ORIGINAL ARTICLE

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Aflibercept in a Persistent Diabetic Macular Edema Refractory to Previous Ranibizumab Therapy

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Abstract

Objective: To investigate the visual acuity and anatomical outcomes of intravitreal aflibercept treatment in patients with diabetic macular edema (DME) who were unresponsive to ranibizumab.

Methods: Patients with refractory DME treated with at least 3 consecutive injections of ranibizumab, 4-6 weeks apart, before switch and with at least 2 aflibercept injections after that in the period of May 2013 to October 2017 were considered eligible for study participation. "The patients" demographic characteristics, best-corrected visual acuity (BCVA), and central foveal thickness (CFT) were recorded at baseline, pre-switch, the first month post-switch, and the final visit.

Results: A total of 33 eyes of 28 patients were investigated. The average number of ranibizumab injections before switching to aflibercept was 4.97±1.94 and that of the subsequent aflibercept injections was 2.54±0.6. The mean baseline BCVA was 0.56 ± 0.38 logMAR. After the switch, the BCVA during the first and final visits was 0.41±0.34 logMAR (p=0.19) and 0.36±0.34 (p=0.16), respectively. After switching, clinical follow-up data for at least 6 months were available for all eyes. The mean baseline CFT was 504±123.7 µm (264-844 µm).One month after the switch, the average CFT had significantly reduced to 338.8±105.3 µm (225-615 µm) (p=0.0001). At the final visit, the average CFT was 345.7±137.4 µm (136-892 µm) (p=0.0002). Before and after the switch, the mean intraocular pressure (IOP) was 14.18±3.66 mmHg and 13.54±3.81 mmHg respectively (p=0.46).

Conclusion: Switch to aflibercept from ranibizumab in patients with recalcitrant DME resulted in significant anatomical improvements. Although the BCVA increased and the IOP decreased, these changes were not statistically significant.

Keywords: Aflibercept, diabetic macular edema, ranibizumab, switch, treatment resistance/refractory

INTRODUCTION

Diabetic macular edema (DME) is an important cause of visual impairment in patients with diabetes and significantly affects the quality of life (1). Elevated intraocular levels of vascular endothelial growth factor (VEGF) support retinal vascular permeability, leading to macular edema in patients with diabetes (2). Recently, intravitreal injections of anti-VEGF agents have been proven as the essential treatment for DME (3) owing to their efficacy in diminishing macular edema in diabetic eyes with the use of drugs, such as ranibizumab (3,4), bevacizumab (5), pegaptanib (6), and aflibercept (7,8).

After the RISE and RIDE phase 3 clinical trials (3,4), ranibizumab (Lucentis; Genentech, South San Francisco, California, USA) became the first VEGF inhibitor certified by the Food and Drug Administration for DME in 2012. Ranibizumab is an antibody fragment with a binding affinity toward all forms of VEGF-A.

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Aflibercept (Eylea; Regeneron, Tarrytown, New York) is a 115-kDA recombinant fusion protein that includes the key VEGF-binding domains of human VEGF receptors 1 and 2 fused to the constant region of human G1 (9). Aflibercept has shown to have a higher binding affinity to VEGF-A than to ranibizumab and immunoglobulin bevacizumab in a preclinical trial (10). Unlike ranibizumab and bevacizumab, aflibercept also binds to VEGF-B and placental growth factor that may inhibit vascular permeability and retinal neovascularization (10).

Currently, many patients who have undergone ranibizumab or bevacizumab treatment for DME and have failed to respond to these drugs are being switched to aflibercept. Differences in the pharmacodynamics of aflibercept compared with those of ranibizumab and bevacizumab are the basis of this strategy. However, thus far, there has been no consensus regarding the ideal time to consider a therapeutic switch (11). Some practitioners choose an "early switching" strategy because they believe that long-standing macular edema may lead to chronic retinal damage and worse prognosis; however, this scenario does not account for late responders (11). According to the first-year results of the DRCR (protocol T), aflibercept achieved the best results in low-vision patients (8). However, a recent trial on low-vision patients demonstrated no difference in the effect of aflibercept and ranibizumab (p=0.18) at the 2-year follow up (12).

