outcomes when timely switching is implemented. This stepped strategy may be relevant in resource limited settings where substantially lower cost of bevacizumab, as highlighted by Knezović et al., represent a significant consideration.[16]

From a clinical decision making perspective, the present findings support aflibercept as an effective option when rapid anatomical improvement and early vision gain are priorities, particularly in eyes presenting with relatively poor baseline vision. But, treatment choice in low resource settings cannot be based on efficacy alone. Economic analyses based on Protocol AC have shown that a bevacizumab-first strategy is substantially less costly than aflibercept monotherapy, with lower total cost over two years and a very high incremental cost-effectiveness ratio for aflibercept monotherapy. [20,21]

CONCLUSION

Intravitreal aflibercept showed better early functional and anatomical response than bevacizumab in patients with center involving diabetic macular edema. These findings suggest that aflibercept may be the more effective choice when rapid visual improvement and macular drying are clinically important. However, treatment selection should also consider affordability, access and expected follow-up, particularly in low resource settings.

Limitations & Recommendations

This study has certain limitations that should be considered while interpreting the findings. The follow-up period was limited to two months, therefore the durability of response, recurrence of macular edema, long-term injection burden and delayed adverse events could not be evaluated. As the study was conducted at a single center, the generalizability of the findings may be restricted. In addition, optical coherence tomography morphological subtypes of diabetic macular edema were not assessed separately, which may have influenced treatment response patterns. Future studies should therefore include larger multicenter samples, longer follow-up and stratified analyses based on baseline visual acuity, optical coherence tomography characteristics and metabolic profile. Comparative evaluation of long-term cost-effectiveness and step-up treatment strategies would also be valuable, particularly in resource-constrained settings where both clinical benefit and affordability must be considered.

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