Intravitreal Bevacizumab for Diabetic Macular Edema Previously Treated With Focal Laser Photocoagulation

Fokal Lazer Fotokoagülasyon ile Tedavi Edilmiş Diyabetik Makula Ödeminde İntravitreal Bevacizumab

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ABSTRACT

Objective: Our study aimed to analyze the efficacy of intravitreal bevacizumab (IVB) therapy on visual acuity and macular thickness in patients previously treated by focal laser photocoagulation (FLP) and who did not respond or only partially responded to this treatment.

Materials and Methods: Medical records comprising 40 eyes of 32 patients treated with IVB who previously underwent FLP due to diabetic macular edema (DME) but diagnosed as clinically significant macular edema (CSME), or those with ≥250 µm central macular thickness (CMT) were analyzed retrospectively. Outcome measures were the change in mean best corrected visual acuity (BCVA) and CMT during the one year follow-up period.

Results: Mean CMT were 403.64 ± 118.34 µm and 319.39 ± 99.57 µm before and after treatment, respectively. CMT was significantly reduced at the last follow-up visit (p = 0.0001) compared to the baseline. Pre-treatment and post-treatment Log MAR values were 0.45 (range 0.20-0.95) and 0.50 (range 0.30-1.00) before and after treatment. The difference was not significant (p> 0.05).

Conclusion: This study suggests that if the treatment is initiated as prompt FLP and is followed by IVB therapy, good anatomic results may be obtained however; functional benefit may not be observed. Anti-vascular endothelial growth factor (VEGF) therapy should be the first treatment in diabetic macular edema or be initiated immediately in patients who had FLP treatment before in order to have at least better anatomic results.

Key words: Bevacizumab; diabetic retinopathy; macular edema; laser photocoagulation; optical coherence tomography.

ÖZ

Amaç: Çalışmamızda, daha önce fokal lazer fotokoagülasyon (FLF) ile tedavi edilen, ancak bu tedaviye yanıt vermeyen veya kısmen yanıt veren hastalarda görme keskinliği ve makula kalınlığına intravitreal bevacizumab (IVB) tedavisinin etkinliğini analiz etmek amaçlanmıştır.

Gereç ve Yöntemler: Diyabetik maküla ödemi (DMÖ) tanısıyla daha önce FLF tedavisi uygulanan, klinik olarak anlamlı makula ödemi (KAMÖ) tanısı alan, ya da ≥250 um santral makula kalınlığı (SMK) bulunan ve sonrasında IVB ile tedavi edilmiş 32 hastanın 40 gözünün medikal kayıtları geriye dönük olarak incelendi. Bir yıllık takip süresince ortalama en iyi düzeltilmiş görme keskinliği (EİDGK) ve SMK'daki değişim değerlendirildi.

Bulgular: Tedavi öncesi ve sonrası SMK sırasıyla 403,64 ± 118,34 µm ve 319,39 ± 99,57 µm olarak ölçüldü. SMK başlangıçla kıyaslandığında son kontrolde anlamlı olarak azalmıştı (p = 0.0001). Tedavi öncesi ve sonrası Log MAR değerleri sırasıyla 0.45 (aralık 0,20-0,95) ve 0.50 (aralık 0,30-1,00) idi. Bu değerler arasındaki fark anlamlı değildi (p> 0.05).

Sonuç: Bu çalışma, eğer tedavi FLP ile başlatılır ve bunu IVB ile takip eder ise, fonsiyonel fayda gözlenemese bile iyi anatomik sonuçlar elde edilebileceğini düşündürmektedir. Anti-vasküler endotelyal büyüme faktörü (VEBF) tedavisi, diyabetik maküla ödeminde ilk tedavi olmalı ya da daha önce FLF tedavisi gören hastalarda en azından daha iyi anatomik sonuçlar elde etmek için hemen başlanmalıdır.

Anahtar kelimeler: Bevacizumab, diabetik retinopati, maküler ödem; lazer fotokoagülasyon; optik koherens tomografi.

