Comparison of Aflibercept and Ranibizumab Treatment in Patients with Macular Edema Secondary to Central Retinal Vein Occlusion

Santral Retinal Ven Tıkanıklığına İkincil Gelişen Maküla Ödeminde Aflibercept ve Ranibizumab Tedavilerinin Karşılaştırılması

Alper Halil BAYAT[1], Selim BÖLÜKBAŞI[1], Burak ERDEN[1], Akın ÇAKIR[1], Mustafa Nuri ELÇİOĞLU[2]

ABSTRACT

Purpose: To compare the efficacy and safety of intravitreal ranibizumab (IVR) and intravitreal aflibercept (IVA) injections in patients with macular edema (ME) secondary to central retinal vein occlusion (CRVO)

Materials and Methods: 50 eyes of 50 patients with ME due to CRVO were reviewed retrospectively. The patients were divided into two groups according to the treatment they received: IVA group and IVR group. Both groups were treated with three monthly injections followed-up in PRN regimen. At baseline and after every injection best-corrected visual acuity (BCVA), central macular thickness (CMT), anatomical findings, edema types, intraocular pressure changes were noted from optical coherence tomography (OCT) images and patients' files.

Results: 25 eyes of 25 patients were studied in both groups. The groups were similar in terms of baseline characteristics ($p>0,05$). The changes in BCVA and CMT were statistically significant within both groups during the 6-month follow-up ($p<0,001$ and $p<0,001$ respectively). When the two groups were compared, there was not a statically significant difference in terms of visual gain ($p=0,057$). In terms of anatomical gain, IVA group was better at first month ($p=0,016$), but similar at the final 6th month visit ($p=0,312$).

Conclusion: Both intravitreal ranibizumab and intravitreal aflibercept injections were found to be effective for visual and anatomical gain in macular edema secondary to central retinal vein occlusion. Aflibercept provided faster anatomical recovery. There is no difference between two drugs in terms of visual gain, anatomical success and side effects at the end of the six months.

Key Words: Aflibercept, Central retinal vein occlusion, Edema types, macular edema, Ranibizumab.

ÖZ

Amaç: Santral retinal ven tıkanıklığına (SRVT) ikincil gelişen maküla ödeminde (MÖ) aflibercept (Af) ve ranibizumab (Ra) tedavileririnin etkinliklerinin ve güvenirliklerinin karşılaştırılması

Gereç ve Yöntem: SRVT'ye bağlı MÖ'i olan 50 hastanın 50 gözü geriye dönük olarak incelendi. Hastalar aldıkları tedaviye göre 2 gruba ayrıldılar; Af ve Ra grupları. Her iki grupta ardaşık 3 enjeksiyon sonrası PRN rejimiyle takip edildiler. Başlangıçta ve her enjeksiyon sonrasında hastaların en iyi düzeltilmiş görme keskinlikleri (EİDGK), santral maküla kalınlıkları (SMK), anatomik bulguları, ödem tipleri ve göz içi basınç değişimleri not edildi.

Bulgular: Her iki grupta da 25 hastanın 25 gözü geriye dönük olarak incelendi. Gruplar başlangıç özellikleri açısından benzerdi ($p>0,05$). EİDGK ve SMK değişimleri altı ay boyunca her iki grupta da istatiksel olarak anlamlıydı (sırasıyla $p<0,001$ ve $p<0,001$). İki grup kıyaslandığında görme kazanımları açısından fark saptanmadı ($p=0,057$). Anatomik kazanım açısından Af grubu ilk ayda daha iyi saptandı ($p=0,016$) ancak altıncı ayda gruplar benzerdi ($p=0,312$).

Sonuçlar: Hem aflibercept hem de ranibizumab tedavileri SRVT'ye ikincil MÖ tedavisinde görme ve anatomik kazanım açısından etkili bulunmuştur. Aflibercept tedavisi hızlı anatomik iyileşme sağlamıştır. İki ilaç arasında altıncı ayda görme, anatomik kazanım ve yan etkiler açısından fark bulunmamıştır.

Anahtar Kelimeler: Aflibercept, Ödem tipleri, Maküler ödem, Ranibizumab, Santral retinal ven tıkanıklığı.

