Comparison of the Efficacy of Aflibercept, Bevacizumab, and Ranibizumab After Bevacizumab Loading Doses in Diabetic Macular Edema

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ABSTRACT

Objective: This study aimed to evaluate the 12-month functional and anatomical outcomes of continuing bevacizumab, switching to aflibercept, or switching to ranibizumab following a three-dose bevacizumab loading regimen in the treatment of diabetic macular edema (DME).

Materials and Methods: A total of 120 treatment-naïve patients with DME were included. After completing three loading doses of bevacizumab, patients were divided into three groups according to the subsequent anti-vascular endothelial growth factor (anti-VEGF) treatment: Group 1 received bevacizumab (n=40), Group 2 received aflibercept (n=40), and Group 3 received ranibizumab (n=40). Best-corrected visual acuity (BCVA) and central macular thickness (CMT) were compared at baseline and at months 3, 6, and 12.

Results: All three groups demonstrated statistically significant BCVA improvement at all time points compared with baseline, whereas no significant differences were observed between the groups at any time point ($p<0.001$ and $p=0.89$, respectively). Baseline CMT values were 513.47 ± 123.97 µm, 529.82 ± 93.63 µm, and 486.63 ± 81.56 µm for Groups 1, 2, and 3, respectively; at month 12, CMT values improved to 426.21 ± 101.26 µm, 435.26 ± 84.40 µm, and 407.18 ± 83.63 µm, respectively. All groups showed significant CMT reduction from baseline ($p<0.001$). There was no significant difference in CMT change among the three groups at any time point ($p=0.593$).

Conclusion: Following bevacizumab loading, continuation with bevacizumab or switching to aflibercept or ranibizumab provides comparable functional and anatomical improvement over a 12-month follow-up period in patients with DME.

Keywords: Diabetic macular edema, Treatment strategies, Anti-VEGF

INTRODUCTION

Diabetic retinopathy (DR) is a microvascular complication of diabetes mellitus (DM) and is a major cause of visual impairment worldwide among adults. Diabetic macular edema (DME) is the main reason why people with diabetes have trouble seeing. Vascular endothelial growth factor (VEGF), a pro-inflammatory mediator that promotes angiogenesis and increases vascular permeability, plays a crucial role in the pathophysiology of DME.[1]

In recent years, intravitreal anti-VEGF drugs have been accepted as the standard treatment for DME. The three main anti-VEGF drugs that are commonly used and have proven efficacy are bevacizumab (Avastin®), ranibizumab (Lucentis®), and aflibercept (Eylea®). Randomized prospective studies have shown that these drugs provide both anatomical and functional improvements in DME.[2-4] In a clinical study comparing the efficacy of intravitreal aflibercept, bevacizumab, and ranibizumab in DME, all three agents were shown to improve visual acuity at the end

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of two years. Visual acuity outcomes were similar between treatment groups in eyes with better baseline visual acuity.[5]

Visual impairment and the high costs associated with DME treatment represent a significant burden. With the increasing global prevalence of diabetes, DME has become an important worldwide health concern.[6] Among the various costs of anti-VEGF agents, bevacizumab is generally the most economical option. In a study evaluating the cost-effectiveness of aflibercept monotherapy versus a bevacizumab-first treatment strategy for DME, substantial cost savings could be achieved over a two-year period without compromising visual acuity gains.[7] This situation necessitates initiating treatment with bevacizumab, particularly in healthcare systems with limited funding, and then switching to more expensive drugs (ranibizumab or aflibercept) for patients who show an inadequate or partial response. However, evidence regarding the most effective strategy after loading therapy is limited, and it is a fact that unnecessary agent switching can increase both the burden on the patient and the cost.

The aim of this study is to compare the 12-month anatomical and functional outcomes in treatment-naïve eyes with DME that either continued intravitreal bevacizumab (IVB) following three loading injections or switched to intravitreal aflibercept (IVA) or intravitreal ranibizumab (IVR).

