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Annals of Clinical and Analytical Medicine
Original Research

Should we continue with aflibercept after bevacizumab in diabetic macula edema?

Aflibercept versus bevacizumab in diabetic macula edema

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Abstract

Aim: In this study, we aimed to compare the effects of intravitreal aflibercept (IVA) to combined intravitreal bevacizumab (IVB) and IVA on best corrected visual acuity (BCVA), central macular thickness (CMT) in diabetic macular edema (DME).

Methods: Twenty-one eyes of 21 patients with DME with a CMT greater than 250 µm in optical coherence tomography (OCT) measurements were retrospectively included in the study. BCVA and CMT measurements of patients were performed before therapy, in the first, third, and sixth months. Patients were followed up for an average of 9 ± 3 (6-12) months. After a 3-month injection of 1.25 mg/0.05 ml bevacizumab in 11 eyes in Group 1, intravitreal aflibercept therapy was started. Ten patients in Group 2 were given 3 loading doses monthly followed by 3 months of maintenance intravitreal aflibercept treatment.

Results: The BCVA (log-MAR) of the patients in the pre-treatment period was 0.7 ± 0.3 in Group 1; 0.6 ± 0.4 at 1 month post-treatment; 0.4 ± 0.2 at 3 months; and 0.4 ± 0.2 at 6 months. The BCVA was 0.7 ± 0.27 before treatment in Group 2; 0.6 ± 0.4 at 1 month post-treatment; 0.4 ± 0.2 at 3 months; and 0.4 ± 0.21 at 6 months. While the mean CMT before the application was 294.5 ± 47.0 µm in Group 1, it was 345.7 ± 62.32 µm in Group 2. The CMT was 274.9 ± 30.1 µm in the 1st month, 274.3 ± 42.3 µm in the 3rd month, and 252.8 ± 24.1 µm in the 6th month after injection in Group 1. It was measured as 286.2 ± 40.99 µm at 1 month, 264.3 ± 34.05 µm at 3 months, and 245.0 ± 32.38 µm at 6 months in Group 2. No complications were encountered after the injections. There was no significant difference between the groups in CMT and BCVA ($P > .05$).

Conclusion: Bevacizumab is an effective and safe treatment method in DME. In this study, it was shown that treatment with intravitreal aflibercept and bevacizumab injection provides a similar anatomical and functional improvement in patients with DME.

Keywords

diabetic macula edema, aflibercept, bevacizumab

DOI: 10.4328/ACAM.21461 Ann Clin Anal Med 2023;14(2):139-143
Received: 22.10.2022 Accepted: 22.11.2022 Published Online: 26.11.2022 Printed: 01.02.2023
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Introduction

Diabetes is a metabolic disease with vasculopathy. With the use of insulin and oral anti-diabetics, life expectancy has increased in diabetic patients and this has increased the incidence of diabetes-related complications. Diabetic retinopathy is one of the most important causes of vision loss in adults, and the pathology largely responsible for this process is diabetic macular edema (DME), which is characterized by exudation and accumulation of extracellular fluid and plasma components.1 Vascular endothelial growth factor (VEGF) is an important agent responsible for abnormal vascular permeability in DME, and many studies have shown visual gains and anatomical improvements in treatment with intravitreal anti-VEGFs.2,3 The use of bevacizumab, as an anti-VEGF agent in DME, is an alternative treatment method that is gaining in popularity over time. Bevacizumab is used in many diseases such as senile macular degeneration, pseudophakic cystoid macula edema, and in proliferative diabetic retinopathy, including DME, and successful results were obtained in these diseases.4-7 However, some people respond poorly to bevacizumab or ranibizumab, and it was also observed that resistant edema persisted despite repeated injections.8

In Protocol T study, all 3 anti-VEGF (aflibercept (Eylea; Regeneron Pharmaceuticals, Inc [Tarrytown, NY]), bevacizumab (Avastin; Genentech [South San Francisco, CA]), and ranibizumab (Lucentis; Genentech) groups showed visual acuity (VA) improvement from baseline at 2 years, and also there was decreased number of injections at 2 years. Visual acuity outcomes were similar for eyes with better baseline VA. Aflibercept and ranibizumab are more effective in eyes with worse baseline VA at 2 years compared with bevacizumab. Even though aflibercept is superior to ranibizumab in 1 year, there is no difference after that.9

