Comparison of Efficacy of Three Different Anti-Vascular Endothelial Growth Factor Agents in Treatment of Macular Edema Secondary to Branch Retinal vein Occlusion

Retinal Ven Dal Tıkanıklığına Bağlı Maküla Ödeminin Tedavisinde Üç Farklı Anti Vasküler Endotelyal Büyüme Faktörünün Etkinliğinin Karşılaştırılması

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ABSTRACT

Purpose: To compare the efficacy of intravitreal anti-vascular endothelial growth factor (VEGF) agents for the treatment of macular edema (ME) following branch retinal vein occlusion (BRVO).

Materials and Methods: Totally 69 eyes of 69 patients with macular edema secondary to non-ischemic BRVO were retrospectively reviewed. Totals of 27 patients treated with intravitreal bevacizumab (IVB), 22 with intravitreal ranibizumab (IVR), and 20 with intravitreal aflibercept (IVA) were included in the study. Best corrected visual acuity (BCVA), central macular thickness (CMT) and intraocular pressure (IOP) measurements were reviewed at 1st, 3rd, 6th, 9th and 12th months after treatment.

Results: BCVA was significantly better in IVR and IVA groups, compared with the IVB group in 6th month (p=0.002). Similarly, CMT was significantly lower in IVR and IVA groups, at 6th month (p=0.001). Regarding 12th month results of BCVA, CMT and IOP values, there was not any statistically significant difference between groups (p=0.72, p=0.34, p=0.40, respectively). The mean injection number was significantly higher in IVB group and lower in IVA group (4.70±1.10, 3.40±0.50, p=0.001, respectively).

Conclusion: All three anti-VEGF agents found effective in the treatment of ME after BRVO. Total injection number was significantly lower in IVA group than other 2 groups.

Key Words: aflibercept, bevacizumab, branch retinal vein occlusion, macular edema, ranibizumab.

ÖZ

Amaç: Retinal ven dal tıkanıklığına (RVDT) bağlı maküla ödemi tedavisinde anti vasküler endotelyal büyüme (VEGF) faktörlerinin etkinliğini araştırmak

Gereç ve Yöntemler: İskemik olmayan RVDT'ye bağlı maküla ödemi olan 69 hastanın 69 gözü geriye dönük olarak incelendi. Çalışmaya, intravitreal bevacizumab (İVB) ile tedavi edilen 27 hasta, intravitreal ranibizumab (İVR) ile tedavi edilen 22 hasta ve intravitreal aflibercept (İVA) ile tedavi edilen 20 hasta dahil edildi. Tedaviden sonra 1., 3., 6., 9. ve 12. aylarda en iyi düzeltilmiş görme keskinliği (EİDGK), merkezi maküla kalınlığı (MMK) ve göz içi basıncı (GİB) ölçümleri kaydedildi.

Bulgular: EİDGK, İVR ve İVA gruplarında 6. ayda İVB grubuna göre anlamlı olarak daha iyiydi (p = 0.002). Benzer şekilde, MMK 6. ayda İVR ve İVA gruplarında anlamlı olarak daha düşüktü (p = 0.001). EİDGK, MMK ve GİB değerlerinin 12. ay sonuçları ile ilgili olarak gruplar arasında istatistiksel olarak anlamlı fark yoktu (sırasıyla p = 0.72, p = 0.34, p = 0.40). Ortalama enjeksiyon sayısı İVB grubunda anlamlı olarak yüksek, İVA grubunda ise anlamlı derecede düşüktü (sırasıyla 4.70 ± 1.10, 3.40 ± 0.50, p = 0.001).

Sonuç: Her üç anti VEGF ajanı RVDT sonrasında gelişen maküla ödemi tedavisinde etkili bulundu. Toplam enjeksiyon sayısı İVA grubunda diğer iki gruba göre anlamlı olarak düşüktü.

Anahtar Kelimeler: aflibercept, bevacizumab, makuler ödem, ranibizumab, retinal ven dal tıkanıklığı.

