Intravitreal Ranibizumab Injection in the Treatment of Refractory Diabetic Macular Edema

Refrakter Diabetik Maküler Ödem Tedavisinde İntravitreal Ranibizumab Enjeksiyonu*

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ABSTRACT

Purpose: To evaluate the efficacy of intravitreal ranibizumab injection in the treatment of refractory diabetic macular edema (DME).

Matterials and Methods: 58 eyes of 43 patients with refractory DME were enrolled into the study. The mean age of the patients were 61.60±8.72 years. Patients were applied 3 doses of 0.5 mg intravitreal ranibizumab injection with interval period of one month. Best corrected visual acuities (BCVA) and optical coherence tomography (OCT) images of patients before and after injection were recorded.

Results: The mean duration was 8.4 months. Mean BCVAs before and after the treatment were 0.87±0.40 logMAR, and 0.84±0.42 logMAR, respectively. The change at BCVA between before and after the treatment was not significant (p>0.05). At the first month after 3 doses of injection the visual acuity of 11 eyes (18.96%) were increased 1 line (5 letters) and more. There was not any significant increase in visual acuity in 41 eyes (70.70%) The visual acuity decreased in six eyes (10.34%). The mean central macular thickness (CMT) before and after injections were calculated as 528.27±111.31 and 450.34±128.29 µm, respectively. The mean reduction amount in CMT was 77.93±127.11 µm and it was significant (p<0.001). After 3 doses of injection, OCT showed that the macular edema in 38 eyes (65.52%) were reduced compare to before the injection. There was no changing in 10 eyes (17.24%. Macular edema was increased in 10 eyes (17.24%).

Conclusion: It was observed that ranubizumab injections anatomically improved macular edema but not visual acuity.This discrepancy might be related to foveal photoreceptor damage or poor regulation of blood sugar level.

Key Words: Diabetes, refractory macular edema, ranibizumab.

ÖZ

Amaç: Refrakter diyabetik maküla ödemi (DMÖ)'nde intravitreal ranibizumab enjeksiyonunun etkinliğini değerlendirmek.

Gereç ve Yöntem: Refrakter DMÖ olan 43 hastanın 58 gözü çalışmaya alındı. Hastaların ortalama yaşı 61.60±8.72 yıldı. Hastalara birer ay arayla 3 doz 0.5 mg intravitreal ranibizumab enjeksiyonu uygulandı. Hastaların enjeksiyon öncesi ve enjeksiyon sonrası en iyi düzeltilmiş görme keskinlikleri (EDGK) ve optik koherens tomografi (OKT) görüntüleri kaydedildi.

Bulgular: Hastaların ortalama takip süreleri 8.4 aydı. Ortalama EDGK tedavi öncesi ve tedavi sonrası sırasıyla 0.87±0.40 logMAR,ve 0.84±0.42 logMAR olarak idi. Tedavi öncesi ve sonrası EDGK'ndeki değişim anlamlı değildi (p>0.05).Onbir gözde (%18.96) 3 doz enjeksiyon sonrası 1. ayda görme keskinliklerinde 1 sıra (5 harf) ve üzerinde artış saptandı. Kırkbir gözde (%70.70) görme keskinliği stabil kaldı. Altı gözde (%10.34) ise görme keskinliğinde düşüş saptandı. Ortalama santral maküla kalınlığı (SMK) enjeksiyon öncesi ve sonrası sırasıyla 528.27±111.31 ve 450.34±128.29 µm olarak hesaplandı. SMK'ndaki azalma ortalama 77.93±127.11 µm idi ve anlamlıydı (p<0.001). Üç doz enjeksiyon sonrası 1. ayda 38 gözde (%65.52) enjeksiyon öncesine göre OKT'de maküla ödeminde azalma saptandı, 10 gözde (%17.24) maküla ödeminde değişiklik olmadı, 10 gözde (%17.24) ise maküla ödeminde artış saptandı.

Sonuç: Ranibizumab enjeksiyonlarının görme düzeyini olmasa da maküla ödemini anatomik olarak iyileştirdiği gözlendi. Bu hastalardaki foveal fotoreseptör hasarı veya hastaların kötü kan şekeri regülasyonu ile ilişkili olabilir.

Anahtar Kelimeler: Diabet, refrakter maküler ödem, ranibizumab.

