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Original Article

Short-term Effects of Intravitreal Dexamethasone Implant on Choroidal Structure in Eyes with Refractory Diabetic Macular Edema

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Abstract

Objectives: The objective of the study was to evaluate choroidal structural changes after intravitreal dexamethasone implant (IDI) in eyes with diabetic macular edema (DME) refractory to antivascular endothelial growth factor (VEGF) therapy.

Methods: Twenty-three eyes of 14 patients with DME refractory to anti-VEGF therapy were included in this retrospective study. Detailed ophthalmological examinations were recorded, and optical coherence tomography images were obtained before and 3 months after IDI. Choroidal images were binarized into the luminal area and total choroidal area. Subfoveal choroidal thickness and choroidal vascularity index (CVI) were calculated.

Results: The mean best-corrected visual acuity (BCVA) and central macular thickness (CMT) were improved significantly (from 0.94 to 0.81 LogMAR, p=0.02, and from 464 to 371 μ, p=0.01, respectively) after IDI. There were no significant changes in both SCFT and CVI at the end of the follow-up period (from 446.3 to 428.8 μ, p=0.51 and from 63.1 to 63.7 p=0.35, respectively).

Conclusion: IDI in eyes with DME refractory to anti-VEGF therapy improves BCVA and CMT but has no significant effect on SCFT and CVI in the short term.

Keywords: Choroidal thickness, choroidal vascularity index, diabetic macular edema, intravitreal injection, ozurdex

Introduction

Diabetic macular edema (DME) is a leading cause of vision loss in the working-age population (1). Antivascular endothelial growth factor (VEGF) agents have been used as the first-line therapy for DME (2,3). However, some patients had an inadequate response to anti-VEGF treatment (2,4). DME has a multifactorial and complex pathogenesis, in which a variety of inflammatory mediators such as interleukin (IL)-6, IL-8, matrix metalloproteinase, angiopoietin-2, tumor necrosis factor-alfa, and intercellular adhesion molecule-1 besides VEGF take a role (5,6). Therefore, intravitreal steroids are useful agents as an alternative or adjunctive treatment strategies in case of poor response to anti-VEGF treatment (3). Intravitreal dexamethasone implant (IDI) (Ozurdex; Allergan, Irvine, CA, USA) has been proven as an effective treatment method for DME in the recent multicenter studies (7,8).

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The blood supply of the outer retina is provided by choroidal vasculature and choroidal abnormalities in diabetic patients may cause severe functional damage to the retina and lead decrease in visual acuity (9,10). The newly developed marker of the choroidal vascularity index (CVI), which provides information on the proportion of the luminal area (LA) to the total choroidal area (TCA), has been widely used to assess the vascular status of the choroid in many ocular diseases (11-14). It has been reported that CVI has a good correlation with the severity of diabetic retinopathy (DR) and therefore it may be a sensitive marker of choroidal vascular change in DME (12,13). Although some studies evaluated CVI changes with anti-VEGF or steroid treatments in DME, the effect of IDI on CVI in eyes with DME resistant to anti-VEGF agents has not been adequately discussed (15-18). Thus, in this study, we aimed to investigate the short-term effect of IDI on choroidal structural changes in eyes with refractory DME.

Methods

This retrospective study was conducted with 23 eyes of 14 patients who were treated with IDI due to refractory DME despite at least 3 consecutive monthly intravitreal anti-VEGF therapy at Zonguldak Bülent Ecevit Hospital between September 2021 and June 2022. The study was approved by the Ethics Committee of Zonguldak Bülent Ecevit University and adhered to the tenets of the Declaration of Helsinki. All patients were informed about the potential side effects, and their consent was taken before the procedure.

All participants underwent an ophthalmic evaluation before and 3 months after IDI, including the measurement of best-corrected visual acuity (BCVA) in LogMAR units, slit-lamp biomicroscopy, fundoscopy, fluorescein angiography, and enhanced depth imaging – optical coherence tomography (EDI-OCT) imaging (Spectralis®, Heidelberg Engineering Inc., Heidelberg, Germany). All EDI-OCT images were obtained between 10:00 and 12:00 h to minimize the effect of diurnal variations in the choroidal structures. Evidence of macular ischemia, history of any systemic disease other than diabetes, previous ocular surgery and/or laser photocoagulation, epiretinal membrane, vitreomacular traction or adhesion, glaucoma/ ocular hypertension, and presence of media opacities that could distort image quality were determined as exclusion criteria. The diagnosis of DME was based on the results of OCT and fluorescein angiography. Refractory DME is defined as central macular thickness (CMT) of 300 µm or more with persistent increased intraretinal fluid and no morphological improvement of DME on OCT despite at least 3 consecutive monthly anti-VEGF therapy. CMT was measured manually as the distance from the internal limiting membrane to the retina pigment epithelium. Subfoveal choroidal thickness (SFCT) was measured vertically from the outer surface of the retinal pigment epithelium to the choroidal-scleral interface.