The DRCR.net study compared the effectiveness of 3 drugs in center-involved DME and showed vision gains in all 3 drugs at the 2-year visit. It was demonstrated that there was decrease in the number of injections, frequency of visits, and amounts of focal/grid laser photocoagulation treatment in all 3 groups in the second year. Among eyes with better VA at baseline, no difference was identified in vision outcomes through the 2-year visit. For the eyes with worse VA at baseline, the advantage of aflibercept over bevacizumab for mean VA gain was still present at 2 years, although the difference at 2 years was diminished. The VA difference between aflibercept and ranibizumab for eyes with worse VA at baseline was significant at 1 year but this difference decreased at 2 years.10

In this study, we aimed to compare the effects of the switch to aflibercept after bevacizumab injection to maintenance treatment with aflibercept injection on visual acuity and central macular thickness (CMT) in diabetic macular edema (DME).

Materials and Methods

Twenty-one eyes of 21 patients with DME with a CMT greater than 250 µm in optical coherence tomography (OCT) measurements in the Eye Clinic of Abdurrahman Yurtaslan Oncology Training and Research Hospital were retrospectively studied. The approval of the local ethics committee was obtained for the study. The patients were followed up for an average of 9 ± 3 (6-12) months. Patients over 40 years of age, with best visual acuity between 0.3 and 1.2 with Log-Mar, and without high-risk or active proliferative retinopathy were included in the study. Patients with uncontrolled diabetes, glaucoma, and hypertension, patients whose fundus could not be evaluated well because of cataract and corneal opacity, patients who had cataract surgery or underwent Nd-YAG laser capsulotomy and panretinal photocoagulation in the last 6 months, were excluded from the study.

Ophthalmological examinations of all patients were evaluated before intravitreal injection application. The best corrected visual acuity (BCVA) was corrected according to the Log-MAR, anterior segment and fundus examinations with biomicroscopy, CMT measured with Zeiss Stratus Optical Coherence Tomography (OCT), and intraocular pressure (IOP) measured with Goldmann applanation tonometry were recorded.

After a 3-month injection of 1.25 mg/0.05 ml bevacizumab in 11 eyes in Group 1, it was switched to intravitreal 2 mg/0.05 ml aflibercept therapy. Ten patients in Group 2 were given 3 loading doses monthly followed by 3 months of maintenance intravitreal aflibercept treatment (2 mg/0.05 ml). Before the injection, VA (log-MAR), anterior segment, fundus, and OCT findings in the 1st, 3rd, and 6th months were evaluated.

Ethical Approval

This study was approved by the local Ethics Committee of Abdurrahman Yurtaslan Oncology Training and Research Hospital.

Statistical Analysis

Data analysis was done using IBM SPSS 25.0 statistical package program. While evaluating the study data, the Chi-Square (x^2) test was used to compare qualitative data as well as descriptive statistical methods (frequency, percentage, mean, standard deviation, median, min-max). The conformity of the data to the normal distribution was evaluated with the Kolmogorov-Smirnow and Shapiro-Wilk tests. The Mann-Whitney U test was used for intergroup comparisons of data that did not show normal distribution, and the Friedman test was used for within-group comparisons. Dunn's post-hoc test was used to find the source of the difference in cases where there was a difference in the group comparisons. Values with probability (p) less than a = 0.05 were accepted as significant and there was a difference between groups, higher values were considered insignificant and there was no difference between groups.

Reporting Guidelines

This study was reported in accordance with the STROBE guideline.

Results

The study included 21 eyes of 21 patients, 9 (42.85%) females and 11 (57.14%) males. Their ages ranged from 40 to 76 (mean = 59.15 ± 8.54 years). The mean follow-up period was 9.32 ± 2.8 months.