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INTRODUCTION

Diabetic macular edema (DME) is the leading cause of visual impairment in patients with diabetic retinopathy. It may be caused by a breakdown of the inner and/or the outer blood retinal barrier (BRB).[1,2]. The retinal pigment epithelium (RPE) forms the outer BRB, and it contributes to the normal fluid dynamics in the subretinal space. RPE dysfunction is thought to affect the formation and continuity of the macular edema. Several treatment options were tried to treat the inner and outer BRB dysfunction resulting from DME, but the results were not satisfactory.[1-3]

According to the Early Treatment Diabetic Retinopathy Research Group Study (ETDRS), if the macula is not affected diffusely, focal laser photocoagulation (FLP) is recommended for retinal focal vascular leakage. In ETDRS, it was shown that FLP reduced the risk of moderate visual loss by 50%. However, eyes with macular edema are often resistant to this treatment.[4,5] Additiononally, FLP has severe adverse effects such as foveal burns, visual field defects and macular scars.

Increased level of VEGF in the vitreous play a role in the development of DME. Thus, intravitreal anti-VEGF injection is an attractive therapeutic method for the eyes with diabetic retinopathy.[6] VEGF is released by endothelial, glial and RPE cells and Muller cells and it causes increased the vascular permeability via the stimulation of protein kinase C isoforms.[5,6] VEGF-A isoform is the one have most strong relationship with angiogenesis and it is the main target of anti-VEGF treatment.[6-8]

Intravitreal corticosteroids have potent anti-inflammatory effects and they have been widely used in the treatment of DME. However, they have serious ocular adverse effects such as glaucoma and cataract. Thus, antiVEGF agents have been usually preferred over corticosteroids for the treatment of DME.[1, 4, 6-9]

Ranibizumab is recombinant humanized mouse monoclonal antibody fragment with small molecular size and high affinity. Ranibizumab has 5-10 times higher affinity to VEGF comparesd to bevacizumab and it is safer than bevacizumab due to for the treatment of choroidal neovascular membrane (CNVM) secondary to AMD.[1,4,6-9]

Refractory DME is clinically significant macular edema lasting at least three months and unresponsive to one or more treatments of FLP and/or intravitreal steroid injection. The aim of this study is to evaluate the results of intravitreal injection of ranibizumab in the treatment of refractory DME.

MATERIAL AND METHODS

Fifty eight eyes of 43 patients with refractory DME who were taken under follow-up in the outpatient clinic of Firat University Hospital were enrolled in this study. The study was designed as, a prospective clinical trial. The tenets of the Helsinki declaration were followed throughout the study. Informed consent was obtained from each subject, including detailed explanations of all procedures before participation in the study.

Injections were given to 13 patients (30.24%) only to their right eye, in 15 patients (34.88%) only to their left eye, and in 15 patients (34.88%) to their both eyes, respectively. Twenty three (53.48%) of these patients were female, and 20 (46.52%) of them were male and the mean age of the patients was 61.60±8.72 years.

All patients had refractory DME. Refractory (recalcitrant, persistent) DME was defined as clinically significant macular edema lasting at least three months and unresponsive to one or more treatments of FLP and/or intravitreal steroid injection. Additionally, the patients with foveal ischemia were excluded from the study and the absence of foveal ischemia was confirmed using fundus florescein angiography. Prior to injection, all patients were performed full complete ophthalmological examinations including the measurement of best corrected visual acuity (BCVA) and intraocular pressure (IOP), anterior segment biomicroscopy and ophthalmoscopy. Central macular thicknesses (CMT) was measured by using optical coherence tomography (OCT). The main parameters which were evaluated in our study were BCVA (Log MAR) and macular thickness measured by OCT.

The Pars Plana Injection Technique

Before the injection is performed, a drop of oxybuprocaine hydrochloride and washing of ocular surface with 10% povidone-iodine using a flush injector were applied directly to the ocular surface, lid margins, and lashes. After a lid speculum was placed, an additional drop of povidone-iodine and topical anesthetic was applied to the intended injection site. No instrumentation was performed for the globe fixation during the injection because the potential elevation of (IOP) due to fixation might influence reflux.

