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ORIGINAL RESEARCH

Vision, Retinal Thickness, and Foveal Avascular Zone Size After Intravitreal Bevacizumab for Diabetic Macular Edema

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ABSTRACT

Introduction: To investigate three monthly intravitreal bevacizumab (IVB) injections effects in chronic diabetic macular edema (DME).

Methods: A prospective, noncomparative study in which inclusion criteria were; DME with central macular thickness (CMT) of at least 250 µm, and no treatment for diabetic retinopathy (DR) within 4 months before the first injection. All eyes received three monthly 1.25 mg IVB injections. CMT by optical coherence tomography, visual acuity (VA), foveal avascular zone (FAZ) greatest linear dimension (GLD), and area of FAZ by fundus fluorescein angiography were documented initially and 1 month after last injection. Outcomes ($P < 0.05$ were significant) and correlations (r values) were analyzed.

Results: A total of 29 eyes of 29 patients (group 1, 19 female, 10 male), aged 60.7 ± 6.6 years were analyzed. The patients were split into two groups; group 2 included 15 mild-to-moderate nonproliferative DR, and group 3 included 14 more-severe DR. VA gain was significant in all groups ($P < 0.05$). Mean CMT decrease was approximately 46, 36, and 55 µm in groups 1, 2, and 3, respectively ($P < 0.05$ only in group 1). A 0.045-mm^2 increase in FAZ area was obtained in group 1 ($P < 0.05$). In group 2, an increase in GLD and area of FAZ was 0.048 mm and 0.058 mm^2, respectively ($P < 0.05$), whereas in group 3, FAZ enlargement was nonsignificant. VA and CMT were significantly correlated (r values = 0.5–0.6), except for the final VA-final CMT in group 2. FAZ dimensions and other parameters (VA and CMT) were noncorrelated.

Conclusion: According to the authors' short-term results, three monthly IVB injections can be used for chronic DME regardless of VA, CMT, or FAZ dimensions, despite the FAZ enlargement encountered, especially in cases with milder DR.

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Keywords: Bevacizumab; Central macular thickness; Diabetic macular edema; Diabetic retinopathy; Foveal avascular zone; Intravitreal injection; Visual acuity

INTRODUCTION

According to the World Health Organization, diabetic retinopathy (DR) and age-related macular degeneration (ARMD) are two of the most common etiologies of visual impairment worldwide [1]. ARMD is a degenerative disease, whereas DR is a local complication of a metabolic disease. However, the role of vascular endothelial growth factor (VEGF) in the pathogenesis of ARMD and DR has been described, and VEGF inhibitors, including bevacizumab, have been used with success in both pathologies [2, 3].

Bevacizumab is a full-length, humanized, monoclonal antibody that binds to all isoforms of VEGF. Use of this antibody has been approved by the US Food and Drug Administration for the treatment of colorectal cancer [4]. Off-label use of intravitreal bevacizumab (IVB) for ARMD [2], DR [3], severe retinopathy of prematurity [5], and many other retinal vascular disorders [6] have been considered safe. However, it is well known that VEGF has many physiological activities in normal retina, and nonselective inhibition of VEGF may disturb the normal retinal circulation [7]. Especially in cases where retinal ischemia is the main characteristic of the disease (such as in DR), IVB injection may aggravate pre-existing retinal ischemia.

Retinal ischemia and increased vascular permeability are the main features of DR, and diabetic maculopathy is the most common cause of visual impairment in the diabetic population [8]. Macular grid laser treatment has been the major treatment modality in diabetic macular edema (DME) for three decades [9]. However, a significant proportion of diabetics still lose their vision despite adequate laser photocoagulation [10]. Alternative treatments, including intravitreal steroids and VEGF injections, have been studied extensively and continue to be investigated.

Although there have been many reports on the efficacy of IVB injections for diabetic maculopathy [11–13], the possible adverse effects of the drug on retinal circulation have not been studied extensively. It remains unclear whether it is necessary to follow a strict treatment regimen, with respect to how often the IVB injections should be repeated (or not). To the best of the authors' knowledge, there is no published data describing any drug-related toxic effects to any retinal structure with IVB injections, but enlargement of the foveal avascular zone (FAZ) after IVB injections has been reported [14–16]. Since bevacizumab is a nonselective VEGF inhibitor [17], it was not surprising to receive some reports of adverse effects in diabetic patients due to deterioration of the normal retinal and choroidal circulation.