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INTRODUCTION

Branch retinal vein occlusion (BRVO) is a common sight-threatening retinal vascular disorder; in which macular edema (ME) is the main cause of visual impairment.[1] Retinal ischemia after vascular occlusion can cause elevations in both vitreous and aqueous vascular endothelial growth factor (VEGF) levels.[2,3] Increased VEGF levels result in higher vascular permeability and associated ME in patients with BRVO. For many decades, the treatment for BRVO has been directed by the pivotal Branch Vein Occlusion Study (BVOS),[4] which suggested grid-pattern laser photocoagulation for angiographically perfused ME as a standard of care for selected eyes that do not exhibit spontaneous resolution within 3 months of onset. However, in recent years, there has been a significant advancement in the pharmacotherapy for ME associated with BRVO. Inhibitors of VEGF, also known as anti-VEGFs, have revolutionized the treatment of ME associated with BRVO.

Intravitreal injections of anti-VEGF, such as bevacizumab (Avastin™, Genentech Inc., South San Francisco, CA,USA), ranibizumab (Lucentis; Genentech, Inc., South San Francisco, CA, USA) and aflibercept (Eylea™, Regeneron Pharmaceuticals, Inc., Tarrytown, NY, USA, and Bayer Pharma AG, Berlin, Germany), can effectively lower intraocular level of VEGF and reduce vascular permeability related to ME in BRVO.[5-7] Although the data about the efficacy of intravitreal anti-VEGF in ME associated with BRVO is accumulating, to the best of our knowledge, studies comparing these agents is lacking in the literature. Herein, we performed a study comparing the efficacy of intravitreal bevacizumab (IVB), intravitreal ranibizumab (IVR) and intravitreal aflibercept (IVA) treatments for ME following BRVO.

MATERIALS AND METHODS

Patient Selection

We conformed to the Declaration of Helsinki to accomplish this study. The study was approved by the local research ethics committee of Bagcilar Training and Research Hospital. Totally 69 eyes of 69 patients with ME secondary to non-ischemic BRVO were retrospectively reviewed. All included patients did not have any history of intravitreal anti-VEGF injection, macular laser (grid or focal) or other associated treatments. Patients who were previously diagnosed to have diabetic retinopathy, vitreomacular traction or epiretinal membrane were excluded. The patients with non-ischemic BRVO were diagnosed with a retinal non-perfusion area less than 5 disc diameters by fluorescein angiography (FA). Macular edema was defined as macular leakage on FA and central macular thickness (CMT) of more than 300 µm detected by spectral-domain optical coherence tomography (SD-OCT) scans (Retinascan RS-3000; NİDEK, Gamaori, Japan) through the fovea in all patients. Baseline best-corrected visual acuity (BCVA) using the Snellen chart (converted into logMAR for statistical comparison), intraocular pressure (IOP) via pneumotonometer (CT-80, Topcon, Tokyo, Japan), and biomicroscope of anterior segment were examined in all patients. Once the patients were diagnosed with ME secondary to BRVO; IVB, IVR or IVA treatments were administered within one week. From January 2014 to December 2016, consecutively 27 patients treated with 3-monthly loading dose injections followed by pro-re-nata (PRN) IVB (1.25mg/0.05mL), 22 patient with 3+PRN IVR (0,5mg/0.05 mL), and 20 patient with 3+PRN IVA (2mg/0.05 mL) were included in the study.

Intravitreal Treatment Technique and Data Acquisition

Following topical anesthesia and disinfection of eyelid and conjunctiva, bevacizumab, ranibizumab or aflibercept was injected into the vitreous cavity using a 30-gauge needle inserted through the superotemporal pars plana, 3.5-4 mm posterior to the limbus. After the procedure, 0.5% moxifloxacin dropped into the conjunctival sac. The eye was patched for two hours. The patch was removed after, patients were instructed to instill one drop of 0.5% moxifloxacin into the injected eye five times daily for five days.