Thus, the purpose this study was to demonstrate the short-term functional and anatomical responses of intravitreal aflibercept in a series of patients with persistent DME who failed to respond to multiple intravitreal ranibizumab injections.

METHODS

The protocol of this study was approved by the Institutional Review Board of the Eye Clinic of the Ankara Training and Research Hospital Ethic Committee (approval number: 308, approval date: 06.12.2017). This was a retrospective, non-comparative, consecutive case series of patients treated with DME. All the research was carried out in accordance with the Helsinki Declaration and by obtained written informed consent from the patients.

The eligible patients were aged ≥18 years, had a history of diabetes mellitus (type 2), evidence of clinically significant macular edema as defined by the Early Treatment Diabetic Retinopathy Study (13) and center-involving DME which is described as central 1 mm area of more than ≥300 µm measured by spectral-domain optical coherence tomography [(SD-OCT); Heidelberg Engineering, Heidelberg, Germany].

We identified DME patients who were unresponsive to ranibizumab; unresponsiveness was defined as no reduction in the CFT, increase in CFT (using SD-OCT), or gain in BCVA of less than 1 line at 1 month following at least 6 months of continuous ranibizumab treatment compared to that at baseline. All patients with center involving DME who had received at least three monthly ranibizumab injections before the switch and had received at least 2 aflibercept injections after the switch were eligible for study inclusion.

Patients were excluded if they had previous ocular trauma, macular pathologies, vitreomacular adhesion or traction, the presence of intraretinal/sub- retinal fluid using 12 radial line scans through the fovea, epiretinal membrane, tractional retinal detachment, vitreous hemorrhage, had received intravitreal or sub-tenon injection corticosteroids, or had any history of prior intraocular surgeries (except uncomplicated cataract surgery). Aflibercept was injected >4 weeks after the ranibizumab therapy was completed.

The demographic, examination, and treatment data of the eligible patients were extracted from their clinical charts. The BCVA of patients was recorded using Snellen's chart and then converted to logMAR for statistical analysis. Intraocular pressure (IOP) recordings performed using pneumotonometry (non-contact tonometer 10; Shin-Nippon Machinery Co, Japan) before dilatation and injection at every visit, as well as the results of biomicroscopic examination of the anterior segment and fundus using an indirect ophthalmoscope were recorded. Follow-up SD-OCT scans were performed at each visit for documentation.

Data regarding the patients' demographic characteristics; glycosylated hemoglobin levels; presence of coexisting chronic disease; lens status; quantity of pre-switch ranibizumab and post switch aflibercept injections; as well as the BCVA, IOP, and CFT at baseline, pre-switch, the first visit post-switch, and final visit were recorded.

Statistical Analysis

The study data were analyzed using the Statistical Package for Social Sciences (SPSS), version 24.0 for Windows (SPSS Inc., Chicago, IL). Descriptive data were presented as the mean ± standard deviations, frequency distributions, and percentages.

RESULTS

We studied 33 eyes in 28 patients who were eligible according to the inclusion criteria with DME unresponsive to ranibizumab treatment. The mean patient age was 58.85±10.37 years (range 36-80 year). Basic demographic and ocular characteristics are

shown in Table 1. Some patients exhibited the coexistence of chronic disease, such as hypertension, coronary artery disease, and chronic renal failure.

Treatment Characteristics

The average number of ranibizumab injections in the 6-month period before switching to aflibercept was 3.66±0.77. Patients received an average total of 2.54±0.6 injections at 6 months after switching to aflibercept. No cases of endophthalmitis, retinal detachment, or elevated IOP were observed. The most common adverse effects were local hyperemia or subconjunctival hemorrhage at the injection site.