MATERIALS AND METHODS

This retrospective study examined clinical archive records of patients who underwent intravitreal anti-VEGF injections for DME at a single center from January 2020 to January 2024. The study adhered to the principles of the Declaration of Helsinki and received approval from the Institutional Non-Interventional Scientific Research Ethics Committee (Approval No: 2025/427). As the study was designed retrospectively, it was exempt from the requirement for informed consent.

Inclusion criteria were age over 18 years, newly diagnosed DME secondary to type 2 DM, no prior treatment for DME (including intravitreal injections, laser therapy, or surgery), baseline best-corrected visual acuity (BCVA) between Snellen 20/400 and 20/40, central macular thickness (CMT) greater than 300 µm, and availability of at least 12 months of regular follow-up data. Exclusion criteria included the presence of proliferative diabetic retinopathy (PDR), vitreomacular traction or clinically significant epiretinal membrane, other macular diseases (such as macular degeneration, retinal vein occlusion, or uveitic macular edema), a history of intraocular surgery within the previous 3 months, vitrectomized eyes, high myopia (spherical equivalent >6 D), or coexisting ocular conditions such as uncontrolled glaucoma. Additionally, patients who underwent any intraocular surgery (such as cataract surgery or vitrectomy) during the study period or who received other treatments such as focal laser photocoagulation or intravitreal dexamethasone were excluded from the study.

According to the Social Security Institution's Health Implementation Guideline (SUT) in Türkiye, all eyes included in the study initially received three loading doses of intravitreal bevacizumab (IVB, 1.25 mg/0.05 mL). At the 1-month follow-up after loading, if optical coherence tomography (OCT) demonstrated persistent intraretinal and/or subretinal fluid (CMT >300 µm), patients were reassessed considering their socioeconomic status. Eyes meeting the criteria either received an additional three monthly IVB injections or were switched to three monthly intravitreal aflibercept (IVA, 2.0 mg/0.05 mL) or three monthly intravitreal ranibizumab (IVR, 0.5 mg/0.05 mL) injections. Following the first six injections (after month 6), all groups were treated using a **Pro Re Nata (PRN)** regimen and monitored until month 12. PRN retreatment criteria included a decrease in BCVA, CMT exceeding 300 µm on OCT, or an increase of more than 50 µm.

Based on the applied treatment protocol, eyes were classified into three groups:

- **Group 1 (Bevacizumab Monotherapy):** Eyes that continued treatment with bevacizumab.
- **Group 2 (Switch to Aflibercept):** Eyes switched to aflibercept after IVB loading.
- **Group 3 (Switch to Ranibizumab):** Eyes switched to ranibizumab after IVB loading.

All patients underwent a complete ophthalmologic examination at baseline, month 3, month 6, and at monthly visits after month 6. At each visit, BCVA according to the Snellen chart, intraocular pressure (IOP), dilated fundus examination, and CMT measurement using optical coherence tomography (OCT; Carl Zeiss Meditec, Dublin,

CA, USA) were performed. Additionally, demographic and clinical data—including age, sex, lens status (phakic/pseudophakic), duration of DM, type of DM treatment (oral antidiabetic agents, insulin, or combination therapy), comorbidities (none, hypertension, coronary artery disease, cerebrovascular stroke, chronic kidney disease, etc.), and the total number of intravitreal injections administered during the 12-month follow-up—were recorded. BCVA and CMT measurements obtained at baseline, month 3, month 6, and month 12 were documented.

SPSS software (Version 25.0, IBM, USA) was used for statistical analysis. Continuous variables were expressed as mean ± standard deviation (SD) or median (interquartile range, IQR), while categorical variables were expressed as frequency (n) and percentage. Snellen BCVA values were converted to the logarithm of the minimum angle of resolution (logMAR) for statistical analysis. Continuous variables were analyzed using analysis of variance (ANOVA) or the non-parametric Kruskal-Wallis test, depending on the distribution of the data. The Bonferroni post-hoc test was applied in cases of significant differences. For repeated measurements, pairwise comparisons were performed using the Dunn-Bonferroni post-hoc test following ANOVA analysis. Categorical variables were evaluated using the chi-square test and Fisher's exact test. $P<0.05$ was considered statistically significant.

