Comparison of Intravitreal Aflibercept and Ranibizumab for Macular Edema Secondary to Branch Retinal Vein Occlusion

Retina Ven Dal Tıkanıklığına Sekonder Gelişen Makula Ödeminde İntravitreal Aflibercept ve Ranibizumab Karşılaştırması

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ABSTRACT

Purpose: To compare the efficacy of intravitreal injection of ranibizumab and aflibercept on the treatment of macular edema due to branch retinal vein occlusion (BRVO).

Materials and Methods: In this retrospective study; eyes with macular edema secondary to BRVO which treated with intravitreal ranibizumab (IVR) or aflibercept(IVA) and followed at least 12 months between September 2012 and March 2016 were reviewed. Mean number of injections and changes in two groups' best-corrected visual acuity (BCVA) and central macular thickness (CMT) measured by optical coherence tomography at month 1, 3, 6 and 12 were reviewed and compared.

Results: Mean BCVA improved significantly in IVR group (p=0.03, 0.04, 0.02 and 0.03 respectively) and IVA group (p=0.02, 0.04, 0.03 and 0.03 respectively ; and CMT decreased significantly in IVR group (p=0.02, 0.02, 0.02 and 0.03 respectively) and IVA group (p=0.001, 0.03, 0.01 and 0.02 respectively) at 1, 3, 6 and 12th months. Mean number of injections per eye within twelve months were 3.4±1.2 in ranibizumab group, and 2.2±1.1 in aflibercept group (p=0.03). There were no significant differences between two groups at month 12, including final BCVA, changes in BCVA, final CMT, and changes in CMT (p> 0.05)

Conclusion: Aflibercept presented similar decrease in CMT and improvement in BCVA with lesser number of injections for macular edema due to BRVO.

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

ÖZ

Amaç: Retina ven dal tıkanıklığına (RVDT) sekonder gelişen macula ödeminde intravitreal ranibizumab ve aflibercept enjeksiyonunun etkinliğinin karşılaştırılması.

Gereç ve Yöntemler: Retrospektif çalışmamızda Eylül 2012 ve Mart 2016 arasında RVDT'na sekonder gelişen macula ödemi için intravitreal ranibizumab (IVR) ve aflibercept (IVA) enjeksiyonu uygulanmış ve az 12 ay takip edilmiş hastalar değerlendirildi Ortalama enjeksiyon sayısı, iki grup arasındaki 1,3,6 ve 12. aylarda ölçülenen en iyi düzeltilmiş görme keskinliği (EDGK) ve optic koherens tomografide ölçülmüş santral maküler kalınlık (SMK) farkları değerlendirildi ve karşılaştırıldı.

Bulgular: 1, 3, 6 ve 12. aylarda ortalama EDGK; IVR (sırasıyla p=0.03, 0.04, 0.02 ve 0.03) ve IVA grubunda (sırasıyla p=0.02, 0.04, 0.03 ve 0.03) anlamlı olarak artarken SMK; IVR (sırasıyla p=0.02, 0.02, 0.02 ve 0.03) ve IVA grubunda (sırasıyla p=0.001, 0.03, 0.01 ve 0.02) anlamlı olarak azaldı. 12 ay sonunda ortalama enjeksiyon sayısı ranibizumab grubunda 3.4±1.2, aflibercept grubunda 2.2±1.1 oldu (p=0.03). 12 ay sonunda iki grup arasında son EDGK, EDGK değişimi, son SMK ve SMK değişimi açısından anlamlı fark yoktu (p> 0.05).

Sonuç: RVDT'na bağlı macula ödeminde aflibercept daha az enjeksiyon sayısı ile ranibizumaba benzer şekilde SMK'da azalma ve EDGK'da artış sunmuştur.

Anahtar Kelimeler: Retina ven dal tıkanıklığı, maküla ödemi, ranibizumab, aflibercept.

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Branch retinal vein occlusion (BRVO) is a common retinal vascular disorder which causes vision loss in elderly. Macular edema is the main cause of visual impairment [1]. BRVO is associated with some risk factors such as diabetes mellitus, senility, hypertension, smoking and hyperlipidemia those cause thickening of walls of retinal arterioles and constriction of retinal veins at crossings between arterioles and veins [2]. Luminal pressure increases due to obstruction and it results in transudation of blood and plasma which causes macular edema. Reduced capillary perfusion and retinal ischemia after vascular occlusion can cause increased vascular endothelial growth factor (VEGF) levels in vitreous and aqueous [3] and they behave as a trigger for macular edema. High intravitreal VEGF levels have been detected in eyes with BRVO [4,5]. Increased level of VEGF is associated with deterioration of the blood-retina barrier, increased vascular permeability, stimulation of endothelial cell growth and neovascularization [6,7]. Intravitreal injections of anti-VEGF seem to lower intraocular level of VEGF and decrease vascular permeability and macular edema in BRVO [8-12]. In this study; we wanted to compare the efficacy of intravitreal injection of two anti VEGF agent; ranibizumab and aflibercept for macular edema due to BRVO.