All patients were followed up at 1st, 3rd, 6th, 9th and 12th months, with the anterior segment and fundus examination and BCVA, CMT, and IOP measurements. At the end of 6th month of follow-up, a control FA was performed to all patients and in patients who showed ischemia larger than 5 optic discs at FA; a scatter laser was performed to the ischemic areas. In the first year of follow-up, grid or focal macular laser was not performed in any of the cases. The follow-up SD-OCT scans used the baseline scan as a reference. Visual testing was done in the same room at each visit. Re-treatment was based on findings of SD-OCT including CMT more than 300 µm, or presence of persistent or recurrent macular cysts or sub macular fluid affecting the visual acuity even if CMT is less than 300 µm. Primary outcome measures included alterations in CMT and BCVA at 12th month of follow-up. Complications after injections were recorded.

Statistical Analysis

All analyses were performed with the Statistical Package for Social Sciences (SPSS) for Windows 21.0 program. Descriptive statistics were used for analyses of demographic data. Comparisons of mean values of BCVA, CMT and IOP at different time periods of different treatment groups were performed with student t test. Demographic data and treatment results of 3 different subgroups were performed with chi square test and one way Anova with post-hoc Tukey test. Results were expressed as mean ± S.D. The p value of < 0.05 was considered as statistically significant.

RESULTS

The study was performed on overall 69 eyes of 69 patients (29 female (%42), 40 male (%58)) with a mean age of 69.91± 4.32 years, with ME secondary to BRVO. Among those 69 patients, 27 were in IVB group, 22 were in IVR group and 20 were in IVA group. Table 1 shows some of the demographic data of the patients and includes periods between symptoms of the patients and first intravitreal injection (pre-treatment period). There were not any statistically significant differences in pretreatment values of BCVA, IOP or CMT among groups (Table 2, 3).

Table 1. *Comparison of demographic features of treatment groups.*

	Bevacizumab Group (IVB) (n:27)	Ranibizumab Group (IVR) (n:22)	Aflibercept Group (IVA) (n:20)	p
Age (years)	69.19 ±4.67	70.32 ±4.30	70.45± 3.89	0.54
Gender (F/M)	13/14	8/14	8/12	0.69
Pre-treatment period (months)	2.55 ± 0.51	2.54 ± 0.50	2.65± 0.49	0.76
Injection number	4.70± 1.10	4.05± 0.99	3.40± 0.50	**0.001**

p: One way ANOVA

Table 2. *Comparison of best corrected visual acuity and central macular thickness of treatment groups.*

	Bevacizumab Group (IVB) (n:27)	Ranibizumab Group (IVR) (n:22)	Aflibercept Group (IVA) (n:20)	p^1
Pre-BCVA	0.62± 0.14	0.64 ±0.13	0.66±0.14	0.66
Post-BCVA-1st month	0.33±0.11	0.32± 0.12	0.29 ±0.09	0.46
Post-BCVA-3rd month	0.30±0.13	0.25±0.09	0.25± 0.08	0.15
Post-BCVA-6th month	0.35± 0.15	0.24± 0.11	0.23±0.09	**0.002**
Post-BCVA-9th month	0.30± 0.09	0.27± 0.12	0.26± 0.09	0.48
Post-BCVA-12th month	0.29± 0.09	0.27± 0.14	0.26± 0.08	0.72
p^2	**0.001**	**0.001**	**0.001**	
Pre-CMT	472.07±88.94	496.18±99.98	491.60±97.89	0.64
Post-CMT-1st month	306.74±39.43	300.59±36.26	297.45±29.69	0.66
Post-CMT-3rd month	293.89 ±37.12	281.82±40.59	268.80±29.86	0.07
Post-CMT-6th month	325.89 ±52.65	288.77±48.08	265.75±29.66	**0.001**
Post-CMT-9th month	284.63± 31.79	287.59±44.47	279.90±32.88	0.79
Post-CMT-12th month	286.89± 28.92	280.45±45.98	271.05±33.69	0.34
p^2	**0.001**	**0.001**	**0.001**	