Table 1. Demographic and ocular characteristics of patients with DME converted from prior ranibizumab treatment to aflibercept therapy

Age (y)	
Mean (SD)	58.85 (10.37)
Median (min, max)	57 (36-80)
Sex (%)	
Male	16 (57%)
Female	12 (43%)
Duration of known diabetes (y)	
Mean (SD)	12.98 (4.35)
Median (min, max)	12 (3-25)
Glycosylated hemoglobin level	
Mean (SD)	7.90 (1.49)
Median (min, max)	7.80 (6.50-11.80)
Lens status (%)	
Pseudophakic	13 (39.4%)
Phakic	20 (60.6%)
Total pre-switch ranibizumab injections	
Mean (SD)	4.97 (1.94)
Median (min, max)	5 (3-8)
Number of ranibizumab injections in the previous 6 months	
Mean (SD)	3.66 (0.77)
Median (min, max)	3 (3-5)
Number of aflibercept injections post-switch	
Mean (SD)	2.54 (0.6)
Median (min, max)	2 (2-7)
Other prior treatments (>6 months from conversion) (%)	
Pan retinal photocoagulation	9 (27%)
Focal macular laser	2 (6%)
Intravitreal triamcinolone	2 (6%)
Dexamethasone implant	7 (21%)

y: Years, SD: Standard deviation, min: Minimum, max: Maximum, DME: Diabetic macular edema

Visual Outcomes After Switch to Aflibercept

Before the administration of the ranibizumab injections, the mean baseline BCVA was 0.56±0.38 logMAR, while after an average 4.97±1.94 injection, the pre-switch BCVA was 0.44±0.33 logMAR; the difference was not statistically significant. After the switch, the first-visit BCVA was 0.41±0.34 log MAR (p=0.19), and the final visit BCVA was 0.36±0.34 (p=0.16) (Figure 1). Seventeen of the 33 eyes (51.5%) were treated with 2 consecutive aflibercept injections. In the post-hoc analyses, there was no significant difference between the eyes that had received 2 consecutive aflibercept injections and those that had received 3 or more injections. Notably after at least 2 aflibercept injections, 6 eyes (18%) had been preserved in their initial visual acuity, 15 eyes (45%) exhibited an improvement of 1-2 lines of vision, and 4 eyes (12%) showed improvement in 3-4 lines of vision. Eight eyes had worse vision after switching to aflibercept. Consecutive visual acuity (VA) measurements recorded at the subsequent visits are outlined in Table 2. There was no correlation between the last BCVA (logMAR) and the number of post-switch injections (Spearman's rho-0.056, p=0.7). Subgroup analyses were performed to identify the effect of the pre-switch VA, classified as VA ≥20/40 (17 eyes) and VA <20/40 (16 eyes), on the visual response to change in therapy. After switching to aflibercept, better final vision was achieved in the VA ≥20/40 (17 eyes) group than in the VA <20/40 (16 eyes) group (p=0.000073).

Anatomic Outcomes After Switch to Aflibercept

Before the ranibizumab injections were administered, the mean baseline CFT was 504±123.7 µm (264-844 µm). After the ranibizumab injections were given, the pre-switch CFT was 451.5±113 µm (286-822 µm) (p=0.06), while the CFT on the first post-switch visit was significantly lower at 338.8±105.3 µm (225-615 µm) (p=0.0001). The CFT at the final visit was 345.7±137.4 µm (136-892 µm), a significant improvement over the pre-switch CFT (p=0.0002) (Figure 1). There was no correlation between the CFT at the final visit and the number of post-switch injections (Spearman's rho +0.310, p=0.07).

Intraocular Pressure After Switching to Aflibercept

The average IOP registered at the pre-switch visit was 14.18±3.66 mmHg (median: 13; range: 10-22 mmHg). At the final visit, the average IOP was 13.54±3.81 mmHg (median: 13; range, 10-25 mmHg), indicating a mean decrease of 0.7 mmHg (p=0.46) (Figure 1).

DISCUSSION

During DME treatment, physicians may choose to switch among anti-VEGF agents for various reasons. The clinical reasons include the theoretically greater affinity of aflibercept for VEGF and the fact that it also binds to and neutralizes the placental