1- Uz. Dr., Okmeydanı Eğitim ve Araştırma Hastanesi, Göz Kliniği, İstanbul, Türkiye

2- Prof. Dr., Okmeydanı Eğitim ve Araştırma Hastanesi, Göz Kliniği, İstanbul, Türkiye

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Yazışma Adresi / Correspondence Adress:
Alper Halil BAYAT
Okmeydanı Eğitim ve Araştırma Hastanesi, Göz Kliniği, İstanbul, Türkiye

Phone: +90 505 218 1959
E-mail: alperhalil76@hotmail.com

INTRODUCTION

Central retinal vein occlusion (CRVO) is the second most common retinal vascular disorder after diabetic retinopathy.[1] It can cause severe vision loss.[2,3] Elevated levels of proinflammatory mediators such as interleukin-6, interleukin-8, pentraxin-3, endothelin-1 and vascular endothelial growth factor (VEGF) has been shown in vitreus fluid of the patients with CRVO.[4-7] The main causes of vision loss in CRVO are macular edema (ME) and ischemia which has correlation with elevated vitreal VEGF levels.[8,9] Varies treatment modalities have been used to treat ME secondary to CRVO such as laser photocoagulation, intravitreal triamcinolone asetenoid, intravitreal dexamethasone implant and anti-VEGFs. Ranibizumab 0.5 mg (Lucentis; Novartis Pharmaceuticals AG, Basel, Switzerland, and Genentech Inc, South San Francisco, California, USA) which is an anti-VEGF agent, was approved in June 2010 for the treatment of macular edema due to CRVO in the United States, based on results of phase III, randomized, double-masked, controlled studies.[10-12] Aflibercept 2 mg (Eylea VEGF Trap-Eye; Regeneron Pharmaceuticals, Inc., Tarrytown, NY and Bayer HealthCare Pharmaceuticals, Berlin, Germany) is a recombinant fusion protein consisting of portions of human VEGF receptors 1 and 2 extracellular domains fused to the Fc portion of human IgG1 formulated as an iso-osmotic solution for intravitreal administration. It has proven effective in resolution of ME due to CRVO in COPERNICUS and GALILEO studies.[13-15] In this studies the patients were treated with 6 monthly anti-VEGF injections. But the question of whether such an injection frequency is necessary or not, is controversial. So the aim of the current study is to compare of the three monthly injections of ranibizumab and aflibercept followed by PRN regimen in real life data over a 6 months follow-up.

MATERIALS AND METHODS

This study was conducted in accordance with the Declaration of Helsinki. All necessary authorizations were obtained from the Institutional Review Board of Okmeydanı Research&Traning Hospital, İstanbul, Turkey.

In this retrospective study; the patients were divided into two groups according to the treatment they received: intravitreal aflibercept (IVA) and ranibizumab (IVR). All the patients were treatment naive and had three monthly IVA or IVR injections followed by a PRN regimen based on their clinical course. The inclusion criterias were; ME secondary to CRVO, central macular thickness>300 μm, a follow-up period of at least 6 months. The exclusion criterias were; ME due to any other disease, cataract or vitreoretinal surgery with in 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. Reinjection criterias were a decrease in BCVA ≥ 1 snellen line, an increase in CMT≥50 μm, 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.

All of the patients had had standard ophthalmic examinations at baseline and postoperative 1st month visit following each injection. The examinations included slit-lamb microscopy, BCVA, tonometry, SD-OCT, indirect ophthalmoscopy. Patients were with an intraocular pressure elevation ≥ 5 mm Hg treated with topical anti-glaucomatous agents. 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.

The patients were divided into three groups according to type of edema and the difference of treatment response was investigated in these sub-groups. Diffuse retinal thickening (DRT) is defined as diffuse retinal edema at the fovea, cystoid macular edema (CME) is described as intracellular edema in the inner retina layers, serous macular detachment (SMD) is defined as subfoveal fluid accumulation between neurosensorial retina and retinal pigment epithelium (RPE). The effects of IVA and IVR treatments on CMT and BCVA were evaluated separately in three different types of edema.

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. When prognostic factos investigated multiple regression analysis were used. A $p<0.05$ value was accepted statically significant.

RESULTS

Patient demographics:

25 eyes of patients were included in both groups. The groups were similar in terms of age, gender, baseline CMT and BCVA ($p>0.05$) Baseline characteristics of the patients are presented in Table 1.