The BCVA (log-MAR) of the patients was 0.7 ± 0.3 in Group 1 in the pre-treatment period who received aflibercept for 3 months after bevacizumab, 0.6 ± 0.4 in the 1st month post-treatment; 0.4 ± 0.2 in the 3rd month; and 0.4 ± 0.2 in the 6th month. The mean visual acuity (log-MAR) of the patients before treatment in Group 2 who had 3 months of aflibercept loading followed by 3 months of aflibercept was 0.7 ± 0.27; 0.6 ± 0.4 in the 1st month post-treatment; 0.4 ± 0.2 in the 3rd month; and 0.4 ± 0.21 in the 6th month.

The mean CMT before the application was 294.5 ± 47.0 µm in Group 1 (Figure 1). The mean CMT was 345.7 ± 62.32 µm in Group 2. CMT in Group 1 was 274.9 ± 30.1 µm in the 1st month, 274.3 ± 42.3 µm in the 3rd month, and 252.8 ± 24.1 µm in the 6th month after injection (Figure 2). In Group 2, CMT was 286.2 ± 40.99 µm in the 1st month, 264.3 ± 34.05 µm in the 3rd month, and 245.0 ± 32.38 µm in the 6th month (Figure 3).

No complications were encountered after the injections. There was

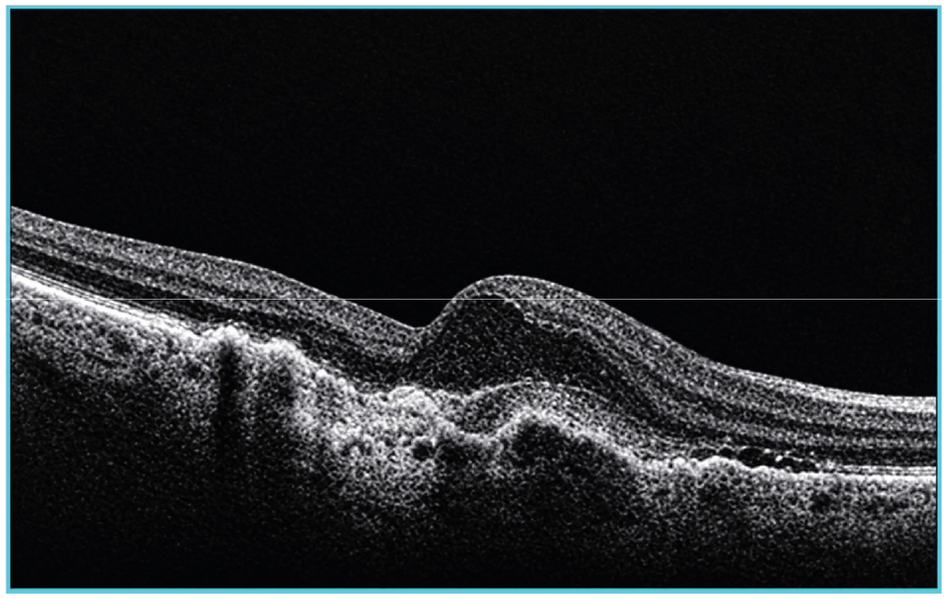

Figure 1. *Pretreatment Visual Acuity: 0.1 CMT: 325 μm*

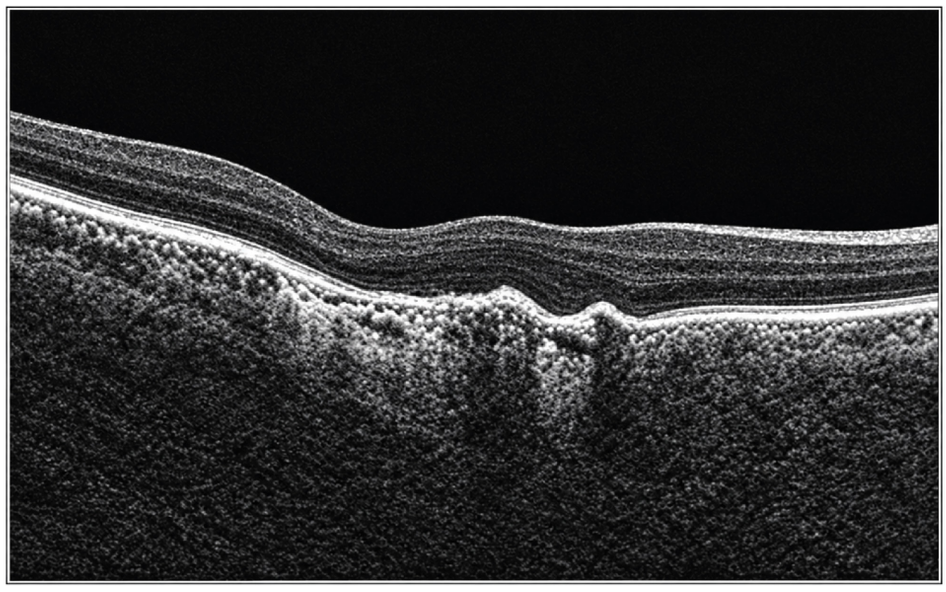

Figure 2. *Visual Acuity After 3 Doses of Bevacizumab +3 Doses of Aflibercept: 0.2 CMT: 207 μm*

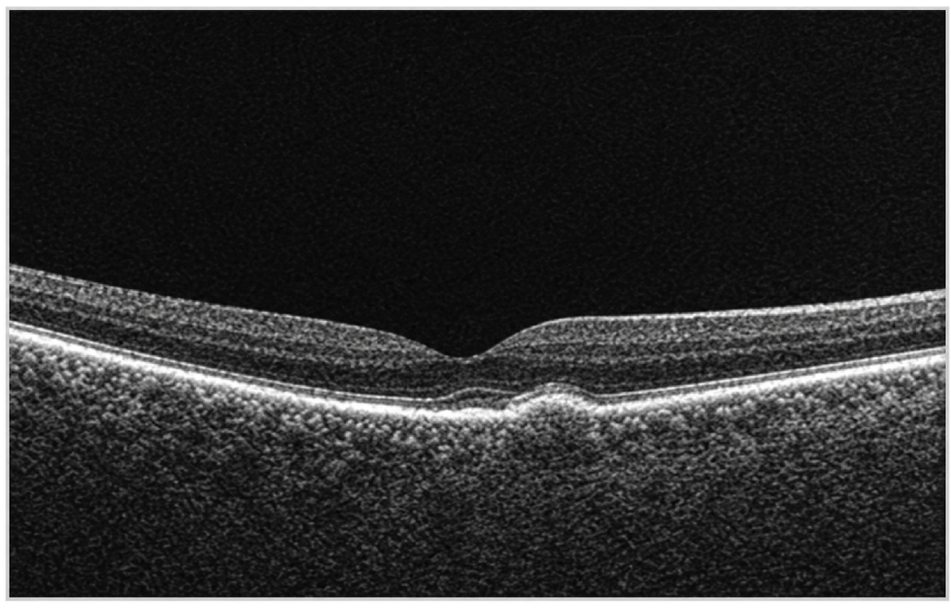

Figure 3. *Visual Acuity After 6 Doses of Aflibercept: 0.3 CMT: 260 μm*

no significant difference between the groups in CMT and visual acuity (P > .05).

Discussion

The two major pathological events responsible for vision loss in diabetic retinopathy are diabetic macular edema resulting from retinal vascular high permeability and retinal neovascularization. VEGF, a potent angiogenic stimulant and vascular permeability factor, can cause both of these conditions. As the degree of diabetic macular edema increases, there is a proportional increase in VEGF levels in aqueous humor.

