

Research Article

Comparative Clinical Outcomes of Intravitreal Aflibercept and Ranibizumab in Patients with Diabetic Macular Edema

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Abstract

Objective: To compare one-year visual and anatomical outcomes after intravitreal aflibercept and ranibizumab in treatment-naïve eyes with center-involving diabetic macular edema (DME) at three tertiary eye centers in Punjab, Pakistan.

Methods: This multicenter comparative cohort included 120 patients, with one study eye per patient and 60 patients in each treatment group. Patients received aflibercept 2 mg or ranibizumab 0.5 mg according to the treating specialist's decision. Three initial monthly injections were followed by monthly assessment and treatment when indicated. Best-corrected visual acuity (BCVA), expressed in Early Treatment Diabetic Retinopathy Study (ETDRS) letters, and optical coherence tomography central subfield thickness (CST) were assessed through month 12. The primary outcome was change in BCVA at one year.

Results: One-year measurements were available for 108 patients, 54 in each group. Mean BCVA increased by 11.3 letters with aflibercept and 9.6 letters with ranibizumab. The between-group difference in mean gain was 1.7 letters (95% confidence interval [CI] -1.9 to 5.3). Mean CST decreased by 151 µm and 130 µm, respectively. At least 10 letters were gained by 28/54 aflibercept-treated eyes (51.9%) and 24/54 ranibizumab-treated eyes (44.4%). Injection numbers were similar. No endophthalmitis was recorded.

Conclusion: Both agents were associated with meaningful improvement in vision and retinal thickness at one year. The study was too small to establish a reliable difference between them. Treatment continuity and baseline vision remained important when interpreting outcomes.

Keywords: Aflibercept, Ranibizumab, Diabetic Macular Edema, Optical Coherence Tomography.

INTRODUCTION

Diabetic macular edema is one of the most consequential causes of visual loss in people living with diabetes. Swelling at the center of the retina can turn familiar activities, such as reading a prescription or recognizing a face, into daily difficulties. Its clinical importance therefore extends beyond the thickness displayed on an optical coherence tomography (OCT) scan.[1,2] Centre-involving DME may also persist or recur over time, making sustained treatment and follow-up central to preserving vision.[3]

Intravitreal inhibition of vascular endothelial growth factor (VEGF) transformed the management of visually significant DME.[4] Aflibercept and ranibizumab both improve visual acuity and reduce retinal swelling, but the choice between them remains clinically relevant.[5,6] Aflibercept and ranibizumab differ in molecular structure and VEGF-binding properties; whether those differences produce a meaningful advantage for an individual patient depends on the starting condition of the eye, treatment schedule and length of observation.[7]

Comparative evidence has given clinicians a nuanced answer rather than a universal preference. A network meta-analysis found no clinically important difference in visual outcomes among anti-VEGF agents at two years, although some anatomical outcomes differed.[8] A direct meta-analysis of aflibercept and ranibizumab likewise found broadly comparable results at commonly reported follow-up points.[9] In individual studies, the apparent advantage of one agent has sometimes changed with baseline visual acuity, the timing of assessment or the number of injections delivered.[10,11] These factors matter when findings from controlled studies are applied to routine clinics.

A year of observation offers a more useful test than the response to three loading injections alone. DME often improves early, yet later visits reveal whether that improvement is maintained, whether edema returns and whether patients can continue treatment.[12] Registry and multicenter studies have shown that both drugs can provide sustained visual benefit, while also documenting differences in treatment exposure and follow-up patterns.[13,14] The comparison should consequently consider visual acuity, OCT findings and the treatment patients actually received.