All dexamethasone implants were injected under sterile conditions in an outpatient operating room. The implant was inserted into the vitreous cavity through the pars plana using a single-use applicator. Patients were treated with a topical ophthalmic antibiotic for 5 days after treatment.

Binarization of EDI-OCT images was performed with ImageJ software (Version 1.50a; National Institutes of Health, Bethesda, MD, USA). 3000 µm wide area with the margins of 1500-µm nasal and 1500-µm temporal from the fovea was selected. Borders of the choroidal area were set manually with the ImageJ ROI Manager. The image was adjusted by the Niblack auto-local threshold. TCA, LA, and stromal area (SA) were measured (Fig. 1) (11). CVI was the ratio between LA and TCA.

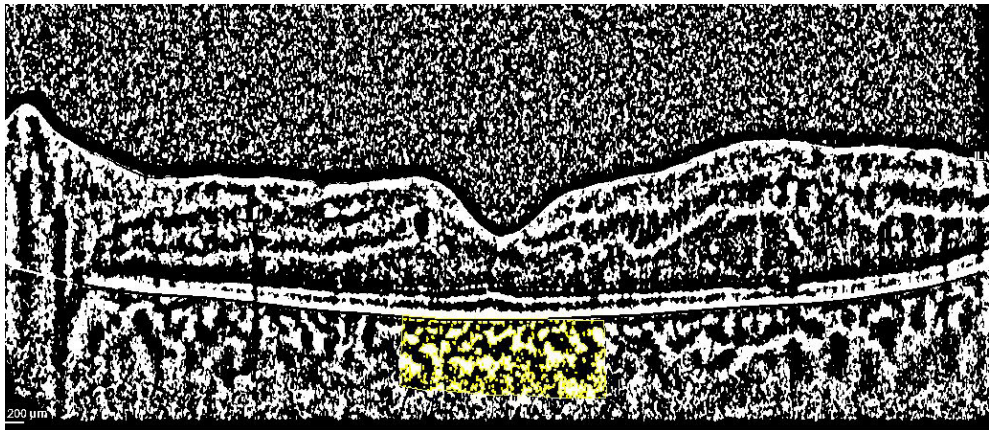

Figure 1. Binarization of EDI-OCT image.

Statistical Analysis

The analysis of the data was done using IBM SPSS 22.0 (SPSS Inc., Chicago, IL, USA) software. Descriptive statistics were defined as mean±standard deviation for variables with normal distribution, median (min-max) for variables with non-normal distribution, and the number of cases (%) for nominal variables. To evaluate the differences in BCVA, CMT, SFCT, CVI, TCA, LA, and SA before and after IDI, paired t-tests were performed. P<0.05 was considered statistically significant. In the power analysis made with the G-power program (version 3.1.9.7), 84.9% power was calculated with a sample size of 23, 0.5 effect size, and a 5% margin of error.

Results

Baseline Characteristics

A total of 23 eyes of 14 patients with refractory DME were enrolled in this study. Of 14 patients, 5 (35.7%) were males and 9 (64.3%) were females, and the mean age was 64.7±7.7 years. The mean number of previous intravitreal anti-VEGF injections was 7.5±3.9 (Table 1).

Visual Acuity

The mean BCVA before and after IDI was 0.94±0.4 and 0.81±0.3 LogMAR, respectively. There was a statistically significant improvement in BCVA after IDI in the short term (p=0.02) (Table 2).

Table 1. Demographics and baseline characteristics of the patients

Eyes/Patients (n)	**23/14**
Mean age (years)	64.78±7.71
Male/Female (n)	5/9
Mean number of anti-VEGF injections	7.56±3.92

CMT

The mean CMT for all eyes decreased significantly from 464.9±168.3 μm at baseline to 371.0±127.0 μm at the final visit after IDI (p=0.01) (Table 2).

Choroidal Thickness

The mean SFCT before and after IDI was 446.3±150.6 and 428.8±122.6, respectively. There was a slight decrease in SFCT after IDI, but it was not statistically significant (p=0.51) (Table 2).

CVI

The mean CVI of eyes with refractory DME was 63.3±2.3 at baseline and 63.7±2.8 at the final visit. There was no significant change in CVI (p=0.35). There were also no significant differences between initial and final visit means of the TCA (1.15±0.45 vs. 1.10±0.36 mm^2, p=0.25), LA (0.73±0.28 vs. 0.70±0.23 mm^2, p=0.295), and SA (0.42±0.17 vs. 0.40±0.14 mm^2, p=0.21), respectively (Table 2).