Injections were performed by using a 27-gauge needle-tipped syringe through the pars plana in temporal quadrants 3 mm (pseudophakic eyes) to 4 mm (phakic eyes) from the limbus. Three doses with an interval of one month of 0.1 cc (0.5 mg) ranibizumab were intravitreally injected into the mid vitreous cavity. The standard straight injection perpendicular to the sclera was slowly created after upward mobilization of the conjunctiva and the syringe needle was then gently withdrawn. In order to avoid vitreous wick syndrome,

the conjunctiva shifted with a cotton-tipped applicator before injection and then, to minimize reflux, this applicator was softly applied over the scleral entry site to the needle withdrawn for about three seconds. After the interventions, at the first and the second days, patients were examined for IOP spikes, ocular infection, and retinal complications.

The patients were performed the measurements for visual acuity, and IOP, and fundus examination at the first and the second day and 1st, 2nd, 3rd, 4th, and 6th months. CMTs were measured at before and, at 1st, 2nd, 3rd, 4th, and 6th months after the interventions.

Statistical Analysis

The means and standard deviations of the data were obtained. Statistical analysis of the study was done using Statistical Package for the Social Sciences, 15 (15.0 SPSS, Chicago, IL, USA). A paired-t test was used for comparisons, before and after the injection. A P value less than 0.05 was considered statistically significant.

RESULTS

The mean follow-up duration was 8.4 months. At baseline, the mean BVCA was 0.87±0.40 logMAR, while at the 6th month after treatment, it was 0.84±0.42 logMAR. The difference (0.02±0.23 logMAR) between mean BCVAs before and after treatment was not statistically significant (p>0.05).

At the 6th month after treatment, BCVA increased by one line (five letters) or more in 11 eyes (18.96%) whileas it decreased by one or more lines in 6 eyes (10.34%). BVCA stabilized in 41 eyes (70.70%).

In 14 of the eyes with no increase in visual acuity, the disruption at the line of foveal inner segment-outer segments connection of photoreceptors was detected. Eleven of 41 nonresponsive eyes had foveal fibrosis formation. The mean CMT was 528.27±111.31 µm and 450.34±128.29 µm before and after injections, respectively.

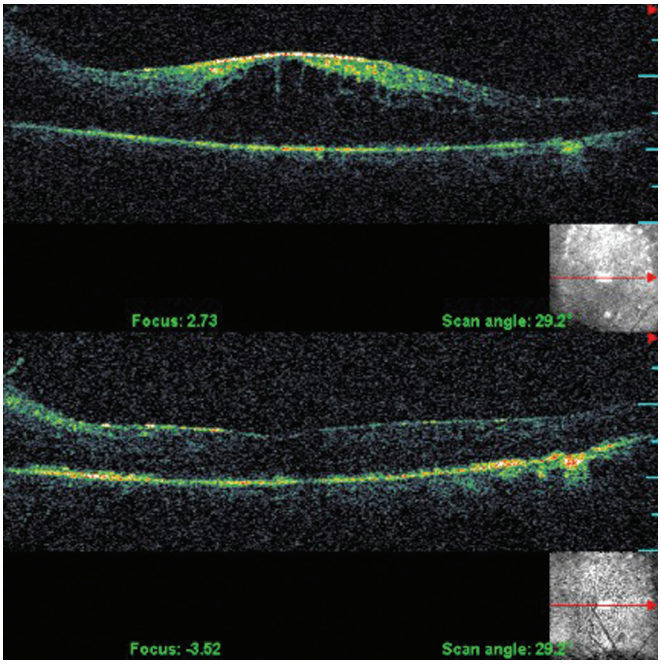

Figure: *OCT images of patients before and after 3 dases of injection.*

The mean reduction amount in macular edema was 77.93±127.11 µm. The reduction of CMT was statistically significant (p<0.001).

At the 6th month after three consecutively injections, OCT showed that the macular edemas in 38 eyes (65.52%) were reduced compared to the results before the injections, whileas it was increased in 10 eyes (17.24%). There was no change in 10 eyes (17.24%) with DME.