In Pakistan, a treatment decision must also fit the practical demands of repeated appointments. Travel, time away from work, clinic capacity and medication costs may interrupt otherwise effective care. These pressures can narrow the gap between drugs seen under ideal schedules or make a small pharmacological advantage less relevant to the outcome a patient experiences

This study compared one-year changes in best-corrected visual acuity (BCVA) and OCT central subfield thickness (CST) after aflibercept or ranibizumab in treatment-naïve eyes with center-involving DME. It also examined meaningful visual gain, treatment frequency, follow-up completion and ocular adverse events. The study assessed the size and precision of the between-group difference to inform clinical interpretation and patient counseling.

MATERIALS AND METHODS

This multicenter comparative cohort was set in the ophthalmology departments of three tertiary hospitals in Punjab, Pakistan. Ethical approval was obtained from each participating center. Written informed consent was obtained

from all participants before enrolment and treatment. Eligible patients entered the study between June, 2024 and December 2024 and were followed for 12 months after their first injection; final follow-up was completed by December 2025. The study included 120 adults, 60 treated initially with aflibercept and 60 with ranibizumab. One eye per patient was included to keep the observations independent.

Adults aged 18 years or older were eligible if they had diabetes, treatment-naïve center-involving DME confirmed on spectral-domain OCT, CST of at least 300 µm and BCVA between 24 and 78 ETDRS letters. When both eyes met the criteria, the eye with poorer BCVA was selected before treatment began. Patients were excluded if the study eye had previously received intravitreal anti-VEGF treatment, an intravitreal corticosteroid or macular laser; had vitreomacular traction requiring surgery; or had another retinal or media condition likely to distort the measurement of vision. Eyes undergoing intraocular surgery during the assessment period were also excluded from the primary one-year comparison.

The treating retinal specialist selected aflibercept 2 mg/0.05 mL or ranibizumab 0.5 mg/0.05 mL as part of clinical care. Treatment allocation was therefore not randomised. Both groups followed the same intended assessment schedule: injections at baseline, month 1 and month 2, followed by monthly review. From month 3, another injection was given when centre-involving fluid persisted or recurred, CST increased, or BCVA declined because of DME. The clinician documented the reason for treatment, deferral or a missed visit. Any change to another anti-VEGF agent, macular laser or intravitreal steroid was recorded as additional treatment rather than attributed to the original drug alone.

At enrolment, age, sex, diabetes duration, hypertension, lens status, diabetic retinopathy grade and the most recent available glycated haemoglobin value were recorded. BCVA was assessed with an ETDRS-style letter chart at baseline and months 3, 6, 9 and 12. OCT was performed at the same visits, and CST was recorded in micrometers. The same OCT instrument was used for each patient throughout follow-up. Scans with segmentation errors or insufficient quality were reviewed before values were accepted. The assessment plan appears in **Table 1**.

Table 1. Study Measurements and Outcome Definitions

Measurement	Timing	Definition
BCVA	Baseline; months 3, 6, 9 and 12	ETDRS letter score; higher scores indicated better vision
OCT central subfield thickness	Baseline; months 3, 6, 9 and 12	Central retinal thickness in μm
Primary outcome	Baseline to month 12	Change in BCVA, in ETDRS letters
Meaningful visual response	Month 12	Gain of ≥ 10 or ≥ 15 ETDRS letters
Treatment exposure	Every visit	Number of injections through month 12
Follow-up continuity	Every visit	Missed scheduled visits and completion of month-12 assessment
Safety	Every visit	Recorded ocular adverse events after treatment

Data were analyzed for patients with available 12-month measurements. Changes in best-corrected visual acuity (BCVA) and central subfield thickness (CST) were compared between treatment groups using the independent-samples *t* test or Mann–Whitney U test, as appropriate. Categorical outcomes were compared using the chi-square or Fisher exact test. Linear regression adjusted the BCVA comparison for baseline BCVA, baseline CST and study center. Results were reported as mean $\pm$ standard deviation or frequency and percentage, with between-group differences and 95% confidence intervals. A

two-sided *p* value < 0.05 was considered statistically significant.

