The Effects of Serous Macular Detachment on Treatment of Patients with Macular Edema Secondary to Central Retinal Vein Occlusion

Seröz Maküla Dekolmanının Santral Retinal Ven Tıkanıklığına Sekonder Gelişen Maküla Ödemi Tedavisine Etkisi

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ABSTRACT

Purpose: To evaluate the effect of serous macular detachment (SMD) on anti-VEGF treatment in patients with macular edema (ME) secondary to central retinal vein occlusion (CRVO)

Materials and Methods: 46 eyes of 46 patients with ME due to CRVO were reviewed retrospectively. The patients were divided into two groups according to presence of the subretinal fluid in optical coherence tomography (OCT): SMD and non-SMD. Both groups were treated with three monthly anti-VEGF (aflibercept or ranibizumab) injections followed-up in PRN regimen. At baseline and after every injection best-corrected visual acuity (BCVA), central macular thickness (CMT), anatomical findings were noted from optical coherence tomography (OCT) images and patients' files.

Results: 19 eyes in SMD and 27 eyes in non-SMD groups were studied. The groups were similar in terms of baseline characteristics ($p>0.05$). Both groups had improvement in BCVA and decrease in CMT during treatment period ($p<0.001$). Although SMD group had higher BCVA than non-SMD group at all time, this difference was statistically significant only at first and second months ($p=0.024$ and $p=0.023$, respectively). The change in BCVA during treatment period was higher in SMD group than non-SMD group ($p=0.047$). The groups were similar in terms of anatomical gain ($p>0.05$).

Conclusion: The patients with SMD had higher anatomical gain and BCVA than patients with non-SMD during the first months of the anti-VEGF treatment. SMD has good impact on visual gain in patients with CRVO.

Keywords: Anti-VEGF, central retinal vein occlusion, macular edema, serous macular detachment.

ÖZ

Amaç: Seröz maküla dekolmanının (SMD) santral retinal ven tıkınalıklığına (SRVT) sekonder gelişen maküla ödemli hastaların anti-VEGF tedavisine olan etkisini araştırmak

Gereç ve yöntem: SRVT'ye seconder gelişen maküla ödemli 46 hastanın 46 gözü geriye dönük olarak incelendi. Hastalar optic koherans tomografi (OKT) görüntülerinde subretinal sıvı olup olmamasuna göre iki gruba ayrıldılar: seröz maküla dekolmaı olan grup (SMD) ve SMD olmayan grup. Her iki grup da 3 aylık ardışık anti-VEGF (ranibizumab veya aflibercept) tedavi sonrası PRN rejimiyle takip edildiler. Başlangıçta ve her enjeksiyon sonrası hastaların en iyi düzeltilmiş görme keskinlikleri (EİDGK), santral maküla kalınlıklar (SMK) ve anatomik bulguları hasta dosyalarından ve OKT görüntülerinden not edildi.

Bulgular: SMD olan grupta 17, SMD olmayan grupta 26 hasta vardı. Gruplar demografik yapı açısından benzerdi ($p>0.05$). Tedavi süresince her iki grupta da görme ve anatomik kazanım sağlanmıştır ($p<0.001$). SMD olan grup SMD olmayan gruba göre her zaman daha iyi EİDGK'ya sahip olmakla birlikte bu fark sadece 1. ve 2. aylarda anlamlıydı (sırasıyla $p=0.024$ ve $p=0.023$). EİDGK'deki değişim SMD olan grupta daha iyi bulundu ($p=0.047$). Anatomik kazanım açısından gruplar benzer saptandı ($p>0.05$)

Sonuç: SMD olan hastalar anti-VEGF tedavinin ilk aylarında SMD olmayan hastalara göre daha iyi görme kazanımı sağlamıştır. SMD, SRVT'li hastalarda görme kazanımı üzerine olumlu etki sağlamıştır.

Anahtar kelimeler: anti-VEGF, santral retinal ven tıkanıklığı, maküla ödemi, seröz maküla dekolmanı

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INTRODUCTION

Central retinal vein occlusion which causes severe visual loss is the second most common retinal vascular pathology after diabetic retinopathy.[1-3] The patients with CRVO has elevated levels of pro-inflammatory mediators such as interleukin-6, interleukin-8, pentraxin-3, endothelin-1 and vascular endothelial growth factor (VEGF) in vitreus fluid.[4-7] The main causes of visual loss in CRVO were macular edema (ME) and ischemia.8 Due to elevated VEGF levels, anti-VEGFs were found to be useful in the treatment of ME.[9-16] Although this anti-VEGF treatment was found to be successful, not all patients give similar response. Several optical coherence tomography (OCT) findings have been analyzed as predictive factors for visual gain.[17-21] In a study Özdemir et al. showed that 81.8% of the patients with CRVO had SMD in their study.[22] Presence of SMD was found to be poor predictive factor in diabetic macular edema.[23-25] But predictive value of SMD in CRVO is not clear.