IVB: Intravitreal bevacizumab, **IVR**: Intravitreal ranibizumab, **IVA**: Intravitreal aflibercept, **BCVA**: Best corrected visual acuity, **CMT**: Central macular thickness.
P1:One way ANOVA between all groups , **p2**: General lineer model for each group

Table 3. *Comparison of intraocular pressure of treatment groups.*

	Bevacizumab Group (IVB) (n:27)	Ranibizumab Group (IVR) (n:22)	Aflibercept Group (IVA) (n:20)	p^1
Pre-IOP	16.96 ±1.02	16.41± 0.73	16.55 ±0.99	0.09
Post-IOP-1st month	16.63 ±0.79	16.14±0.99	16.80± 0.77	**0.04**
Post-IOP-3rd month	17.26±1.13	16.09 ±1.02	17.05± 0.88	**0.001**
Post-IOP-6th month	16.70± 0.95	16.41± 0.91	16.75± 0.79	0.39
Post-IOP-9th month	15.81± 0.88	16.22± 1.34	16.50± 0.70	0.07
Post-IOP-12thmonth	15.78± 0.97	15.95± 0.95	16.15± 0.81	0.40
p^2	**0.06**	**0.08**	**0.07**	

IVB: Intravitreal bevacizumab, **IVR**: Intravitreal ranibizumab, **IVA**: Intravitreal aflibercept, **IOP**: Intraocular pressure
p1: One way ANOVA between all groups, p2: General lineer model for each group

The mean injection number was significantly higher in IVB, IVR groups and lower in IVA group (4.70±1.10, 4.05±0.99, 3.40±0.50, p= 0.001, respectively). IOP was significantly lower in IVR group compared with other 2 groups in 1st and 3rd months of treatment. BCVA was significantly improved in IVR and IVA groups, compared with the IVB group in the 6th month of follow-up. Similarly, CMT was significantly lower in IVR and IVA groups, compared with the IVB group at the 6th month of follow-up. Regarding 12th month results of BCVA, IOP and CMT values, there was not any statistically significant difference between the 3 groups. Alterations in BCVA, IOP and CMT values of treatment groups in different time periods are shown in figures 1-3.

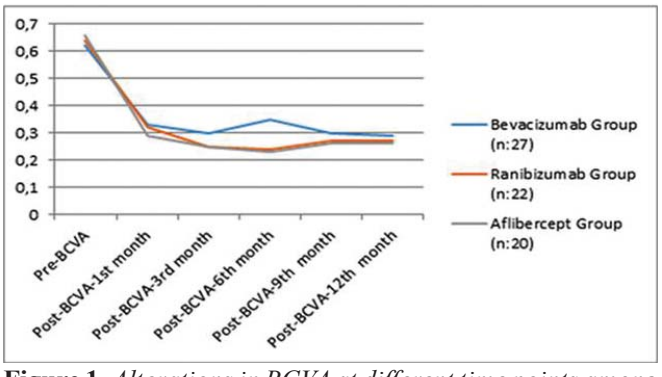

Figure 1. *Alterations in BCVA at different time points among 3 treatment groups.*

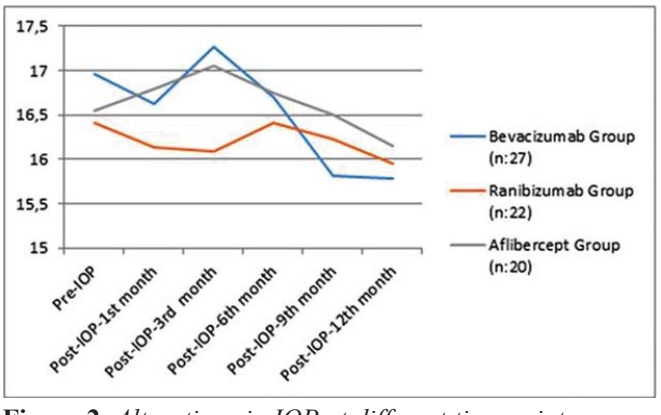

Figure 2. *Alterations in IOP at different time points among 3 treatment groups.*