RESULTS

Of the 120 patients included at baseline, 108 had a recorded month-12 BCVA and OCT assessment: 54 of 60 in each treatment group. The other 12 did not contribute to the primary one-year comparison. Baseline characteristics of all enrolled patients are presented in **Table 2**. Mean starting BCVA was similar between groups; the aflibercept group had slightly greater mean retinal thickness. These starting measurements were considered in the adjusted comparison.

Table 2. Baseline Characteristics of Enrolled Patients

Characteristic	Aflibercept (n = 60)	Ranibizumab (n = 60)
Age, years, mean $\pm$ SD	57.2 $\pm$ 9.0	57.8 $\pm$ 8.7
Women, n (%)	28 (46.7)	30 (50.0)
Diabetes duration, years, mean $\pm$ SD	12.1 $\pm$ 5.5	12.4 $\pm$ 5.8
Hypertension, n (%)	36 (60.0)	38 (63.3)
HbA1c, %, mean $\pm$ SD*	8.5 $\pm$ 1.4	8.6 $\pm$ 1.5
Phakic study eye, n (%)	47 (78.3)	45 (75.0)
BCVA, ETDRS letters, mean $\pm$ SD	56.9 $\pm$ 11.6	57.6 $\pm$ 11.2
CST, μm , mean $\pm$ SD	452 $\pm$ 96	443 $\pm$ 93

*Based on available baseline laboratory records.

Visual acuity improved in both groups during follow-up (**Table 3**). Most of the increase had appeared by month 6, with smaller additional gains thereafter. At month 12, the mean gain was 11.3 letters in the aflibercept group and

9.6 letters in the ranibizumab group. The confidence interval around the 1.7-letter between-group difference crossed zero and included differences in either direction. Adjustment for starting BCVA, CST and center did not materially change that interpretation.

Table 3. Visual Acuity among Patients Completing Month-12 Assessment

BCVA outcome	Aflibercept (n = 54)	Ranibizumab (n = 54)
Baseline, ETDRS letters	57.1 $\pm$ 11.4	57.8 $\pm$ 11.0
Month 3	63.7 $\pm$ 11.7	63.4 $\pm$ 11.5
Month 6	66.5 $\pm$ 12.0	65.8 $\pm$ 11.8
Month 9	67.7 $\pm$ 12.1	66.9 $\pm$ 12.0

Month 12	68.4 ± 12.3	67.4 ± 12.1
Gain from baseline to month 12	11.3 ± 9.2	9.6 ± 9.0
Between-group difference in mean gain	1.7 letters (95% CI –1.9 to 5.3)	—

OCT measurements showed substantial reduction in central retinal thickness in both groups (Table 4). Mean CST fell to 301 µm after aflibercept and 313 µm after ranibizumab at one year. The difference in mean reduction

was 21 µm, with uncertainty around that estimate. The numerical anatomical difference was larger than the difference in visual gain; the two measures therefore conveyed related, but not identical, aspects of response.

Table 4. Central Subfield Thickness among Patients Completing Month-12 Assessment

CST outcome	Aflibercept (n = 54)	Ranibizumab (n = 54)
Baseline, µm	452 ± 95	443 ± 92
Month 3	364 ± 88	369 ± 86
Month 6	329 ± 79	339 ± 81
Month 9	310 ± 75	322 ± 78
Month 12	301 ± 73	313 ± 76
Reduction from baseline to month 12	151 ± 92	130 ± 89
Between-group difference in mean reduction	21 µm (95% CI –15 to 57)	—

The distribution of visual responses and treatment delivered is shown in **Table 5**. Just over half of aflibercept-treated eyes and just under half of ranibizumab-treated eyes gained at least 10 letters. A gain of at least 15 letters occurred in approximately one-third and one-

quarter of eyes, respectively. Few eyes lost 10 letters. The average number of injections was similar, while missed appointments affected patients in both groups. The table places the visual outcomes alongside the amount of care required to achieve them.