The aim of this study is to analyze the impact of SMD in visual prognosis of the patients with CRVO undergoing anti-VEGF treatment.

METHODS

In this retrospective and comparative study; the patients who were admitted department of ophthalmology between 2016-2018 were included. The patients were divided into two groups according to presence of subretinal fluid on OCT: SMD and non-SMD. All the patients were treated with three monthly intravitreal aflibercept (IVA) or ranibizumab (IVR) injections followed by a PRN regimen based on their clinical course. The patients which had ME secondary to CRVO, central macular thickness>300 μm and a follow-up period of at least 6 months were included. The patients with ME due to any other disease, cataract or vitreoretinal surgery within the last 6 months prior to the loading phase, history of laser photocoagulation treatment, dense cataract, presence of uncontrolled glaucoma, presence of neovascularization at baseline were excluded. Reinjection criterias were a decrease in BCVA ≥ 1 snellen line, an increase in CMT≥50 μm and intraretinal or subretinal fluid in OCT.

All intravitreal injections were performed under aseptic conditions in the operating room. Following the injection, a topical antibiotic drop was administered. No complication was seen during the injections.

The standard ophthalmic examinations were performed at baseline and postoperative 1st month visit following each injection. The examinations included slit-lamb microscopy, BCVA, tonometry, SD-OCT, indirect ophthalmoscopy. The BCVA was measured with Snellen chart, and the decimal visual acuity was converted to the logarithm of the minimal angle of resolution (logMAR) units for the statistical analyses. The OCT acquisition was performed on the SD-OCT (Cirrus HD-OCT; Carl Zeiss Meditec). At baseline and at 6th month visit, patients underwent fundus fluorescein angiography to evaluate retinal ischemia. Ischemic type of CRVO was defined as usual as an area of retinal non-perfusion greater than 10 disc diameters.

Statistical analysis was performed using the SPSS software version 21. Descriptive analyses were presented using means and standard deviations for normally distributed variables. When investigating the changes in BCVA and CMT by time; repeated measures of analysis of variance test (ANOVA) was used. Student T test were used to compare the groups. A $p<0.05$ value was accepted statically significant.

RESULTS

The patients:

The mean age was 59.7±10.7 years in SMD and 65.1±7.8 in non-SMD group. Ten (52%) patients in SMD and 14 (51%) in non-SMD group were female. The groups were similar in terms of age, gender, baseline CMT and BCVA ($p>0.05$). Table-1 shows the baseline characteristics of the patients.

Table 1. *The baseline characteristics of the patients*

	SMD group	Non-SMD group	P values
Age (years)	59.7±10.7	65.1±7.8	0.055
Gender(female/male)	10/9	14/13	0.768
Initial BCVA (logMAR)	1.45±0.78	1.55±0.62	0.657
Initial CMT (μm)	673±285	657±211	0.825
Diabetes mellitus	5/19(26%)	5/27(18%)	0.528
Hypertension	11/19(57%)	20/27(74%)	0.249
Hyperlipidemia	9/19(47%)	14/27(51%)	0.765
Pseudophakia	2/19(10%)	1/27(3%)	0.356
Ischemic/non-ischemic CRVO	5/14	5/22	0.788
Time period between the initial symptoms and first injections	19.5±3.06 days	21.5±3.65 days	0.147

SMD:serous macular detachment, BCVA: best-corrected visual acuity, CMT: central macular thickness

Change in macular thickness

The mean CMT had decreased significantly in both groups (p<0.001). In SMD group mean CMT at baseline was 673±285 µm and it decreased to 372±129 µm at first month (p<0.001), 321±143 µm at second month (p<0.001), 296±122 µm at third month (p<0.001) and 285±70 µm at six month (p<0.001). In non-SMD group mean CMT was 657±211 µm at baseline and it decreased to 326±92 µm at first month (p<0.001), 274±67 µm at second month (p<0.001), 256±54 µm at third month (p<0.001) and 269±51 µm at six month (p<0.001). There was not any statistically significant difference between groups all the time in terms of anatomical gain (p>0.05). The trend in CMT is presented in figure-1.