DISCUSSION

Diabetic macular edema is the most important cause of decreased vision in diabetic retinopathy. Due to increased vascular permeability, intraretinal and subretinal fluid accumulations and typical cystoid changes occur, and macular edema is developed. If the leaks are caused by microaneurism, a focal macular edema will occur and if leaks are caused by common disruption of BRB, it will affect larger areas and diffuse macular edema will develop.[1-4]

Table: *Change at BCVA and macular edema detected by OCT and the mean CMKs before and after the treatment.*

The mean BVCA (logMAR)	Change at BCVA	The mean CMK (µm)	Change at macular edema in OCT
Before treatment 0.87±0.40 After treatment 0.84±0.42 Mean change 0.02±0.23 p>0.05	Increase 5 letters or more 11 eyes (18.96%) No change 41 eyes (70.70%) Decrease 5 letters or more 6 eyes (10.34%)	Before treatment 528.27±111.31 After treatment 450.34±128.29 Mean reduction 77.93±127.11 P<0.001	Increase 10 eyes (17.24%) No change 10 eyes (17.24%) Reduction 38 eyes (65.52%)

BCVA; Best Corrected Visual Acuity; OCT; Optical Coherence Tomography; CMK; Central Macular Thichness.

According to ETDRS, if the macula is not affected by diffuse, FLP is recommended for the treatment of retinal focal vascular leakage.[5] However, eyes with DME are often resistant to FLP treatment. Consequently, DME progresses and the percent of the patients losing more than two lines of visual acuity within two years is more than 50%. The results of FLP and intravitreal triamcinolone acetonide (IVTA) injections were not satisfactory in many cases because of recurrent or refractory DME. It was shown that the effect of grid laser photocoagulation is limited and macula could get affected as a result of progressive growth in macular laser scar.[10-12] These results have led to new ways to treat macular edema. For this purpose, intravitreal applications of corticosteroids has been raised. The major mechanisms of actions of these drugs are the inhibition of VEGF, anti-inflammatory effect, improvement of BRB breakdown and the reduction of vascular.[3] Various studies emphasized that, the improvement of visual acuity and regression of macular edema obtained with IVTA treatment, are not permanent and that DME relapses 4-5 months after the disappearance of IVTA particles.[13-14] Most researchers consider that IVTA therapy should be repeated after three to six months. However, the IOP elevation and cataract formation due to corticosteroids are the main complications limiting repeatedly applications of these agents.[13-15] VEGF is the most important factor that causes an increase in vascular permeability during retinal diseases and in the development of the neovascularization. VEGF is also known as a chemoattractant for macrophages and monocytes. These cells play a role in addition to the increase of vascular permeability by creating proinflammatory molecules. Ranibizumab has been widely used for the treatment of AMD, DME and macular edema caused by retinal vein occlusion.[8, 16]

The READ-2 study investigated the results of long-term (2 years) of intravitreal ranibizumab monotherapy for DME. In the patients with DME which decreased visual acuity and increased CMT, the combination therapy, including focal/grid FLP and ranibizumab was found to be successful and to be able to reduce frequency of injection.[17,18]

In the RESTORE study, ranibizumab monotherapy, laser monotherapy and combined ranibizumab plus laser treatments were compared. In this study, a total of 345 patients was evaluated based on 12 months observations. The most successful treatment for the improvement of the visual acuity was ranibizumab monotherapy, and after that treatment ranibizumab plus laser combined treatment, respectively.[19]

The RESOLVE study shows that the ranibizumab monotherapy is effective in improving BCVA and is generally well tolerated in DME in the 12-month period, compared with sham treatment (along with rescue laser treatment).[20]

In our study, we did not observe the expected increase in visual acuity after three doses of ranibizumab injection. However, the macular edema anatomically improved. Our results are not compatible with the results of other studies. The reason for this discordance between anatomic and visual improvements might be poor blood sugar regulation. However, we did not make multivariate analysis or correlation to find any relation to poor blood sugar regulation of the patients. However, the photoreceptor damage or fibrosis of fovea in refractory cases may be also cause this condition.

There are some limitations in this study. The correlation analysis to find any relation to the poor blood sugar regulation was not performed. There were 58 eyes of 43 patients, which enrolled in this study. Because the patients with foveal ischemia were excluded and also, the study group included only refractory eyes to previous treatments, the number of the participants is limited. However, when the power analysis was performed according to previous studies in literature, the number of patients required to conclude in our study and the power of the study were as 54 patients and as at least 0.8, respectively. As the power of our study is 0.9, we can consider that the sample size is satisfactory for the study.

Intravitreal injection of ranibizumab in the treatment of refractory DME was found to be effective in anatomically reducing macular edema but not in improving visual acuity. However, long-term, randomized, comperative studies, including a higher number of cases are required on this subject.

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