Table 5. One-Year Visual Response and Treatment Exposure

Outcome	Aflibercept (n = 54)	Ranibizumab (n = 54)
Gain of ≥10 ETDRS letters, n (%)	28 (51.9)	24 (44.4)
Gain of ≥15 ETDRS letters, n (%)	18 (33.3)	15 (27.8)
Loss of ≥10 ETDRS letters, n (%)	2 (3.7)	3 (5.6)
Injections through month 12, mean ± SD	6.4 ± 1.5	6.3 ± 1.6
At least one missed scheduled visit, n (%)	17 (31.5)	19 (35.2)
Additional DME treatment, n (%)	3 (5.6)	4 (7.4)

Safety observations and follow-up completion are summarised in **Table 6**. Transient discomfort and subconjunctival haemorrhage were the most frequently recorded ocular events. No endophthalmitis appeared in either

group. The six patients per group without a month-12 measurement were included in the follow-up count; their absence remains relevant to interpretation of the primary analysis.

Table 6. Follow-Up and Recorded Ocular Events

Outcome	Aflibercept (n = 60 enrolled)	Ranibizumab (n = 60 enrolled)
Completed month-12 assessment, n (%)	54 (90.0)	54 (90.0)
Transient post-injection discomfort, n (%)	9 (15.0)	10 (16.7)
Subconjunctival haemorrhage, n (%)	7 (11.7)	6 (10.0)
Recorded rise in intraocular pressure, n (%)	2 (3.3)	2 (3.3)
Clinically significant intraocular inflammation, n	0	0
Endophthalmitis, n	0	0

DISCUSSION

The central finding of the study was improvement after both treatments over a full

year, accompanied by a small and uncertain difference between drugs. The 1.7-letter difference in mean gain was much smaller than the improvement observed within either group. Its confidence interval did not establish a dependable advantage for aflibercept or ranibizumab. This distinction matters when patients and clinicians weigh a drug choice against the effort and cost of completing treatment.

The direction of the findings was consistent with a one-year real-world comparison in which both agents improved BCVA, while their final visual outcomes did not differ significantly. [15] Another 12-month comparison found an earlier difference in retinal thickness that was no longer evident at one year. [16] These studies help explain why an early OCT response should not, by itself; determine a claim of longer-term superiority. Morphological patterns of DME may also influence the degree of retinal thinning and the number of treatments required. [17]

The study results showed a somewhat larger numerical reduction in CST with aflibercept than with ranibizumab, without a comparably clear separation in visual gain. This is clinically plausible: reducing fluid is an important treatment aim, but an OCT measurement cannot capture every determinant of visual recovery. A recent review of OCT biomarkers has emphasized the value of assessing retinal structure beyond central thickness alone.[18] Baseline visual acuity and the condition of retinal tissue should therefore remain part of any interpretation of treatment response.

One-year follow-up also brought treatment continuity into view. Patients received a mean of approximately six injections, and about one-third of month-12 completers had missed at least one scheduled visit. Reviews of routine practice have found that anti-VEGF treatment commonly involves fewer injections than in controlled trials, alongside smaller average visual gains.[19] Work focused on countries with fewer resources has described the effect of travel, financial constraints and service capacity on sustained DME care.[20] Patient surveys and qualitative research likewise show that treatment burden is experienced well beyond the injection itself.[21,22] Recording missed appointments alongside clinical outcomes provided a fuller picture of DME care in the participating Pakistani centers.

The study was strengthened by its multicenter setting, one study eye per patient, a consistent 12-month follow-up schedule, and

combined assessment of visual acuity, retinal thickness, and treatment exposure.

CONCLUSION

Over 12 months, both aflibercept and ranibizumab were associated with improved visual acuity and reduced macular thickness in patients with diabetic macular edema. These findings suggest that either agent may provide meaningful visual and anatomical benefit when treatment and follow-up are maintained. The choice of therapy can be guided by the patient's clinical needs, treatment access and ability to attend regular visits.

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