RESULTS

A total of 120 eyes of 120 patients were included in the study. The mean age of the patients was 61.4 ± 7.87 years (range: 39–72). The groups were comparable in terms of age and sex (p = 0.419 and p = 0.147, respectively). The mean duration of diabetes was 14.4 ± 5.3 years (range: 5–25), with no statistically significant difference among the groups (p = 0.812). Fifty-six eyes were phakic and 64 were pseudophakic, and lens status did not differ significantly between the groups (p = 0.58). Demographic and clinical characteristics are summarized in Table 1.

After the intravitreal bevacizumab loading phase, 40 patients received IVB, 40 received IVA, and 40 received IVR. There was no statistically significant difference in the mean number of injections administered over the 12-month follow-up period (Group 1: 7.83 ± 0.78, Group 2: 7.63 ± 0.87, Group 3: 7.80 ± 0.76; p = 0.57). Similarly, the number of injections administered after the initial bevacizumab loading phase was comparable among the three groups (Group 1: 4.83 ± 0.78, Group 2: 4.63 ± 0.87, Group 3: 4.80 ± 0.76; p = 0.56).

At baseline, the mean BCVA (logMAR) values did not differ significantly among the three groups (Group 1: 0.627 ± 0.230, Group 2: 0.637 ± 0.239, Group 3: 0.642 ± 0.251; p=0.967). No significant differences in BCVA were observed between groups at 3, 6, and 12 months post-treatment (p=0.902, p=0.813, and p=0.763, respectively). All three groups exhibited notable visual improvement following bevacizumab loading therapy. Intragroup analyses indicated a significant improvement in BCVA at all time points when compared to baseline (p<0.001 for all groups). The analysis of net change in visual acuity revealed no significant differences in improvement between groups at 3, 6, and 12 months (p=0.312, p=0.482, and p=0.571, respectively) (Table 2).

Before treatment, the baseline CMT values were similar for all three groups (Group 1: 513.47 ± 123.97 µm; Group 2: 529.82 ± 93.63 µm; Group 3: 486.63 ± 81.56 µm; p=0.177). There were no significant differences between the groups when CMT was measured 3, 6, and 12 months after therapy (p=0.222, p=0.646, and p=0.386, respectively). All groups demonstrated substantial morphological improvement, and within-group analysis showed a significant reduction in CMT from baseline at all time points (p<0.001 for all groups). The assessment of CMT change levels indicated that the decrease at 3 and 12 months was similar among groups (p=0.673 and p=0.439, respectively). At the 6-month visit, Group 2 exhibited a greater reduction in CMT compared with the other groups; however, this difference did not reach statistical significance (p=0.081) (Table 3).

No local or systemic complications such as endophthalmitis, intraocular inflammation, or post-injection vascular events associated with intravitreal anti-VEGF injections were observed.

Table 1. *Baseline demographic and clinical characteristics*

	Group 1 (n=40) Mean ± SD	**Group 2 (n=40)** Mean ± SD	**Group 3 (n=40)** Mean ± SD	***p* value**
Age (years)	62.5 ± 9.8	63.1±10.1	61.9 ±9.5	0.419
Gender, n (%) Female Male	 19 (47.5) 21 (52.5)	 22 (55) 18 (45)	 17 (42.5) 23 (57.5)	0.147
Lens status, n (%) Phakic Pseudophakic	 21 (52.5) 19 (47.5)	 19 (47.5) 21 (52.5)	 17 (42.5) 23 (57.5)	0.580
Duration of diabetes (years)	14.44 ± 5.28	14.80 ± 5.37	13.93 ± 3.66	0.812
DM treatment n (%) OAD Insulin Combination	 23 (57.5) 10 (25.0) 7 (17.5)	 21 (52.5) 12 (30.0) 8 (17.5)	 20 (50.0) 13 (32.5) 7 (17.5)	0.874
Comorbidities, n (%) None Hypertension CAD CVD CKD	 8 (20.0) 29 (72.5) 5 (12.5) 2 (5.0) 12 (30)	 5 (12.5) 24 (60) 12 (30) 1 (2.5) 13 (32.5)	 5 (12.5) 21 (52.5) 18 (45.0) 2 (5.0) 10 (25.0)	0.555