The aim of the present study was to investigate the effects of IVB injections on retinal thickness, visual acuity (VA), and FAZ in cases with DME following a strict treatment regimen that lasted 3 months.

METHODS

The current study was a prospective and noncomparative study that was conducted in the authors' department between September 1, 2009 and August 31, 2010. The study had been approved by the Institutional Review Boards and all the procedures pertaining to the study had been conducted in accordance with the Declaration of Helsinki and local laws and regulations. Informed consent was procured from the patients prior to inclusion in the study. All examinations and injections were performed

under the supervision of an experienced retina specialist (N.E.). All cases were determined to have chronic diffuse DME based on stereoscopic biomicroscopy examination of the retina using a 78-diopter lens, fundus fluorescein angiography (FFA; IMAGEnet 2000®, Topcon Corporation, Tokyo, Japan), and optical coherence tomography (OCT). Diffuse chronic DME was defined as diffuse thickening of the retina up to the vascular arcades, lasting at least 12 months, and/or resistant to previous therapies. Cases were included in the study if they met all of the following criteria: 1) individuals with adult-onset diabetes mellitus, who have been under the care of an endocrinologist for at least 3 months; 2) central macular thickness (CMT) of at least 250 μm, as measured by spectral OCT (OCT/scanning laser ophthalmoscope [SLO]® 2006; OTI Inc., Toronto, Canada); 3) best-corrected VA below 90 letters using the Early Treatment Diabetic Retinopathy Study (ETDRS) standard charts at a distance of 4 m, or 1 m in cases with VA below five letters at 4 m; 4) no previous vitreoretinal surgeries; 5) no cataract surgery within 6 months prior to the first injection; 6) no treatment for DR within 4 months prior to the first injection; 7) no ocular diseases, including any lens opacities that interfere with visualization of the retina; 8) no extensive hemorrhage or hard exudates that interfere with measuring the dimensions of the FAZ; 9) no vitreoretinal traction revealed by OCT.

Cases were analyzed as three groups. Group 1 included all cases. The whole group was allocated into two groups: group 2 included mild-to-moderate nonproliferative diabetic retinopathy (NPDR), and group 3 included severe NPDR or proliferative DR. Under topical anesthesia by proparacaine hydrochloride ophthalmic solution (Alcaine®, Ophthetica®; Alcon, TX, USA), a standard intravitreal injection protocol with 5% topical povidone-iodine was employed. According to this protocol, 1.25 mg (0.05 mL) bevacizumab (Avastin®, Genentech, San Francisco, CA, USA) was injected intravitreally using a 27-gauge needle placed 3.5 mm behind the limbus. Perfusion of the optic nerve heads was then confirmed by indirect ophthalmoscopy. After treatment, 0.5% moxifloxacin drops (Vigamox®; Alcon, TX, USA) (four drops a day for 1 week) were prescribed. The injections were applied monthly and all patients received a total of three IVB injections.

Ophthalmic examinations were performed 1 day before injection, 1 week after the injection, and then monthly. The final examination was performed a month after the third injection. At each visit, all cases underwent a complete ophthalmic examination, including the assessment of VA, intraocular pressure, and fundus biomicroscopy.

ETRDS charts were used to assess the VA. If fewer than four letters were read correctly at 4 m, the VA was equal to the total number of letters read correctly at 4 m plus the total number of letters read correctly at 1 meter. If four or more letters were read correctly, the VA was equal to the total number of letters read correctly at 4 m plus 30.

FFA and OCT were performed for all eyes at baseline and final examinations. The greatest linear dimension (GLD) and area of the FAZ were measured by the FFA using IMAGEnet R-2.55 measuring software. Both parameters were assessed during the early phase of the angiograms by using 100% magnification. The initial and final sizes were recorded.

Macular scanning using spectral OCT was performed in all eyes. The pupils were dilated with drops containing 0.5% tropicamide and 2.5% phenylephrine. CMT was recorded at baseline and final visits. CMT was defined as the thickness in the central 1 mm ring, as generated by the OCT machine.

Statistical Analysis

Statistical analysis was performed using SPSS 15.0 (SPSS Inc., Chicago, IL, USA). All measurements were evaluated by the Shapiro-Wilk test for normality before use of the paired-samples *t*-test, independent samples *t*-test, chi-square test, or nonparametric tests. The VA, CMT, FAZ GLD, and FAZ area recorded before treatment was compared with the values obtained at the final visit. Pearson's correlation coefficients (*r*) were used to investigate the relationship between the VA, CMT, and FAZ measurements. Significance was attributed when $P < 0.05$.