Change in visual acuity:

The mean value of BCVA had increased statistically significantly after treatment in both groups ($p<0.001$). When two groups were compared, there was not any statically

Table 1. *The baseline characteristics of the patients.*

	IVR group	IVA group	P value
Age	63,76±10,77 year	64,92±10,31 year	0,699
Gender (W/M)	13(%52)/12(%48)	14(%56)/11(%44)	0,779
Pseudophakia	2	2	1,00
Ischemia	6	5	0,733
Hypertension	17/25 (%68)	18/25 (%72)	0,758
Diabetes	5/25 (%20)	6/25 (%24)	0,733
Hyperlipidemia	13/25 (%52)	12/25 (%48)	0,777
Edema type:			
CME	7 (%28)	6 (%24)	
DRT	9 (%36)	9 (%36)	0,937
SMD	9 (%36)	10 (%40)	
Initial CMT	667,52±234.45µm	662,64±237,76 µm	0,942
Initial BCVA	1,47±0,76 logMAR	1,62±0,56 logMAR	0,451

CME: cystoid macular edema, **DRT**: diffuse retinal thickning, **SMD**: serouse macular detachment, **CMT**: central macular thickness, **BCVA**: best-corrected visual acuity

significant difference in BCVA changes during 6 months (p>0.05). Changes in BCVA are presented in table 2 and figure 1.

In our whole study group, there was no statistically significant difference in edema sub-groups (p>0.05). In SMD patients, however, IVA treatment had a slightly better visual gain, but it was statistically insignificant (p=0.111) (Figure 2).

Change in macular thickness:

The mean value of CMT had decreased significantly after treatment in both groups at the final visit (p<0.001). While in IVA group, the mean CMT decreased from 662,64±237,76µm to 288,40±66,91µm after the first injection, it decreased from 667,52±234,45µm to 384,28±127,79µm in IVR group. Compared to IVR group, IVA group had statistically better anatomical gain after the first injection (p=0.016). After

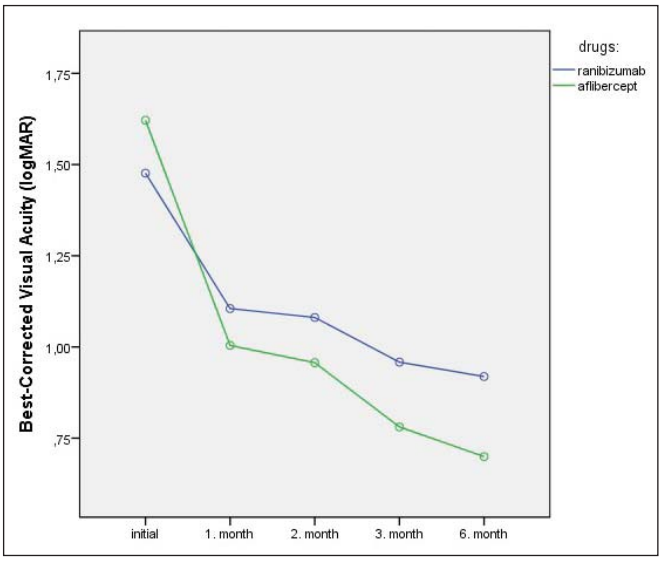

Figure 1. *Change in BCVA over time.*

Table 2. *Change in BCVA.*

	IVR group	IVA group	P değeri
Initial BCVA	1,47 ± 0,76 logMAR	1,62 ± 0,56 logMAR	0,451
First month BCVA	1,10 ± 0,73 logMAR	1,00 ± 0,77 logMAR	0,638
Second month BCVA	1,08 ± 0,79 logMAR	0,95 ± 0,67 logMAR	0,555
Third month BCVA	0,95 ± 0,76 logMAR	0,78 ± 0,74 logMAR	0,411
Sixth month BCVA	0,91 ± 0,77 logMAR	0,69 ± 0,78 logMAR	0,324