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INTRODUCTION

Diabetic macular edema (DME) is a leading cause of severe visual loss in patients with diabetic retinopathy.[1] In 1985, the Early Treatment Diabetic Retinopathy Study (ETDRS) established macular laser treatment as the standard method of care by demonstrating that patients with clinically significant DME treated by laser experienced 50% reduction in moderate vision loss over time, compared with untreated patients.[2] However, the insufficient effect of laser photocoagulation in the remaining significant proportion of patients with DME, and the fact that laser treatment does not prevent vision loss but only slows the progression, has led researchers to explore different treatment methods.[3-6] There are several studies demonstrating that treatment with anti-VEGF agents provided greater improvement in visual acuity, whether used as monotherapy or in combination with laser photocoagulation, when compared to laser photocoagulation alone.[7-10] There are also studies reporting that primary intravitreal bevacizumab (IVB) for diabetic macular edema provided improvement or stability in visual acuity, optical coherence tomography (OCT) and fundus fluorescein angiography (FFA) findings. [11-15]

In this study we aimed to analyze the efficacy of intravitreal bevacizumab (IVB) therapy on visual acuity and macular thickness in those patients previously treated by FLP and who either did not respond or only partially responded to this treatment.

MATERIALS AND METHODS

The cases treated with IVB for DME who were previously underwent focal laser photocoagulation (FLP) between April 2009 and June 2011 but diagnosed as clinically significant macular edema (CSME) or those with ≥250μ central macular thickness (CMT) were evaluated retrospectively. To assess the efficacy of treatment, changes in visual acuity, changes in central macular thickness by time-domain OCT comprised the main parameters of the investigation. Patients with any additional eye disease and other macular diseases that could result in macular edema and those who underwent surgical procedures other than an uncomplicated cataract extraction (performed 3 months from inclusion in this study) were excluded from this study. The complete medical record of each patient was scanned. Informed consent for the study was obtained from all the study participants. The study adhered to the tenets of the Declaration of Helsinki.

Each patient's best corrected visual acuity (BCVA), measured by use of a Snellen chart, was recorded and converted to the logarithm of the minimum angle of resolution (log MAR). Anterior and posterior segment slit lamp biomicroscopy was performed with intraocular pressure measurement. OCT imaging was done with time domain Stratus OCT (Stratus Tomographer, Model 3000, Carl Zeiss Ophthalmic System Inc., Humphrey Division, Dublin, CA, USA). CMT was measured and the morphology of macular edema was evaluated in all cases before and after IVB. The cases were classified into 3 subgroups according to their morphological appearance on OCT as described previously by Otani; diffuse retinal thickening (DRT), cystoid macular edema (CME), and serous retinal detachment (SRD).[16] These images were evaluated by three independent researchers. The morphological pattern, which was agreed on by two researchers, was recorded. There was no case in which two of the three observers did not agree on the morphology.

IVB injection was done in 40 eyes of 32 patients under sterile operating room conditions. Bevacizumab (Avastin, Genentech, Inc.) 1.25mg/0.05ml was injected into the vitreous cavity 3.5 mm to the limbus in pseudophacic and aphacic patients and 4.0 mm to the limbus in phacic patients. The principles of the Helsinki Declaration were taken into consideration. All patients were informed about the treatment procedures and complications, and written consent was obtained from all patients.

The patients underwent three injections (months 0, 1 and 2) and were examined at the first day and first week after the intervention and every month in a 12 months period. The same procedures of ophthalmic evaluation were carried out at each follow-up visit, FFA and/or repeat injections were performed if CMT was thicker than ≥ 250μ or there was a ≥ 100μ increase from the last visit . IVB had been injected at four- to six-week intervals. .

Visual acuity and CMT as measured by OCT before and after IVB were evaluated. Statistical analyses were performed with SPSS 19.0 software. Distribution of data was determined by Shapiro-Wilk test. Continuous variables were expressed as mean±std. deviation or median (minimum-maximum). The Wilcoxon signed rank sum test was used for comparisons of pre and post-treatment visual acuity and CMT. *P* value of less than 0.05 was considered statistically significant for all tests.