RESULTS

A total of 15 right eyes and 14 left eyes from 29 cases with chronic diffuse DME were enrolled in the study. The DME had been present for an average of 35.5 ± 14.5 (12–60) months in group 2 and for an average of 36.3 ± 12.6 (12–55) months in group 3, as recorded in patient charts ($P = 0.87$). Group 1 ($n = 29$; 19 females; age, 60.7 ± 6.6 years) included all eyes, group 2 ($n = 15$) was composed of eyes with mild-to-moderate NPDR, and group 3 ($n = 14$) was composed of eyes with severe NPDR or proliferative DR. All eyes had received three monthly IVB injections without considering the stage of DR, the extent of DME, or FAZ sizes. No injection-related local or systemic adverse effects occurred. The mean pre- and post-injection intraocular pressures were 16.8 versus 16.0 mmHg. The systemic conditions in group 2 and group 3 within 3 months prior to IVB injection are shown in Table 1. The sex, mean age of the cases, and the treatments applied before IVB injections are shown in Table 2.

No treatment for DR was applied within 4 months prior to the first injection. Eighteen out of 29 cases had received laser therapy 14.3 ± 8.5 (4–36) months before the initial injection. The mean pre-injection CMT in these 18 cases was 477.6 ± 161.7 (303–943) μm, while it was 353.7 ± 74.9 (258–512) μm in the remaining cases ($P = 0.03$). The mean post-injection CMT in these 18 cases was 416.4 ± 157.2 (230–840) μm, while it was 341.8 ± 85.9 (247–548) μm in the remaining cases ($P = 0.16$).

The mean VA, CMT, FAZ GLD, FAZ area, and their statistical comparison are shown in Tables 3, 4, and 5 for groups 1, 2, and 3, respectively. The mean gain of VA in ETDRS letters was approximately eight, seven, and nine in groups 1, 2, and 3, respectively. The improvements in VA were all statistically significant. The mean CMT decrease recorded

Table 1 The systemic conditions in group 2 and group 3 prior to intravitreal bevacizumab injection. These values were compared by independent samples *t*-test and chi-square test. The minimum and maximum values are given in parenthesis

	Group 2	Group 3	*P* value
Number of cases with systemic hypertension under treatment	10/15	7/14	0.59
Total cholesterol (mg/dL)	217.6 ± 57.0	178.3 ± 42.3	0.05*
LDL cholesterol (mg/dL)	146.0 ± 47.4	104.2 ± 35.5	0.01*
Fasting blood glucose levels (mg/dL)	200.1 ± 89.3	171.78 ± 57.8	0.32
Hemoglobin A1c levels (%)	8.1 ± 1.7	7.9 ± 2.0	0.78
Number of cases underantiaggregant therapy	4/15	5/14	0.70

* $P < 0.05$ was significant

A1c glycosylated hemoglobin, *LDL* low density lipoprotein

Table 2 The sex, mean age of the study group, and previous treatments applied in the eyes

	Group 1	Group 2	Group 3
Sex (female/male)	19/10	10/5	9/5
Mean age (minimum–maximum)	60.7 ± 6.6 (49–72)	57.0 ± 5.5 (51–70)	62.0 ± 11.0 (49–72)
Previous treatment	18	6	12
Previous FRP	6	6	-
Previous PRP	3	-	3
Previous FRP and PRP	3	-	3
Previous PRP and IVT injection	3	-	3
Previous FRP and IVB injection	3	-	3

FRP focal retinal photocoagulation, *IVB* intravitreal bevacizumab, *IVT* intravitreal triamcinolone, *PRP* panretinal photocoagulation

Table 3 The mean VA, CMT, FAZ GLD, and FAZ a of 29 eyes, including both mild-to-moderate nonproliferative cases and severe proliferative diabetic retinopathies, before injection and following three IVB injections. These values were compared by paired-samples *t*-test. The minimum and maximum values are given in parenthesis