BCVA: Best-corrected visual acuity

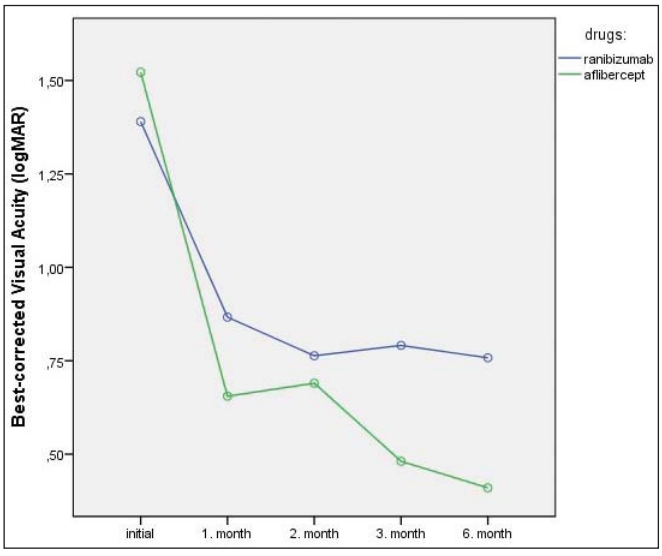

Figure 2. *The BCVA changes in patients with SMD.*

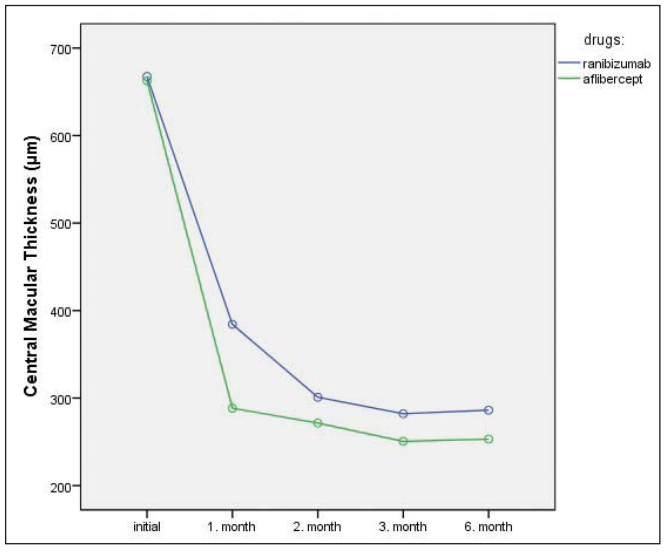

Figure 3. *Change in CMT over time.*

the second injection there was no significant difference either between both study groups or edema type sub-groups (p>0.05). The changes in CMT are presented in Table 3 and Figure 3.

The mean number of injections:

The mean number of injections was 3,88 ± 0,83 in IVA group, while it was 4,40 ± 1,15 in IVR group. Although this difference was statistically significant (p=0.074), in IVA group 20% of the patients had 5 or more injections, whereas in IVR group 44% of the patients had 5 or more injections.

The safety outcomes:

Cataract developed in 2 patients in IVR group and in 3 patients in IVA group (p=0.500). Three patients had increased IOP in each group. In IVR group, IOP was controlled with only one topical anti-glaucomatous drug in a patient, two anti-glaucomatous drugs in other two cases. But IOP elevation could not be controlled in one of these two cases, who undergone incisional glaucoma surgery after the primary endpoint of our study. In IVA group, IOP evelation was controlled with one anti-glaucomatous drug in one patient, while in two other patients two topical anti-glaucomatous agents were indicated. In IVA group; none of the patients underwent surgical glaucoma procedures. There was no significant difference in terms of IOP changes through the follow-up (p=0.666).

Prognostic factors:

We also evaluated prognostic factors for final visual acuity and anatomical results. When the predictive factors on visual gain were examined, ellipsoid zone integrity (EZ) and intact external limiting membrane (ELM) presence were found as the most important predictive factors (p<0,001 and p=0,011, respectively). The most important predictive factor for anatomical success was the number of injections and initial CMT (p<0,001 and p=0,037 respectively). The prognostic factors are presented in Table 4. In macular edema types, there was not statistically significant difference in terms of EZ and ELM status.

DISCUSSION

Ranibizumab had been found to be useful in patients with ME due to CRVO in CRUISE study[16], where 0.5 and 0.3 mg IVR injections and sham injections were compared

Table 3. *The change in CMT.*

	IVR group	IVA group	P value
Initial CMT	667,52±234,45µm	662,64±237,76µm	0,942
First month CMT	384,28±127,79µm	288,40±66,91µm	**0,016***
Second month CMT	300,96±113,18µm	271,48±97,75µm	0,626
Third month CMT	282,12±89,75µm	250,52±88,50µm	0,674
Sixth month CMT	286,20±66,96µm	253,08±51,56µm	0,240

CMT: central macular thickness

Table 4. *Prognostic factors for visual acuity and anatomical gain.*

Prognostic factors	Visual acuity		Anatomical gain	
	Beta coefficient	**P value**	**Beta coefficient**	**P value**
Age	-0,23	0,793	0.10	0.945
Gender	-0,158	0,59	0.68	0.622
Edema type	0,195	0,292	-0.268	0.384
Initial BCVA	0,24	0,850	0.168	0.392
Initial CMT	0,131	0,175	0.256	**0.037**
Number of injection	0,54	0,579	0.506	**<0.001**
Intact ELM	-0,314	**0,011**		
Integrity of EZ	0,373	**0,001**		
Subretinal fluid	-0,253	0,176	0.481	0.119
CRVO type	0,61	0,480	-0.48	0.742

BCVA: Best-corrected visual acuity, **CMT:** central macular thickness, **ELM:** external limiting mebrane, **EZ:** ellipsoid zone, **CRVO:** Central retinal vein occlusion

prospectively. IVR was found to be effective in this trial with six consequtive monthly injections; resulting in a visual gain of 14.9 letters. In this current study the mean number of injections was 4,40 ± 1,15 in the IVR group resulting in a visual gain of 0.56 logmar, so we believe that six monthly injections are not a sine quo non in CRVO disease. Additionally, in the CRUISE study only non-ischemic patients were included, but we found IVR to be effective in both ischemic and non-ischemic patients. Similar to our study design, in CRYSTAL study[17], investigators performed 3 monthly IVR injections in both ischemic and non-ischemic CRVO patients and IVR was found to be effective in both groups.