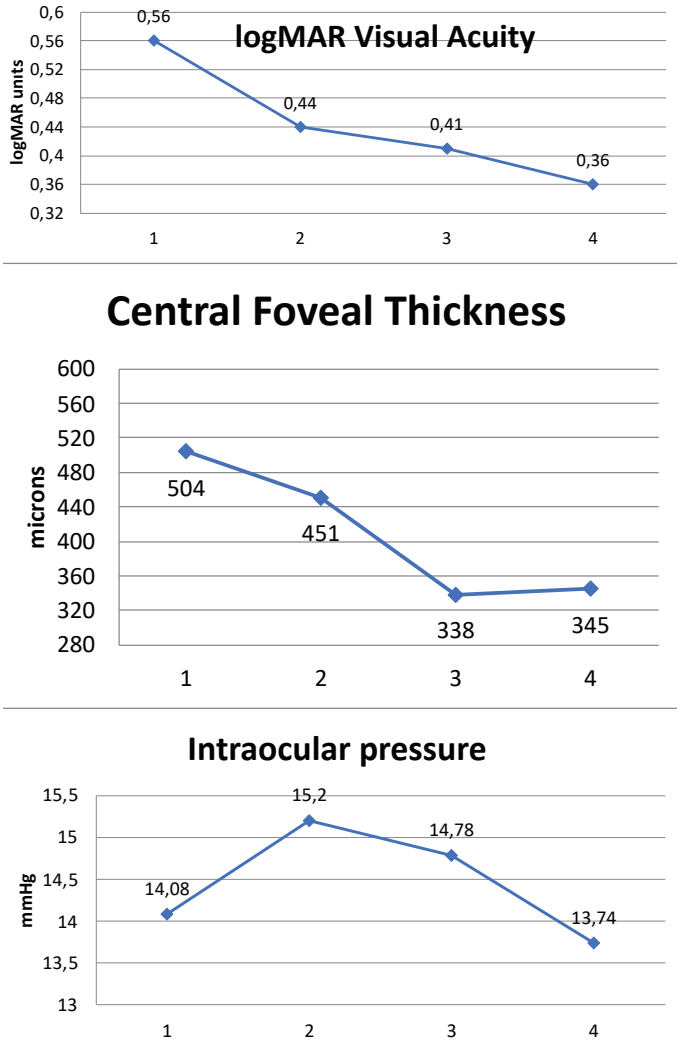

Figure 1. Comparison of visual acuity, central foveal thickness, and intraocular pressure before and after conversion to aflibercept for diabetic macular edema (1: At baseline, 2: At the pre-switch visit, 3: At the first visit post-switch, 4: At the final examination)

growth factor. These pharmacodynamic differences may be particularly useful in situations where a patient is unresponsive to ranibizumab or bevacizumab. Additionally, physicians may choose to switch a patient to aflibercept owing to its reportedly longer duration of action. A group patients with diabetes with macular edema may lead to resistance to ranibizumab or bevacizumab therapy. Additionally, tachyphylaxis, which is a fair response to ranibizumab, or bevacizumab, may also be observed in a group of patients.

Our results confirm the important role of aflibercept in patients with DME who do not respond to ranibizumab injections. In this study, 33 patients with persistent DME refractory to prior ranibizumab therapy were treated with at least 2 aflibercept injections. Although anatomical improvements were significantly reduced in both post-switch first month and final visit CFT compared with pre-switch CFT, it was not statistically significant. After the switch, the number of injections performed in our study may appear limited. However, as per our correlation analyses, there is no substantial change in BCVA and CFT with the respect to the number of injections. Similar to our findings, Chen et al. (14) demonstrated that nearly 50% of the patients showed no significant changes 2 or 3 months after the switch. Sub-group analyses were performed to identify the effect of the pre-switch VA, classified as VA ≥20/40 (17 eyes) or <20/40 (16 eyes), on the visual response to the change in therapy. Our study showed that for a good patient outcomes following switch, it is important to have good pre-switch BCVA because a better pre-switch BCVA translated into superior final BCVA in our patients. Dugel et al. (15) demonstrated that patients with a baseline BCVA >70 letters could gain up to an average of >5 letters, similar outcomes were observed in our study. Some recommend early switching because they believe that persistent macular edema leads to further deterioration of VA and may inhibit a functional response; in contrast, others, recommend delayed switching to consider the possibility of late responders (16). Aslan et al. (17) retrospectively reviewed 76 eyes of 50 patients, they stated that the better the first vision, the better the last vision.