	Pre-injection	Post-injection	*P* value
VA (ETDRS l)	53.7 ± 15.4 (20–77)	62.1 ± 12.5 (34–85)	< 0.001*
CMT (μm)	446.172 ± 156.639 (280–943)	400.517 ± 141.103 (230–840)	0.042*
FAZ GLD (mm)	0.835 ± 0.355 (0.41–1.79)	0.855 ± 0.351 (0.36–1.67)	0.172
FAZ a (mm^2)	0.346 ± 0.201 (0.092–0.950)	0.391 ± 0.253 (0.095–1.194)	0.012*

* $P < 0.05$ was significant

CMT central macular thickness, *ETDRS l* Early Treatment Diabetic Retinopathy Study letters, *FAZ a* foveal avascular zone area, *FAZ GLD* foveal avascular zone greatest linear dimension, *IVB* intravitreal bevacizumab, *VA* visual acuity

Table 4 The mean VA, CMT, FAZ GLD, and FAZ a of 15 eyes, including mild-to-moderate nonproliferative cases, before injection and following three IVB injections. These values were compared by paired-samples *t*-test. The minimum and maximum values are given in parenthesis

	Pre-injection	Post-injection	*P* value
VA (ETDRS l)	59.60 ± 12.17 (37–77)	66.87 ± 8.90 (50–85)	0.003*
CMT (μm)	402.80 ± 110.22 (258–602)	366.13 ± 95.48 (230–548)	0.209
FAZ GLD (mm)	0.784 ± 0.274 (0.410–1.350)	0.832 ± 0.288 (0.489–1.470)	0.012*
FAZ a (mm^2)	0.327 ± 0.174 (0.092–0.645)	0.385 ± 0.226 (0.115–0.836)	0.035*

* $P < 0.05$ was significant

CMT central macular thickness, *ETDRS l* Early Treatment Diabetic Retinopathy Study letters, *FAZ a* foveal avascular zone area, *FAZ GLD* foveal avascular zone greatest linear dimension, *IVB* intravitreal bevacizumab, *VA* visual acuity

was approximately 46, 36, and 55 μm in groups 1, 2, and 3, respectively. However, the differences in CMT failed to reach a statistically significant level except in group 1, where the *P* value was 0.042. In group 1, a 0.020-mm increase in FAZ GLD and 0.045-mm^2 increase in FAZ area were observed. The increase in area was statistically significant ($P = 0.012$). In group 2, the increase in FAZ GLD and area was 0.048 mm and 0.058 mm^2, respectively, whereas in group 3,

Table 5 The median or mean VA, CMT, FAZ GLD, and FAZ a of 14 eyes, including those patients with severe nonproliferative diabetic retinopathies and proliferative diabetic retinopathies before injection and following three IVB injections

	Pre-injection	Post-injection	*P* value
VA (ETDRS l)[a]	Median (25th–75th PCL)	Median (25th–75th PCL)	< 0.001*
	51.5 (31.0–60.0)	57.5 (45.0–67.0)	
CMT (μm)[a]	Median (25th–75th PCL)	Median (25th–75th PCL)	0.104
	444.0 (361.0–528.0)	380.5 (308.0–523.0)	
FAZ GLD (mm)[b]	Mean (minimum–maximum)	Mean (minimum–maximum)	0.710
	0.889 ± 0.429 (0.410–1.350)	0.880 ± 0.418 (0.489–1.470)	
FAZ a (mm^2)[a]	Median (25th–75th PCL)	Median (25th–75th PCL)	0.241
	0.347 (0.160–0.455)	0.384 (0.169–0.536)	

* $P < 0.05$ was significant

[a] Values were compared using the Wilcoxon signed-rank test

[b] Values were compared using the paired-samples *t*-test

CMT central macular thickness, *ETDRS l* Early Treatment Diabetic Retinopathy Study letters, *FAZ a* foveal avascular zone area, *FAZ GLD* foveal avascular zone greatest linear dimension, *IVB* intravitreal bevacizumab, *PCL* percentile, *VA* visual acuity

the increase in FAZ GLD and area was 0.01 mm and 0.031 mm^2, respectively (Fig. 1a, 1b). The changes observed in FAZ GLD and area were both statistically significant in group 2, whereas they were nonsignificant in group 3.

The comparison of groups 2 and 3 is in Table 6. The baseline CMT was 90 μm greater in group 3, whereas the final CMT was 71 μm greater in group 3. The pre-injection FAZ area was 0.04 mm^2 greater in group 3, whereas the post-injection FAZ area was 0.013 mm^2 greater in group 3. However, statistical comparison between groups 2 and 3 showed no statistically significant difference for any of the parameters except the VA.