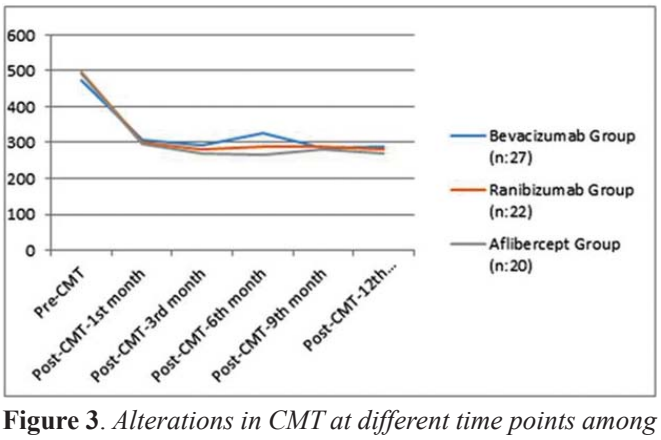

Figure 3. *Alterations in CMT at different time points among 3 treatment groups.*

In this 12 month period, scatter laser treatment requirement at the end of 6th month among patients was recorded. In IVB, IVR and IVA groups, the number of patients who required scatter laser treatment were 6 (22%), 4 (18.2%) and 4 (20%), respectively. There was not any statistically significant difference between groups regarding scatter laser treatment requirement (p: 0.41).

Side effects reported during this time period were also recorded. There were 2 transient ischemic attacks reported in IVB group (2/27, 7.4%), 1 transient ischemic attack and 1 transient numbness on one half of the body reported in IVA group (2/20, 10%), and unreported side effects in IVR group.

DISCUSSION

Due to several side effects and limitations of previously described treatment modalities such as laser photocoagulation or intravitreal corticosteroid injections for ME secondary to BRVO, an emerging interest over intravitreal injections of anti-VEGF is present.[8,9] Up-to-date, three anti-VEGF medications have been evaluated, including bevacizumab, ranibizumab, aflibercept.[10-12] Bevacizumab (149 kDa) is a full-length humanized monoclonal immunoglobulin-G1 antibody that binds all isoforms of VEGF-A which is not approved by Food and Drug Administration (FDA) for the treatment of ME secondary to BRVO.[10] Ranibizumab (48 kDa) is a recombinant humanized immunoglobulin G1 kappa isotype antibody fragment that binds all isoforms of VEGF-A and is FDA approved for the treatment of ME secondary to BRVO.[11] Aflibercept (115 kDa) is a recombinant fusion protein consisting of the VEGF extracellular binding domains of the human VEGF receptors 1 and 2 fused to the Fc domain of human immunoglobulin-G1 and is FDA approved for the treatment of ME secondary to BRVO. In addition to binding VEGF, aflibercept also binds placental growth factors 1 and 2.[12] As much as we know, our study is first that compares these 3 different anti-VEGF agents in the treatment of ME associated with BRVO, and one of the most important results of this study was that total injection number was significantly lower in IVA group compared with the other groups. In addition, BCVA and CMT values were significantly improved in IVR and IVA groups, compared with the IVB group at 6th month; but there were not any statistically significant differences at the end of the 12th month. On the other hand, IOP values were better in IVR group compared with other 2 groups only in 1st and 3rd months of treatment.

The data about the anti-VEGF treatment in ME due to BRVO is accumulating, especially in recent years. In a previous study, twenty-four-month follow-up results of IVB has been investigated and complete resolution was reported in more than one-third of patients while partially resolved in other one third among 35 patients with ME associated with

BRVO and this is consistent with our findings.[13] Farinha et al investigated long-term results (44.8 ± 8.0 months) of IVR treatment in BRVO and reported that with an average of 5.9 injections, visual acuity showed significant improvements.[14] Our study yielded more injection numbers but the small injection number given by the Farina et al may be due to less requirement of anti-VEGF after the first year of treatment. A recent study showed a good control of ME with monthly injections within six months of IVA following 8 weekly repetitions for 52 weeks as 3+ PRN treatment in our study.[15] In our study, three anti- VEGFs were effective for the treatment of ME associated with BRVO within twelve months.