Discussion

DME has complex pathogenesis involving VEGF and other inflammatory mediators (6). Steroids have a more potent anti-inflammatory effect than anti-VEGF therapy, so they can reduce the levels of other inflammatory cytokines in addition to VEGF levels (19). Thus, steroids should be considered for anti-VEGF treatment-refractory cases. Among steroids, 0.7 mg IDI (Ozurdex, Allergan; Irvine, CA) has shown efficacy in DME treatment, specifically in improving visual acuity and decreasing retinal thickness in eyes with anti-VEGF-resistant DME (3). In this study, there were significant improvements in CMT and BCVA after switching to IDI and, no systemic or ocular complications, especially cataract progression. However, the short follow-up period and small sample size in this study may also have contributed to the results.

Diabetes is a metabolic disorder mainly affecting the systemic vasculature. Although the primary changes in diabetic

Table 2. Comparison of visual acuity and EDI-OCT parameters during the follow-up period

	Before dex implant	**At 3 month**	**P**
BCVA (LogMAR)	0.94±0.4	0.81±0.3	0.02
CMT (μ)	464.9±168.3	371±127	0.01
SFCT (μ)	446.3±150.6	428.8±122.6	0.052
CVI (%)	63.3±2.3	63.7±2.8	0.35
TCA (mm^2)	1.15±0.45	1.10±0.36	0.25
LA (mm^2)	0.73±0.28	0.70±0.23	0.29
SA (mm^2)	0.42±0.17	0.40±0.14	0.21

BCVA: Best-corrected visual acuity; CMT: Central macular thickness; SFCT: Subfoveal choroidal thickness; CVI: Choroidal vascular index; TCA: Total choroidal area; LA: Luminal area; SA: Stromal area.

eyes occur in the retinal vasculature, histopathologic studies in diabetic cases showed vascular changes in the choroid such as vascular dropout, areas of vascular non-perfusion, and choroidal neovascularization (10). Postmortem studies also reported that diabetic patients had more focal choriocapillaris degeneration areas than non-diabetic patients (20). Those structural changes in choroid vessels may affect choroidal blood flow. Laser Doppler flowmetry and OCT angiography measurements revealed that patients with DME had significantly decreased choriocapillaris blood flow in the foveal region (21,22). However, the exact role of choroidal abnormalities in the pathology of DME and its impact on the response to treatment modalities remain unclear.

In the recent years, SFCT has been commonly used to evaluate the choroid in DR or DME. However, the results of SFCT in DR or DME in different studies are controversial, since it is an unstable factor affected by various systemic and ocular factors, such as age, axial length, IOP, or systolic blood pressure (23). Kim et al. reported that SFCT was increased in eyes with DME than in those without (13). In contrast, Gerendas et al. revealed that SFCT was significantly decreased in eyes with DME and in non-edematous fellow eyes (24). Similarly, Esmaeelpour et al. reported a decrease in SFCT in eyes with DME (25). In this study, there was also no significant change in SCFT although there were significant changes in VA and CMT. We thought that previously received anti-VEGF therapy may have affected choroidal layers.

Unlike SFCT, CVI discriminates between the luminal and stromal areas, providing more detailed information about changes in the choroidal vessels and showing less variability under the abovementioned physiological factors. Changes in the CVI in DR have been reported in the several recent studies. Gupta et al. reported that the CVI was significantly decreased in eyes with DME and DR compared to controls (12). A decrease in the CVI was observed in patients with diabetes even in the absence of DR, and a further decrease occurred along with the severity of DR (13). Okamoto et al. showed that even a single injection of ranibizumab decreased CVI in DME patients (26). Recently, Liu et al. revealed that CVI and SCFT decrease by sub-Tenon triamcinolone treatment in eyes with DME refractory anti-VEGF therapy (17). Kocamiş et al. also reported a decrease in CVI after IDI in eyes with DME (18). They both attributed that to the decreased vasodilatation in choroidal vessels. On the other hand, Rishi et al. claimed that IDI has no short-term influence on SCFT and CVI in eyes with DME (15). The absence of CVI and SCFT changes after IDI in our study may reflect that IDI has a greater effect on retinal layers than choroidal structures in eyes with resistant DME which previously received anti-VEGF therapy.

Our study had several limitations including its retrospective design, relatively a small number of patients and short duration of follow-up. Therefore, a prospective multicenter clinical study larger sample size and longer follow-up period may be warranted in future to reveal the longitudinal effect of intravitreal dexamethasone on choroidal vasculature.

Conclusion

Switching to IDI may improve BCVA and CMT in DME eyes refractory to anti-VEGF injections. However, it has no significant influence on SFCT or CVI in the short term. This result may indicate that, in previously anti-VEGF therapy received eyes, IDI affects the retinal layers more potently than the choroid.

Disclosures

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Ethics Committee Approval: Ethical approval granted by the Ethics Committee of Zonguldak Bülent Ecevit University (2022/13-05).

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Conflict of Interest: None declared.

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