The correlations between the parameters evaluated are represented in Table 7. None of the *r* values were statistically significant, except the *r* values between initial VA–initial CMT and initial FAZ GLD–FAZ areas in all groups, and final VA–final CMT in groups 1 and 3.

The main outcome measures of the treatment were the improvement of VA of at least three ETDRS letters and/or a decrease in CMT of at least 10 μm. According to the VA changes, three cases in group 2 and three cases in group 3 were

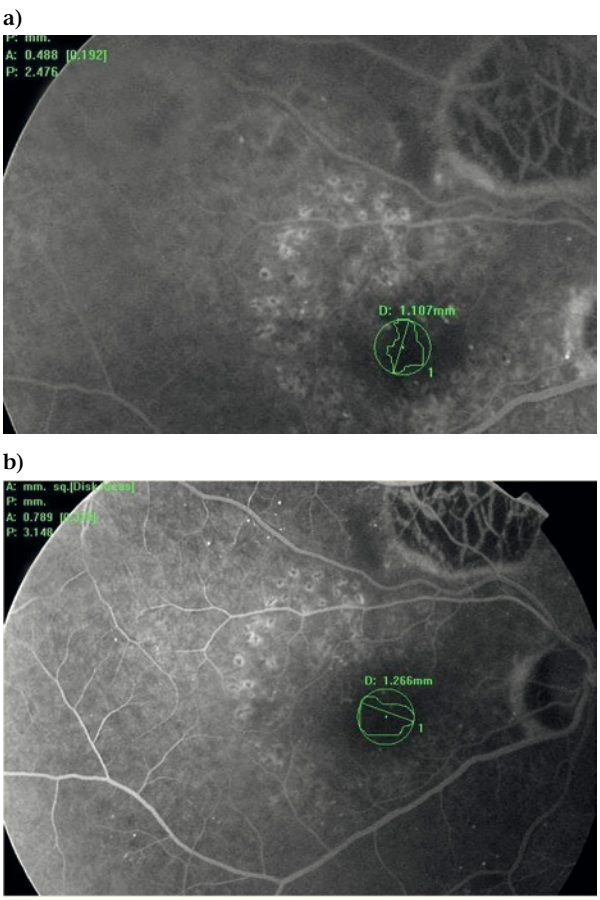

Fig. 1 Greatest linear dimension and area of the foveal avascular zone in one of the studied cases with nonproliferative diabetic retinopathy: (**a**) pre-injection; (**b**) after three monthly intravitreal bevacizumab injections

Table 6 The comparison of VA, CMT, FAZ GLD, and FAZ a at initial and final visits between group 2 (mild-to-moderate NPDR group) and group 3 (severe NPDR and proliferative diabetic retinopathy group). If the independent samples *t*-test was used, the minimum and maximum values in parenthesis are given along with the means

	Group 2	Group 3	*P* value
Pre-injection VA (ETDRS l)[a]	59.6 ± 12.17	47.5 ± 16.51	0.032*
Post-injection VA (ETDRS l)[a]	66.860 ± 8.903	56.929 ± 13.997	0.030*
Pre-injection CMT (μm)[a]	402.800 ± 110.221	492.643 ± 187.794	0.125
Post-injection CMT (μm)[a]	366.133 ± 95.484	437.357 ± 173.893	0.179
Pre-injection FAZ GLD (mm)[b]	Median (25th–75th PCL)	Median (25th–75th PCL)	0.810
	0.749 (0.592–0.896)	0.770 (0.553–1.379)	
Post-injection FAZ GLD (mm)[b]	Median (25th–75th PCL)	Median (25th–75th PCL)	1.000
	0.783 (0.607–0.895)	0.780 (0.554–1.266)	
Pre-injection FAZ a (mm^2)[a]	0.327 ± 0.174	0.367 ± 0.231	0.600
Post-injection FAZ a (mm^2)[a]	0.385 ± 0.226	0.398 ± 0.288	0.893

* $P < 0.05$ was significant

[a] The comparisons were performed by independent samples *t*-test

[b] The comparisons were performed by Mann-Whitney U test

CMT central macular thickness, *ETDRS l* Early Treatment Diabetic Retinopathy Study letters, *FAZ a* foveal avascular zone area, *FAZ GLD* foveal avascular zone greatest linear dimension, *NPDR* nonproliferative diabetic retinopathy, *PCL* percentile, *VA* visual acuity

considered as nonresponders whereas, according to the decrease in CMT, four nonresponders in group 2 were identified, and two in group 3. Only one of the nonresponders was an overlapping case: considered as a nonresponder according to both VA and CMT changes. FAZ area was enlarged in three of the patients classified as nonresponders according to the VA changes (0.210 vs. 0.260, 0.187 vs. 0.197, 0.950 vs. 1.194 μm).