SD, standart deviation; DM, diabetes mellitus; OAD, oral antidiabetic drug; CAD, coronary artery disease; CVD, cerebrovascular disease; CKD, chronic kidney disease

Table 2. *Comparison of Best Corrected Visual Acuity Changes*

	Group 1 (n=40) Mean ± SD	**Group 2 (n=40)** Mean ± SD	**Group 3 (n=40)** Mean ± SD	***p* value**
BCVA (logMAR) Baseline	 0.627 ± 0.230	 0.637 ± 0.239	 0.642 ± 0.251	 0.967
Month 3	0.510 ± 0.193	0.488 ± 0.190	0.501 ± 0.184	0.902
Month 6	0.388 ± 0.152	0.377 ± 0.160	0.403 ± 0.160	0.813
Month 12	0.317 ± 0.117	0.300 ± 0.129	0.323 ± 0.121	0.763
BCVA Change (Δ logMAR) Month 3	 –0.117 ± 0.083	 –0.149 ± 0.091	 –0.141 ± 0.089	 0.312
Month 6	–0.239 ± 0.110	–0.260 ± 0.125	–0.238 ± 0.118	0.482
Month 12	–0.310 ± 0.125	–0.337 ± 0.133	–0.319 ± 0.121	0.571

BCVA, Best corrected visual acuity; SD, Standard deviation; logMAR; Logarithm of the minimum angle of resolution

Table 3. *Comparison of changes in central macular thickness*

	Group 1 (n=40) Mean ± SD	**Group 2 (n=40)** Mean ± SD	**Group 3 (n=40)** Mean ± SD	*p* value
CMT (µm)				
Baseline	513.47 ± 123.97	529.82 ± 93.63	486.63 ± 81.56	0.177
Month 3	475.39 ± 111.16	487.68 ± 92.20	450.61 ± 76.28	0.222
Month 6	453.71 ± 105.97	458.50 ± 85.78	439.50 ± 82.56	0.646
Month 12	426.21± 101.26	435.26 ± 84.40	407.18 ± 83.63	0.386
CMT change (µm)				
Month 3	–38.08 ±25.84	-42.13 ± 35.17	-36.03 ± 29.44	0.673
Month 6	–59.76 ± 36.69	-71.32 ± 41.52	-47.13 ± 58.62	0.081
Month 12	-87.26 ± 41.15	-94.55 ± 52.50	-79.45 ± 58.33	0.439

SD, standart deviation; CMT, central macular thickness

DISCUSSION

In this retrospective study, we compared the 12-month anatomical and functional outcomes of three treatment strategies—continuing IVB monotherapy, switching to IVA, or switching to IVR—following an initial three-dose IVB loading regimen in treatment-naïve DME patients. Our primary finding was that, although all groups demonstrated significant improvement in visual acuity and substantial reductions in CMT over 12 months, no statistically significant differences were observed among the three strategies in terms of visual or anatomical outcomes. These results suggest that switching to an alternative anti-VEGF agent early after loading does not confer a measurable advantage over continuing bevacizumab, at least within the first year of follow-up.

Our results confirm the general efficacy of anti-VEGF agents in the treatment of DME. The DRCR.net Protocol T study compared the effectiveness of aflibercept, bevacizumab, and ranibizumab in treating DME. While all three drugs improved visual acuity after one year, there was no statistically significant difference between the groups with good baseline visual acuity.[8] Another study comparing aflibercept and ranibizumab monotherapies under a PRN protocol also reported functional and anatomical improvement over 12 months; however, in eyes with favorable baseline visual acuity, the degree of improvement did not differ significantly between the two agents.[9] Our study's results, which included patients with relatively good baseline BCVA, align with existing literature findings.