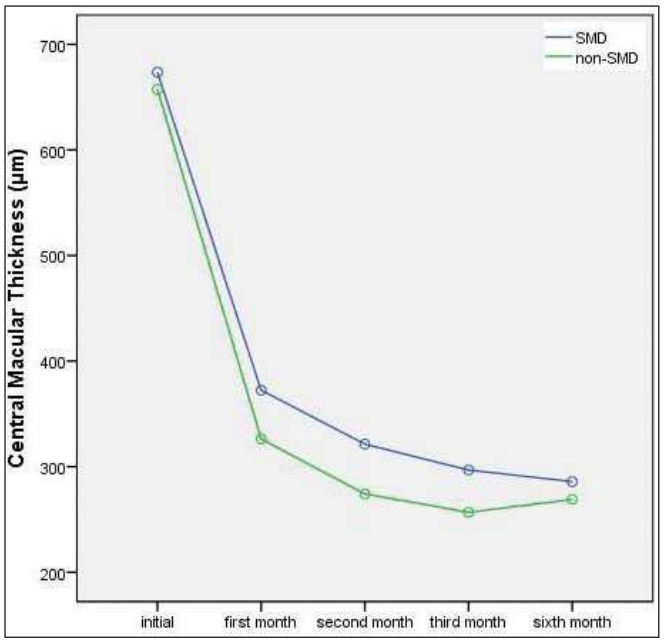

Figure 1. *Changes in CMT over time*

Change in visual acuity

There was statistically significantly improvement in BCVA after treatment in both groups (p<0.001). The mean BCVA was 1.45±0.78 logMAR at baseline in SMD group and it increased to 0.75±0.68 logMAR after first injection (p<0.001), 0.72±0.72 logMAR after second injection (p<0.001), 0.62±0.68 logMAR after third injection (p<0.001) and 0.57±0.69 logMAR at final visit (p<0.001). In non-SMD group the mean BCVA was 1.55±0.62 logMAR at baseline and it increased to 1.26±0.78 logMAR after first injection (p=0.004), 1.23±0.73 logMAR after second injection (p=0.003), 1.06±0.79 logMAR after third injection (p<0.001) and 1.00±0.83 logMAR at final visit (p<0.001). When comparing groups, the SMD group has higher BCVA all the time, however this difference was statistically significant only at first and second month (p=0.024 and p=0.023, respectively). The change in BCVA during treatment period was higher in SMD group than non-SMD group (p=0.047). This comparison is presented in figure-2 and table-2.

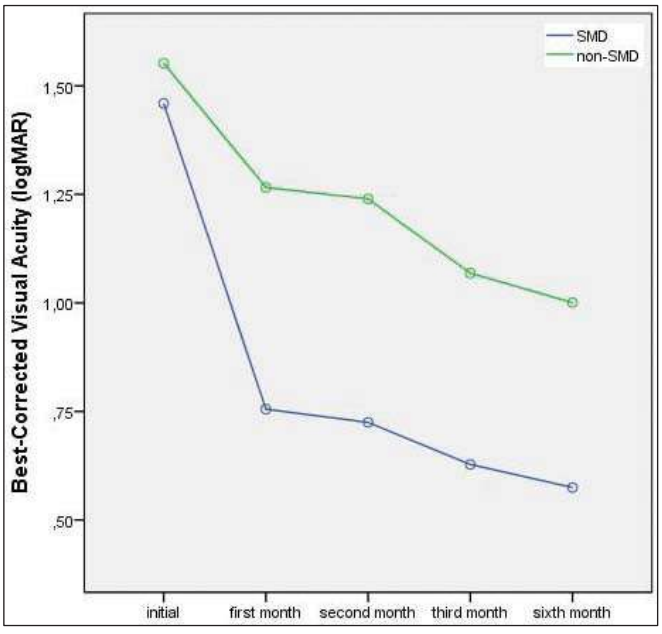

Figure 2. *Changes in BCVA over time*

Mean number of injections

The mean number of injections was 4.1±1.1 in SMD group and 4.2±0.9 in non-SMD group (p>0.05).

Effect of anti-VEGF type

IVA and IVR were compared in SMD and non-SMD groups. The patients had been treated with IVA has better anatomical response at first month in SMD and non-SMD groups

Table 2. *Comparison of BCVA improvement between groups*

	SMD group	Non-SMD group	P value
Initial BCVA	1.45±0.78 logMAR	1.55±0.62 logMAR	**0.671**
First month BCVA	0.75±0.68 logMAR	1.26±0.78 logMAR	**0.024***
Second month BCVA	0.72±0.72 logMAR	1.23±0.73 logMAR	**0.023***
Third month BCVA	0.62±0.68 logMAR	1.06±0.79 logMAR	**0.051**
Six month BCVA	0.57±0.69 logMAR	1.00±0.83 logMAR	**0.066**

SMD:serous macular detachment, BCVA: best-corrected visual acuity

(p=0.045 and p=0.006, respectively). At second, third and six months there was not any statistically significant difference between IVA and IVR in groups. Altough there was not any statistically signifcant difference in terms of visual gain between IVA and IVR, the patients treated with IVA in SMD group has higher BCVA than the patients treated with IVR (p=0.111)(Figure-3). When visual gain was compared in patients treated with IVR, no significant difference was found between SMD and non-SMD groups (p=0.125). When visual gain was compared in patients treated with IVA, no significant difference was found between SMD and non-SMD groups (p=0.087).