DISCUSSION

IVB injection alone or in combination with macular photocoagulation is one of the alternative therapies for chronic diffuse DME [18]. Even in cases of DME unresponsive to conventional therapies, successful outcomes with IVB injections have been reported [11–13]. However, many unknowns continue to exist

Table 7 Pearson correlation coefficients (*r*) between the values obtained in group 1, group 2, and group 3

	r in group 1	*r* in group 2	*r* in group 3
1st VA–1st CMT (μm)	−0.611[a]	−0.527[a]	−0.586[a]
1st VA–1st FAZ a (mm^2)	−0.111	0.019	−0.135
1st CMT (μm)–1st FAZ a (mm^2)	0.065	−0.233	0.166
2nd VA–2nd CMT (μm)	−0.500[a]	0.028	−0.628[a]
2nd VA–2nd FAZ a (mm^2)	−0.270	−0.338	−0.256
2nd CMT (μm)–2nd FAZ a (mm^2)	−0.068	−0.053	−0.090
1st FAZ GLD (mm)–FAZ a (mm^2)	0.815[a]	0.981[a]	0.730[a]

[a] *r* values were considered statistically significant if the *P* value was < 0.05

CMT central macular thickness, *FAZ a* foveal avascular zone area, *FAZ GLD* foveal avascular zone greatest linear dimension, *VA* visual acuity, *1st* pre-injection values, *2nd* post-injection values

with respect to IVB injection in the context of DME. There is no standardized treatment regimen and no consensus as to how often the injections should be repeated. In some reports on the management of DME by IVB injection, the drug was administered once and then re-injected in patients responding to the treatment in terms of VA improvement or decreased CMT [11]. A single injection of IVB, which was performed without considering the response obtained, was evaluated in some studies [18], whereas injections were repeated after a single injection if the recurrence of macular edema was identified according to the OCT findings and/or the deterioration of VA [13]. In the current study, the authors applied three monthly IVB injections independently from the extent of macular edema, stage of DR, VA, and previous treatments as long as no treatment for DR was applied within 4 months before the first injection. IVB was applied at a dosage of 1.25 mg in accordance with the previous studies [11]. An approximate 36-μm decrease in CMT was obtained in milder cases, whereas an approximate 55-μm decrease in CMT was obtained in severe cases. However, these changes in CMT failed to reach a statistically significant level due to inadequate sample size. The improvement in VA was statistically significant in both groups. Eighteen out of 29 cases (62%) had received laser therapy 14 months, on average, before the initial injection. The initial and final CMT was 124 and 75 μm greater, respectively, in cases who had received laser therapy. The possible explanation for this difference is that 12 out of 18 cases belonged to group 3, which included cases with severe DR.

Previous reports showed that VA changes were not always parallel to OCT findings [11, 19]. No correlation between changes in CMT and VA was found in a study investigating the effects of bevacizumab in patients with DME [11], whereas another study showed retinal thickness to be the greatest contributing factor to VA [20]. Haritoglou et al. [12] reported a weak correlation between changes in CMT and VA. There are many possible explanations for this inconsistency in the correlation between OCT findings and VA in DME. First of all, the duration and severity of macular edema, previous macular laser treatments, and the presence of macular ischemia and hard exudates affect VA independently from the CMT [18]. Secondly, increased macular perfusion as well as decreased CMT after IVB injections may be a contributing factor to the improvement in VA [21]. In the current study, the authors found a moderate negative correlation between initial VA and initial CMT in all groups: r was approximately –0.6, –0.5, and –0.6 for groups 1, 2, and 3, respectively. A moderate negative correlation persisted between the final VA and final CMT after three doses of IVB injections in groups 1 and 3, whereas no correlation was shown in the mild-to-moderate NPDR group.