Aflibercept was found to be effective in patients with ME due to CRVO in GALILEO[18] and COPERNICUS[19] studies. In this studies, six monthly IVA injections were performed and after first injection patients had rapid anatomical recovery (approximately 400 µm) and this recovery was sustained with monthly IVA injections. In current study, anatomical recovery had been obtained after first injection (approximately 374 µm) and it was sustained with mean number of 3,88 ± 0,83 injections. We obtained this recovery with less number of injections compared to GALILEO and COPERNICUS studies. As in IVR group, in real life, six monthly injections may not be necessary.

Currently, in the literature there are only two studies which compared aflibercept and ranibizumab in CRVO patients head-to-head. Chatziralli I. and et al.[20] studied efficacy of aflibercept and ranibizumab in CRVO patients over 18 months period. They performed three monthly IVR and IVA injections followed by PRN regimen similar to our approach. In their study, ranibizumab was better visual gain than aflibercept at month six, but there was not any difference at month 12 and 18. In contrast to their findings, in our study aflibercept was found to be slightly better than ranibizumab at month six, although statiscally insignificant (p=0.057). In anatomical gain they did not find any difference at any time. But we found, aflibercept group was found to have better anatomical results than ranibizumab groups. This might be explained by the fact, that aflibercept has a higher affinitiy to VEGF-A than ranibizumab.[21]

Chatziralli I. and et al.[20], divided the patients into two groups according to edema type: diffuse retinal thickening (DRT) and cystoid macular edema (CME). They reported, that CME patients were found to have lower levels of preoperative BCVA. We divided our patients into three different sub-groups according to edema type: diffuse retinal thickening (DRT), cystoid macular edema (CME) and serous macular detachment (SMD). Unlike their results, compared to other sub-groups of edema, our DRT patients had lower BCVA due to possible receptors damages. SMD patients were found to have a slightly better BCVA with IVA injections. In an other study, Seo KH and et al.[22] reported that DRT and CME patients had better BCVA and less number of ranibizumab injections were needed than SMD patients in diabetic macular edema (DME). Kaiho T. and his friends[23] found that SMD patients had higher BCVA and less number of aflibercept injections were indicated than non-SMD patients in DME. Similar to these studies, we found that aflibercept is slightly better in SMD patients with CRVO disease.

In another study, Saishin et al.[24] compared bimonthly IVA and IVR injections in CRVO patients. IVA and IVR groups had similar clinical results in that study. They also investigated VEGF levels in humor aqueous taken from patients' anterior

chamber at the injection sessions. In IVA group in 8 of 11 eyes, VEGF levels were below detectable levels, while there were some fluctuations in IVR group. Considering the intravitreal half-life of ranibizumab (3 days in rabbit and monkey eye) and aflibercept (4.58 days in rabbit eye), aflibercept has longer VEGF suppression time.[25,26] This can explain why IVA group had a lesser number of injections in our study.

Recently, it is frequently debated whether OCT findings have an effect on visual acuity. Studies have shown that the ellipsoid zone is an important marker for the photoreceptor layer.[27] Wolf-Schnurrbusch UE and et al.[28] found that integrity of EZ and presence of intact ELM were most important prognostic factors in CRVO patients. Similar to them we found that integrity of EZ and presence of intact ELM are the most valuable prognostic factors for final BCVA in CRVO patients. Scott IU. and et al.[29] reported that initial CMT is the most valuable prognostic factor in anatomical gain in subgroup analysis of SCORE2 studies. Similar to them, the initial CMT were found to be the most valuable prognostic factor in terms of anatomical gain in our CRVO patients. This means that the greater initial CMT values, the greater anatomical gain.

In conclusion, both intravitreal ranibizumab and intravitreal aflibercept injections were found to be effective for visual and anatomical gain in macular edema secondary to central retinal vein occlusion. Aflibercept provided faster anatomical recovery. There is no difference between two drugs in terms of visual gain, anatomical success and side effects at the end of the six months. The patients which have serous macular detachment have slightly better visual gain with aflibercept injections. The integrity of EZ and presence of intact ELM are the most important prognostic factors for visual gain.

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