Recently, 3 studies have demonstrated the efficacy of intravitreal aflibercept in patients with DME refractory to bevacizumab and ranibizumab. Chen et al. (14) retrospectively reviewed 72 eyes with DME unresponsive to ranibizumab and/or bevacizumab and subsequently switched to aflibercept. About 2/3rd exhibited beneficial effects of the subsequent 3-monthly intravitreal aflibercept injections. Compared with the pre-switch VA and anatomical measurements, especially significant visual gains and anatomical improvements were observed at 1 month but not at 2 or 3 months after the switch to aflibercept. Several non-responders reported having undergone vitrectomy. Rahimy et al. (18) retrospectively reviewed 50 eyes with persistent DME where the treatment was switched to aflibercept. Similar to our results, they found no significant change in VA but there was significant anatomic improvement, after 4.1 aflibercept injections over 4.6 months of subsequent injections. Herbaut et al. (19) retrospectively reviewed 25 eyes with resistant DME after at least 3 ranibizumab and/or one dexamethasone implant intravitreal injection. They observed not only significant anatomical improvements but also significant BCVA improvement between the pre-switch and post switch final visit. In the study by Erden et al. (20), ranibizumab, and aflibercept were shown to be equally effective in visual prognosis.

Aflibercept appears to offer theoretical advantages over other drugs, such as ranibizumab and bevacizumab. First, aflibercept

Table 2. Visual acuity before and after conversion to aflibercept for diabetic macular edema

Eyes with data	First visit	Pre-switch visit	Post-switch first visit	Post-switch second visit	Finally visit
VA levels, n	33	33	33	17	16
20/20	1	2	3	2	1
20/25	1	2	2	3	3
20/30	9	9	12	4	5
20/40	-	4	-	-	1
20/50	5	4	3	-	1
20/60	4	-	1	1	-
20/70	-	-	-	-	-
20/80	-	-	-	-	-
20/100	5	4	3	5	2
20/200	5	7	8	-	3
20/300	1	1	-	-	-
20/350	1	-	-	-	-
20/400	1	-	1	2	-
Mean (SD) logMAR VA	0.56 (0.38)	0.44 (0.33)	0.41 (0.34)	0.37 (0.33)	0.35 (0.37)

SD: Standard deviation, VA: Visual acuity

has demonstrated a greater binding affinity to VEGF-A (10). Second, ranibizumab only binds free VEGF-A inhibiting only VEGFR2, whereas aflibercept binds VEGF-A, VEGF-B, and placental growth factor, inhibiting VEGFR1 and VGEFR2 (19). Nevertheless, some cases, refractory anti-VEGF agents elevated aqueous levels of interleukin-6, interleukin-8, interferon-induced protein-10, monocyte chemotactic protein-1, transforming growth factor β, hepatocyte growth factor, serum amyloid A, and VEGF were found in patients with DME (21).

Study Limitations

Our study is limited by its retrospective design, the relatively small sample size, and the absence of a control group. The possible visual benefits of aflibercept may be negatively affected in patients with persistent DME due to the small number of patients. Additionally, patients with diabetes' metabolic control of may also affect macula thickness. Future studies may evaluate the effect the effects of metabolic control.

CONCLUSION

In conclusion, the management of DME cases that exhibit a suboptimal response to anti-VEGF therapy remains a clinical challenge. Our study provides further evidence of the advantages of switching to aflibercept in patients with refractory DME who have been previously treated with ranibizumab. At least 2 aflibercept injections after the switch resulted in anatomical improvements; however, a similar advantage was not observed for visual gain. The number of aflibercept injections in eyes with refractory DME after the switch is unimportant. Finally, our results emphasize the importance of the pre-switch BCVA.

Ethics

Ethics Committee Approval: The protocol of this study was approved by the Institutional Review Board of the Eye Clinic of the Ankara Training and Research Hospital Ethic Committee (approval number: 308, approval date: 06.12.2017).

Informed Consent: All the research was carried out in accordance with the Helsinki Declaration and by obtained written informed consent from the patients.

Peer-review: Externally and internally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: N.Ü., G.Ü.Ö., D.H., M.A.A., F.Ö., Concept: N.Ü., Design: N.Ü., Data Collection or Processing: G.Ü.Ö., D.H., M.A.A., Analysis or Interpretation: F.Ö., Literature Search: G.A.A., Writing: G.A.A.

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