Notably, the FAZ is a capillary-free central region of the fovea. The region may be considered normal in healthy individuals even when it measures over 1.0 mm in diameter or 2 mm^2 in surface area [22]. In other words, the inter-individual variability in FAZ size is substantial [23]. This may be simply due to anatomical variations or due to subjective measurement techniques. Enlargement of the FAZ may be an important contributing factor to visual loss in diabetics unexplained by the extent of macular edema and/or hard exudates. It is well known that this region enlarges in DR [24, 25], and FAZ size is positively correlated with the stage of DR [26]. However, objective assessment of the amount of visual loss due to FAZ enlargement has not been studied yet. In the current study, the FAZ area was 0.04 mm^2 larger in the severe DR cases compared to the

milder cases. This finding was consistent with the literature, but was not statistically significant.

In addition to the DR itself, the treatment modalities, including laser photocoagulation and intravitreal VEGF inhibitor injections, may affect FAZ size, since all of these treatment procedures are nonselective for normal retinal and choroidal vasculature [27]. There are inconsistencies in the effects of IVB on FAZ. There are several case reports describing decreased VA associated with enlarged FAZ after IVB injection [14–16]. In a study by Chung et al. [17], it was reported that macular ischemia may have a negative effect on short-term outcomes after IVB therapy in DME. In contrast, Kook et al. [11] showed that macular ischemia was not exacerbated after IVB injection. In the current study, chronic diffuse DME cases with CMT above 250 μm were included regardless of the initial FAZ size. The authors obtained both FAZ GLD and area from the FFA. The FAZ GLD and area were strongly correlated. Therefore, both parameters could be used for clinical interpretation or calculating correlations among the other parameters. The authors preferred to use the area, because the contours of the zone were mostly irregular and the measurement of areas could be more informative regarding macular ischemia.

The mean FAZ area was found to be increased in all groups after three IVB injections. The enlargement was statistically significant if all cases were assessed as one and also in group 2, which comprised mild-to-moderate NPDR cases. The increase was smallest in the cases with severe DR. The pre-injection FAZ area was 0.04-mm^2 larger in group 3 compared to group 2. The post-injection area was still smaller in mild cases, but the difference decreased to 0.013 mm^2, which suggests that the effect of IVB on FAZ area was higher in mild cases. Although IVB was found to have significant effects on FAZ, especially in mild cases, the area was not correlated with VA or CMT. The statistically significant improvement in VA and considerable decrease in CMT were obtained in the majority of cases, despite FAZ enlargement. The successful outcomes could, therefore, be attributed to the short-term nature of the follow-up. The study was completed after 1 month had elapsed since the final IVB injections. The three-dose injections led to anatomical changes in the fovea, but the clinical consequences leading to visual deteriorations may be observed later. Long-term follow-up may enable the authors to conclude whether the changes in FAZ are progressive or not. Systemic factors, including lipid profile and blood glucose levels, may also affect the FAZ size [28, 29]. Blood glucose levels were similar in groups 2 and 3, but the lipid profile was superior in cases with severe DR. This laboratory finding is not consistent with the larger FAZ documented in severe cases [28]. Eventually, this inconsistency may be due to poorer medication compliance in milder cases.

The enlargement of FAZ area after IVB injections was exhibited more in mild cases. The authors suggested three possible explanations for this effect. Firstly, macular blood flow in mild cases could be more vulnerable to VEGF inhibition effects compared to the macular blood flow in severe cases. Secondly, it is difficult to differentiate between the natural progression of macular disease and the adverse effects of IVB on FAZ. The natural progression of the disease could exacerbate the macular ischemia in addition to the drug itself. These two factors could overlap in some cases or induce separate effects in others. The contribution of the progression of the maculopathy, independently from the impact of bevacizumab on macular blood flow, could possibly be greater in mild and moderate NPDR, because the macular ischemia and FAZ enlargement had already developed to a greater extent in severe cases. Finally, the technique applied for FAZ area measurement

was a subjective procedure requiring manual outlining of that region, so several of the values could be misleading.

CONCLUSION

In conclusion, three monthly IVB injections can be an alternative therapy for chronic diffuse DME irrespective of VA, CMT, or FAZ dimensions, despite enlargement of the FAZ. However, comparative case series, with various numbers of IVB injections applied, and long-term follow-up are required to investigate the long-term outcomes and the consequences of FAZ enlargement encountered after three doses of IVB injections.

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