RESULTS

There were 40 eyes of 32 patients who met the inclusion criteria. In these eyes FLP was performed one or more times (mean, 3.07±2.11) previously and there was CSME in spite of treatment. Mean age was 58.48 ± 7.34. Fifteen of the patients were female and 17 of them were male. All patients had Type 2 diabetes mellitus. Eighteen patients (50.0%) had systemic hypertension, 6 patients (16.6%) had coronary artery disease, 1 patient (2.7%) had chronic renal failure, 1 patient had (2.7%) hyper-lipidemia. Fifteen (46.9%), 9 (28.1%), 5 (15.6%) and 3 (9.5%) of the patients were followed with the diagnosis of severe, moderate and mild non-proliferative diabetic retinopathy and proliferative diabetic retinopathy, respectively. The median time between the last laser treatment and the first injection of bevacizumab was 3.5 months (range 3-7). Throughout the 12-month follow-up period, the

median number of bevacizumab injections were 5 (range, 4-7).Pre-treatment and post-treatment BCVA were 0.45 logMAR (range 0.20-0.95) and 0.50 logMAR (range 0.30-1.00) before and after treatment, respectively. The difference between visual acuity before and after IVB treatment was not statistically significant (p=0.39, Wilcoxon signed rank sum test) (Table 1).

CMT was 403.64 ± 118.34 µm and 319.39 ± 99.57 µm before and after treatment respectively. CMT was decreased 20.9% at the last follow-up visit compared to the baseline and this improvement was statistically significant ($p < 0.001$, Wilcoxon signed rank sum test). The effect of IVB treatment was evaluated between the 3 subgroups according to their OCT morphology patterns. There was 18.0% decrease in CMT the DRT group, 26.8% decrease in the CME group and 20.8% decrease in the SRD group. The improvement in all groups was statistically significant. There was a 18.0% decrease in mean CMT (Table 2).

The CME and SRD groups had relatively greater improvement among the subgroups in terms of mean CMT. However, there was no statistically significant difference between the subgroups ($p > 0.05$).

DISCUSSION

CSME was defined according to the Early Treatment Diabetic Retinopathy Study classification protocol as the presence of retinal thickening at or within 500µm of the center of the macula or hard exudates at or within 500µm of the center of the macular if associated with thickening of the adjacent retina and/or zones of retinal thickening 1 disc area in size, at least part of which being within 1 disc diameter of the center.[2] Macular edema should be treated as early as

Table 1: *Pre-injection and post-injection measurements of BCVA (logMAR).*

	Pre-injection BCVA	Post-injection BCVA	Change	p-value
Total (mean±SD)	0.64±0.52	0.61±0.46	0.03±0.21	0.39
DRT (mean±SD)	0.64±0.56	0.61±0.47	0.02±0.23	0.65
CME (mean±SD)	0.71±0.53	0.70±0.50	0.01±0.20	0.85
SRD (mean±SD)	0.54±0.44	0.44±0.34	0.10±0.16	0.23

Abbreviations: BCVA, best corrected visual acuity; CME, cystoid macular edema; DRT, diffuse retinal thickening; p, significance; SD, standard deviation; SRD, serous retinal detachment

Table 2: *Pre-injection and post-injection measurements of central foveal thickness.*

	Pre-injection CMT (µm)	Post-injection CMT (µm)	Change	Percent change	p-value
Total (mean±SD)	403.64±118.34	319.39±99.57	84.24±76.6	20.9	< 0.0001
DRT (mean±SD)	367.71±97.66	301.71±93.69	66.00±75.37	17.9	0.001
CME (mean±SD)	550.14±83.83	402.86±101.24	147.29±76.98	26.8	0.002
SRD (mean±SD)	349.40±76.09	279.80±62.85	72.60±27.86	20.8	0.004

Abbreviations: CME, cystoid macular edema; CMT, central macular thickness; DRT, diffuse retinal thickening; p, significance; SD, standard deviation; SRD, serous retinal detachment.