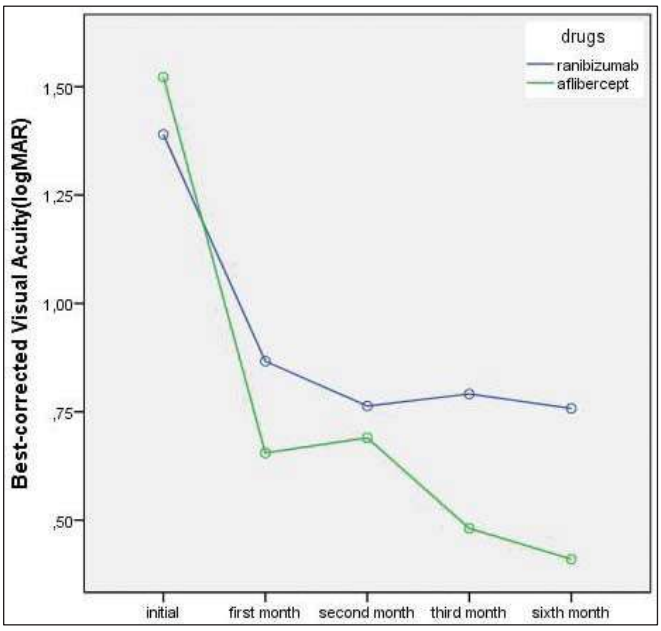

Figure 3. *Effect of drugs in SMD group*

DISCUSSION

Macular edema is one of the leading cause of vision lose in patients with CRVO [8]. The anti-VEGF treatment was found to be successful because of the underlying pathology of CRVO [9-16]. However not all of the patients have same benefit from anti-VEGF treatment in real world. Despite anatomical gain, some patients have poor visual acuity after treatment. This leads to question of whether the initial findings of the patients are influential on final vision. It has been shown that initial findings can be used as a predictive factor in patients with CRVO [17-21].

Özdemir et al reported that SMD, which was not seen in ophthalmoscopy and fundus florecein angiography, was frequently seen on OCT in CRVO patients [22]. In that study, SMD was found in 81.8% of the patients. In current literature, initial OCT findings such as SMD, CME or ellipsoid zone are defined as biomarkers and their effects on the various diseases are discussed. The purpose of the current study is to investigate effects of serous macular detachment which is used as a biomarker on the anti-VEGF treatment and to compare the findings with non-SMD patients.

Various treatment options have been used in the treatment of SMD due to CRVO. Laser photocoagulation has been shown to be ineffective in the treatment of ME secondary to CRVO.[26] In the study investigated by Karacorlu et al, 10 patients with CME and SMD underwent intravitreal triamcinolone acetenoid and all eyes have improved visual acuity at first month. 60% of the patients had improvement in visual acuity at 6 month.[27] Cinal and colleagues have investigated the efficacy of intravitreal bevacizumab injections in patients with SMD developed secondary to CRVO. In that study the patients had increase in BCVA and decrease in CMT.[28] But lack of those two studies is the absence of the control groups. In an comparative study, Dolz-Marca and et al investigated efficacy of the IVR in patients with SMD due to CRVO and BRVO. There was not statistically significant difference in terms of visual gain between SMD and non-SMD groups in CRVO patients.[29] Our article is separated from these studies in terms of study design. In our study, we studied the effects of aflibercept and ranibizumab on SMD and non-SMD patients and compared the two drugs with each other. In current study, there was no difference between SMD and non-SMD patients in the IVR-treated group. As well as we know, this is the first study to describe the efficacy of the aflibercept in patients with SMD due to CRVO. In a study with diabetic macular edema, Kaiho T. and et al found that SMD patients had higher BCVA and less number of IVA injections than non-SMD patients.[30] In our study although there was no statistically significant difference between SMD and non-SMD patients in the IVA treated group, the patients with SMD had slightly better visual acuity (p=0.087).

We found that the patients with SMD had better visual gains than the patients with non-SMD under anti-VEGF treatment at the end of the six month. This finding suggests that serous macular detachment has a protective effect on the photoreceptor layer in CRVO. Kazarian and his colleagues studied the patients with retinal vein occlusion and divided them into two groups according to OCT findings: SMD and CME. They treated the patients with IVR. They showed that serous macular detachment may serve as a preventing factor of photoreceptor damage.[31]

Our study has some limitations, this is a retrospective study and we have small number of the patients. To understand effects of SMD in CRVO patients, larger population and prospective randomized controlled studies are needed.

In conclusion, the patients with SMD have higher visual acuity than non-SMD patients secondary to CRVO on the anti-VEGF treatment. We think that subretinal fluid which is developed in acute period reduces the photoreceptor damage in CRVO patients and provides better visual acuity.

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