Today, anti-VEGF therapy is applied off-label in diabetic retinopathy and retinal vein occlusion, which are the leading diseases of retinal neovascularization, and successful results have been reported with different anti-VEGF drugs in clinical use, with variable responses. There are also studies about the effect of bevacizumab on diseases such as retinopathy of prematurity, Coats' disease, familial exudative vitreoretinopathy, pediatric vitreoretinal, such as incontinentia pigmenti.11

RISE/RIDE studies demonstrate that intravitreal injections of anti-vascular endothelial growth factor (anti-VEGF) agents have progressively replaced focal laser photocoagulation as the primary treatment for center involving macular edema. Anti-VEGF treatment administered monthly demonstrated significant VA gains in a large percentage of patients and reduction of severe VA loss.12

VISTA/VIVID studies demonstrate that IVA administered every 4 or every 8 weeks (after 5 initial monthly doses) significantly improved VA and significantly decreased severe vision loss, while simultaneously improving the diabetic retinopathy severity score, compared with focal laser photocoagulation. Data from these studies will provide additional information regarding the similar efficacy observed with IVA regimens of 2 mg every 4 weeks and 2 mg every 8 weeks. This study also demonstrated that intravitreal aflibercept dosed every 8 weeks (after 5 initial monthly doses) could provide a therapeutic option that may reduce the total number of injections and necessary office visits, substantially reducing the burden on patients, physicians, and the healthcare system.13

In addition to replacing laser therapy, anti-VEGF treatments make it possible to treat with aflibercept at 8-week intervals after a 5-month loading dose. However, it is now known that good results are also obtained with bevacizumab.

Haritoglou et al. administered 1.25 mg/0.05 ml IVB injection to 51 patients with DME. At least 2 injections were applied to 16 patients. 35% of the patients received focal laser treatment, 37% panretinal laser therapy, 12% vitrectomy, and 33% intravitreal triamcinolone injection previously. Mean visual acuity was 0.86 ± 0.38 (logMAR) at baseline, while it increased to 0.75 ± 0.37 logMAR (P = .001) at 6 weeks post-treatment. However, there was a slight decrease (0.84 ± 0.41) at 12 weeks. The visual acuity increase of at least 3 lines was observed in 29% of the patients at 6 weeks and in 26% of the patients at 12 weeks of follow-up. Mean central retinal thickness was 501 ± 163 μ at baseline, then decreased to 425 ± 180 μ (P = .002) at 2 weeks post-treatment, 416 ± 180 μ at 6 weeks (P = .001), and 377 ± 117 μ (P = .001) at 12 weeks. As a result, it has been observed that IVB injection provides improvement in visual acuity and decrease in retinal thickness even in cases unresponsive to laser, IVTA injection, or vitrectomy.4

Arevalo et al. conducted retrospective, multicenter study involving 139 eyes of 115 patients with diffuse DME and applied 1.25-2.5 mg intravitreal bevacizumab injection to the patients. After 24 months of follow-up, VA and CMT changes were examined. The mean number of IVB injections was 5.8 per eye. Mean visual acuity in the 1.25 mg IVB group was 20/150 at baseline, 20/107 (P < .001) at 1 month, 20/75 (P < .001) at the end of the follow-up period. Similar changes were observed in the 2.5 mg IVB administration group. The visual acuity was 20/168 at baseline, 20/118 at 1 month (P = .02), 20/114 (P < .001) at the end of 24 months.

The mean CMT in the 1.25 mg IVB administration group was 466.5 ± 145.2 at baseline, while it was 332.2 ± 129.6 in the 1st month, and 286.6 ± 81.5 at the end of the 24th month. Similar results were observed in the 2.5 mg group. In terms of results, there was no difference between the mg dose administrations.14

The Diabetic Retinopathy Clinical Research Network (DRCR.net) conducted a comparative effectiveness trial comparing 3 commonly used antivascular endothelial growth factor agents, aflibercept, bevacizumab, and ranibizumab for center-involved diabetic macular edema (DME) associated with visual impairment at the 2-year visit. The need for focal/grid laser photocoagulation treatment also decreased in all 3 groups in the second year. This study identified that there is no difference in vision outcomes among eyes with better VA at baseline, over the 2 years. For eyes with worse VA at baseline, the advantage of aflibercept over bevacizumab for mean VA gain persisted through 2 years, although the difference at 2 years was diminished. The VA difference between aflibercept and ranibizumab for eyes with worse VA at baseline that was noted at 1 year, decreased at 2 years.10