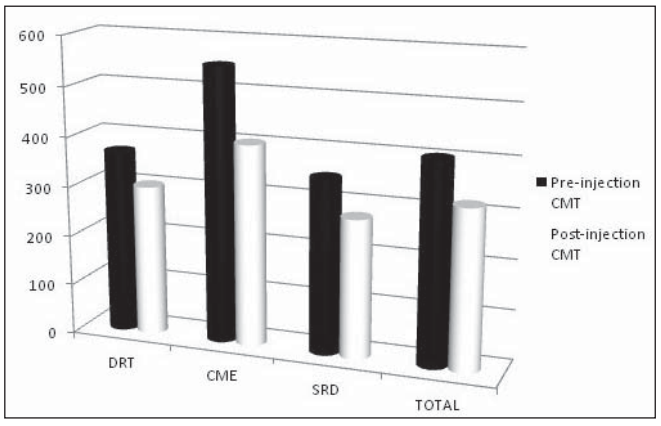

Figure 1: *Change in macular thickness from baseline to six-month study visit.*

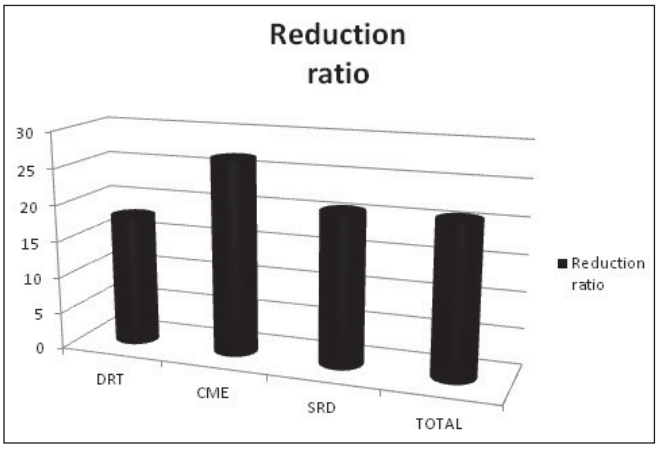

Figure 2: *The reduction ratio of CMT in OCT morphological groups.*

detected, in order to prevent irreversible photoreceptor damage due to structural changes.[17] DME caused by damage to retinal vessels often presents a persistent trend despite focal/grid laser photocoagulation. VEGF blockage is an effective therapeutic approach for the treatment of diabetic macular edema which has been developed in the last decade.[18]

The studies such as RESOLVE, RESTORE, READ-2, Diabetic Retinopathy Clinical Research Network (DRCR.net) reported that intravitreal ranibizumab as monotherapy or laser therapy combined with ranibizumab has resulted in a significant increase in visual acuity compared to laser treatment alone. In the studies mentioned, laser treatment was applied as monotherapy or subsequent to or combined with intravitreal anti-VEGF; so in the study groups which FLP was administered combined with or subsequent to anti-VEGF there is a probability that anti-VEGF injections were administered to patients who might have benefited from FLP treatment as monotherapy.[7-10] Therefore, in some of these patients, visual improvement obtained by intravitreal ranibizumab or ranibizumab combined with laser treatment could be achieved with focal laser therapy alone. In order to reveal the role of focal laser therapy and the contribution of anti-VEGF treatment additional to focal laser in improving visual acuity compared to anti-VEGF treatment, it would be rational to compare the visual acuity outcome in those treatment-naive patients who respond to focal laser therapy with those in whom primary anti-VEGF or combined anti-VEGF and FLP was carried out. If it is proved that the visual outcome is not inferior to the anti-VEGF or combined treatment, then patients may initially receive FLP and the need for anti-VEGF injection in those cases responsive to FLP may be eliminated.

In all the patients included in the study, treatment of macular edema was initiated with FLP. The patients who did not respond or only partially responded to FLP were treated with IVB. Thus, the effect of IVB on macular edema, which could not be eliminated by FLP, was investigated. A significant decrease in central macular thickness was detected and visual acuity was stabilized in the period of follow-up, although there was not a significant improvement in visual acuity.

This study suggests that if treatment is initiated as prompt FLP and followed by intravitreal anti-VEGF if needed, significant anatomic benefit is obtained. However, functional benefit is not gained due to the possible destructive effect of the prolonged macular edema on photoreceptors. We can conclude that anti-VEGF therapy should be the first treatment in diabetic macular edema or be initiated immediately in patients who had FLP treatment before in order to have at least better anatomic results.

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