Although, the efficacies of intravitreal anti-VEGF agent injections were determined in the treatment of ME due to BRVO; the data comparing these agents is limited.[13-15] Regnier et al compared the efficacy and safety of Ranibizumab 0.5 mg PRN, aflibercept 2 mg monthly, dexamethasone 0.7 mg implant, laser photocoagulation, ranibizumab+laser, or sham intervention for ME secondary to BRVO and determined that there was not any statistically significant difference between ranibizumab and aflibercept at month 6 or 12 based on letters gained and they were better than other treatment regimens investigated in this analysis.[16] In another recent study, Narayanan et al (MARVEL study) compared the efficacy and safety of intravitreal bevacizumab with ranibizumab in treatment of ME due to BRVO and determined that although both treatment groups had significant improvements in BCVA and reductions in CMT; there was not any statistically significant difference between 2 groups at the end of 6th months of follow-up.[17] Son et al showed that both ranibizumab and bevacizumab are effective for the treatment of ME associated with BRVO, and both resulted in relatively equal anatomical and functional improvements at the end of 6th months of follow-up.[18] However, in our study, both CMT and BCVA values were significantly improved in IVR and IVA groups compared with the IVB group at the end of 6th months of follow-up. There were not any significant differences between 3 groups at the end of the 12th month.

When the line graphs of this study are analyzed, we can say that both BCVA and CMT lines were very similar for IVB, IVR and IVA groups at 12th month. One of the differences between those 3 groups was the IOP levels, which were generally lower in IVR group at 1st and 3rd month but the differences between those 3 groups were not statistically significant at 6th, 9th and 12th month. One of the other main differences between those 3 groups was the total injection number which was statistically significantly lower in IVA group. In retinal pigment epithelium/choroid organ cultures, aflibercept showed a prolonged VEGF inhibition (up to 59 days), more than the other VEGF antagonists ranibizumab and bevacizumab.[19] On the other hand, there were some differences in line graphs of IVB group compared with other 2 groups. BCVA and CMT values had fluctuations at 6th month of follow-up in IVB group which may be interpreted as a sign of one more injection requirement. We also determined a statistically significant difference between IVR or IVA groups and IVB group regarding total injection number; however, Narayanan et al and Son et al did not determine any differences in total injection number of patients on ranibizumab and bevacizumab treatments at the end of 6th month.[17,18] Hikichi et al reported that with IVB injections, BCVA and CMT improved significantly at all time periods during 24 months of follow-up.[20] However, there were also fluctuations in both BCVA and CMT at 3rd month of follow-up. However, Jaissle et al[21] did not determine any fluctuations in BCVA or CMT during the bevacizumab treatment for 24 months, with a mean injection number of 3.2. Regarding our data, we can suggest that the timing of the bevacizumab injections, especially during the first 6 months of the treatment may be important in order to prevent those fluctuations.

There are some limitations of this study that should be mentioned. First is the retrospective design of the study that may result in some bias. Another drawback is the low number of patients. But these results may set light to further larger studies.

In conclusion, we have compared 3 different anti-VEGF agents in the treatment of ME due to BRVO and determined that, although at the 6th month of follow-up IVR and IVA groups had better results in BCVA and CMT values, there were not any significant differences between 3 groups at the end of the 12th month. On the other hand, total injection number was significantly lower in IVA group than other 2 groups. These results suggest that when bevacizumab, ranibizumab, and aflibercept are placed into the human eye, the biological effects of the three agents are more or less equivalent. Therefore, a study on the precise biological effects of anti-VEGF agents in the human eye should be carried out. Larger studies with longer follow-up periods are warranted to define the clinical differences of those commonly used anti-VEGF agents regarding not only efficacy but also the number of injections required.

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