Lim et al. performed a study evaluating switching strategies to aflibercept and ranibizumab in patients with diabetic macular edema unresponsive to bevacizumab. Following the loading phase, a treat-and-extend protocol was instituted, leading to significant enhancements in both BCVA and CMT in both groups at the 12-month mark; however, no statistically significant differences were observed between the two groups concerning visual or anatomical outcomes.[10] A study assessing the 3-month outcomes of intravitreal bevacizumab, ranibizumab, and aflibercept in diabetic macular edema (DME) indicated notable enhancements in BCVA and CMT in all three groups, with no significant disparities in BCVA outcomes among them. The reduction in central macular thickness was more significant in the ranibizumab and aflibercept cohorts. [11]

Many randomized clinical trials have demonstrated the efficacy of different anti-VEGF agents primarily through monthly monitoring or PRN treatment algorithms. [12-14] However, such strategies may create a significant treatment burden for both healthcare providers and patients in real-world settings. Therefore, alternative treatment approaches that aim to reduce the number of clinic visits while maintaining or increasing the number of injections may be advantageous. In our study, we applied two loading cycles during the first 6 months, followed by PRN injections.

Similar to our approach, most patients in Protocol T received a 6-month anti-VEGF loading phase followed by PRN dosing. Depending on the anti-VEGF agent used, mean visual acuity gains of +13.3, +9.7, and +11.2 ETDRS letters at one year were reported.[5] Unlike Protocol T, our study incorporated three examination visits during the first six months instead of monthly assessments: one at baseline, one month after the first loading dose, and one month after the second loading dose. This approach aimed to optimize clinical workflow and patient follow-up by increasing injection frequency while reducing the number of examinations.

A positive correlation exists between the frequency of anti-VEGF injections and enhancements in BCVA, with patients undergoing more than 6–7 injections annually demonstrating greater visual improvement than those receiving fewer injections.[15] Clinical studies indicate that, in real-life settings, patients receive fewer injections than reported in randomized controlled trials, resulting in lower visual gains. [5,16] In our study, the mean number of injections was 7.75. In our series, the frequency of injections was comparatively high, and the enhancement in BCVA mirrored that observed in randomized studies. This study illustrates that close monitoring and regular administration of injections are as significant as the selection of the agent.

Given the increasing prevalence of diabetes and the high injection frequency required during the initial years of DME treatment, understanding the most cost-effective use of anti-VEGF agents has become increasingly important. A cost-effectiveness analysis evaluating the first-year outcomes of Protocol T reported that aflibercept was not cost-effective compared with ranibizumab for the overall patient population. [17] Grewal et al. compared the 2-year modeled costs of the bevacizumab-first strategy used in DRCR Protocol AC with real-world anti-VEGF monotherapy costs based on physician preference. Their analysis showed that the modeled cost of the bevacizumab-first strategy remained higher over two years, whereas real-world practice achieved substantially lower costs due to fewer clinic visits and injections. Furthermore, even when baseline vision and visual acuity gains were matched, real-world practice remained more cost-advantageous. [6] These findings suggest that treatment protocols are rational only when the intensive follow-up and injection schedules they require can actually be sustained in real-world clinical settings. In our study, the similar injection numbers across groups and the comparable visual and anatomical outcomes support the notion that, in clinical practice, the choice of anti-VEGF agent may be guided more by feasibility, follow-up adherence, and cost considerations rather than strict adherence to treatment algorithms.

While the findings of our study are significant, they are subject to the inherent limitations of a retrospective design. Furthermore, the decision to switch agents in Groups 2 and 3 depends on the physician's decision, including the patient's socioeconomic status. This situation does not completely eliminate the risk of selection bias. The follow-up period is limited to 12 months; longer follow-ups may reveal different outcomes between agents.

In conclusion, this study demonstrates that, in patients with DME, continuing bevacizumab or switching to aflibercept or ranibizumab provides comparable visual and anatomical improvement over a 12-month period. Future studies should focus on long-term real-world analyses to confirm these findings.

DECLARATIONS

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Ethics approval: Ordu University Clinical Research Ethics Committee, Turkey, 2025-427

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