Protocol T study demonstrated that all 3 regimens, on average, produced significant VA improvement over 2 years. However, as in the first year, there were differences between regimens according to the baseline VA. There was no significant difference in mean VA change between the treatment groups at 2 years in eyes with better baseline VA. In eyes with baseline VA of 20/50 or worse, the advantage of aflibercept over ranibizumab was remarkable at 1 year, but this superiority decreased and was no longer statistically significant at 2 years, whereas aflibercept remained superior to bevacizumab. However, aflibercept and ranibizumab were not found to be cost-effective compared to bevacizumab.9

In this retrospective clinical study, the BCVA (log-MAR) of the patients in the pre-treatment period was 0.7 ± 0.3 in Group 1; 0.6 ± 0.4 at 1 month post-treatment; 0.4 ± 0.2 at 3 months; and 0.4 ± 0.2 at 6 months. The BCVA was 0.7 ± 0.27 before treatment in Group 2; 0.6 ± 0.4 at 1 month post-treatment; 0.4 ± 0.2 at 3 months; and 0.4 ± 0.21 at 6 months. While the mean CMT before the application was 294.5 ± 47.0 μm in Group 1, it was measured as 345.7 ± 62.32 μm in Group 2. The CMT was 274.9 ± 30.1 μm in the 1st month, 274.3 ± 42.3 μm in the 3rd month, and 252.8 ± 24.1 μm in the 6th month after injection in Group 1. It was measured as 286.2 ± 40.99 μm at 1 month, 264.3 ± 34.05 μm at 3 months, and 245.0 ± 32.38 μm at 6 months in Group 2. Even though visual acuity did not increase when loaded with bevacizumab, the CMT decreased. With continued treatment with aflibercept, visual acuity stabilized, while CMT continued to decrease. Although visual acuity remained stable from the beginning in the group that was loaded with aflibercept and continued, the final visual acuities were similar in both groups. However, there was also a decrease in the CMT in the 2nd group, but there was no significant difference between the two groups. No complications were encountered after the injections. There was no significant difference between the groups in CMT and BCVA (P > .05).

All these results show that the switch to aflibercept after bevacizumab injection gives similar results to treatment with aflibercept alone. Bevacizumab appears to be superior to other anti-VEGFs in terms of cost-effectiveness. In addition, according to the Protocol T study, although bevacizumab is not as effective as other anti-VEGF agents in low baseline VA levels at 2 years, it seems to be more advantageous due to its accessibility and affordability.

Limitations

The main limitations of this study were its retrospective design, small sample size, and relatively short follow-up period. These factors may limit the generalizability of the findings.

Conclusion

As a result, intravitreal bevacizumab is an effective treatment modality in the treatment of DME, especially in the regions with low accessibility to other anti-VEGF agents. Our study also supported this approach by providing similar anatomical and functional improvement in patients with cystoid DME with intravitreal combined aflibercept and bevacizumab injection treatment when compared to aflibercept injection.

Declarations

Animal and Human Rights Statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed Consent

Informed consent was waived due to the retrospective nature of the study.

Data Availability

The datasets used and/or analyzed during the current study are not publicly available due to patient privacy reasons but are available from the corresponding author on reasonable request.

Conflict of Interest

The authors declare that there is no conflict of interest.

Funding

None.

Abbreviations

BCVA: Best corrected visual acuity
CMT: Central macular thickness
DME: Diabetic macular edema
IOP: Intraocular pressure
IVA: Intravitreal aflibercept
IVB: Intravitreal bevacizumab
OCT: Optical coherence tomography
VA: Visual acuity
VEGF: Vascular endothelial growth factor

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How to Cite

Ceyda Başkan, Duygu Doğan. Should we continue with aflibercept after bevacizumab in diabetic macula edema? Ann Clin Anal Med 2023;14(2):139-143. doi:10.4328/ACAM.21461