MATERIALS AND METHODS

This retrospective study involved 45 eyes of 45 patients with macular edema due to BRVO who were treated with intravitreal injections in our retina service and followed at least 12 months; between September 2012 and March 2016. Two groups were made up; group 1 received intravitreal injections of 0.5 mg/0.05mL ranibizumab (Lucentis™,GenentechInc.,SouthSanFrancisco,CA, USA) and group 2 received intravitreal injections of 2 mg/0.05 mL aflibercept (Eylea™, Bayer Pharma AG, Berlin, Germany) . Our study was appropriate to the tenets of the Helsinki Declaration. Local ethic committee approval was also obtained. Written informed consent was attained from all patients.

Inclusion criteria were macular edema associated with BRVO which were confirmed clinically and angiographically (macular leakage on fundus fluorescein angiography), visual acuity of 20/40 or worse, and central macular thickness of 300 µm or greater on optical coherence tomography (OCT). Patients were included in the study if they had no other ocular disease that affects visual acuity, no previous vitreoretinal surgery or no known allergy to fluorescein, and no bleeding disorders. They were excluded if they had macular ischemia on fundus fluorescein angiography or a brisk afferent pupillary defect. Patients with prior trauma, intravitreal injections, retinal or macular laser, or ocular surgery except uneventful phacoemulsification, patients with vitreomacular traction or epiretinal membrane, diabetic patients with diabetic retinopathy were also excluded.

In preoperative visit, detailed ophthalmic examination was performed including; baseline best-corrected visual acuity (BCVA)in Snellen chart (converted into logMAR), intraocular pressure, slit-lamp biomicroscopy of anterior segment and dilated fundoscopy. Once the patients were diagnosed with macular edema secondary to BRVO, intravitreal bevacizumab or aflibercept was administered within one week. Evaluation of central macular thickness (CMT) was made with optical coherence tomography (Zeiss Corporation. Cirrus HD model 5000, Germany) at the baseline, and postoperative monthly visits. BCVA, dilated fundoscopy, intraocular pressure and complications were noted at each postoperative examination. Baseline investigation also included fluorescein angiography (Kowa Retina Angiograph; Kowa Company Ltd., Tokyo,Japan) that was applied when felt necessary at control visits.We reviewed and analyzed the outcomes which were gained at 1st, 3rd, 6th and 12th months.

All intravitreal injections were applied under aseptic conditions in the operating room with an operation microscope. First, a topical anesthetic drop was instilled to the eye to be injected, then 5% povidone-iodine was carefully applied to the periocular area, eyelids, eyelashes, and conjunctival sac. Either of drugs (0.05 mg/0.05 cc ranibizumab or 2mg/0.05 cc aflibercept) were injected into the vitreous cavity via pars plana; 3.5 mm posterior to inferotemporal limbus in pseudophacic and 4 mm in phacic eyes, with a 30-gauge needle. Following the injection, a topical antibiotic drop as well as an ointment was administered, and the eye was patched overnight. Patients were examined the next day for possible complications and prescribed to administer a topical antibiotic eye drop for one week routinely and a topical glaucoma agent if intraocular pressure exceeds 21 mmHg.

Firstly injections were applied monthly and continued until CMT decreased to <300 µm (baseline injections). We stopped injection in case of CMT <300 µm. Retreatment was based on findings at monthly examination after injection including; optical coherence tomography including CMT more than 300 µm, or findings including persistent or recurrent macular cysts or submacular fluid that affected the visual acuity even if CMT is less than 300 µm in compliance with the PRN protocol. In cases with resistant macular edema, despite 3 monthly consecutive injections, grid laser photocoagulation was applied. Primary outcome measures included change in CFT and BCVA at month 12.

Intergroup differences were evaluated as change in CMT and BCVA compared with baseline using the unpaired t-test or Mann-Whitney rank sum test, as appropriate. Categorical variables were compared by the Fisher's exact test. Changes in BCVA and CMT in two groups were evaluated using paired t-test. Statistical analyses were performed using Statplus software (Analysoft, Walnut, USA). P values <0.05 were considered to be statistically significant.

RESULTS

At the beginning, the patients were applied no any previous treatment and there was no statistically significant difference between two groups in age (P = 0.23), duration of macular edema (P = 0.25), visual acuity (P = 0.24), lens status (P=0.11), central macular thickness (P = 0.15), and intraocular pressure (P = 0.18) (Table 1).

During all follow-up visits (1st, 3rd,6th and 12thmonths after injection), group 1 and group 2 presented statistically significant reduction of central macular thickness (Figure 1), and improvement in visual acuity (Figure 2) compared to baseline values (p<0.05 at all visits). There was no significant difference between two groups in final anatomical and functional outcomes at month 12, including final BCVA, changes in BCVA, final CMT, and changes in CMT (μ>0.05) (Table 2).

Mean number of injections per eye within twelve months were 3.4±1.2 in ranibizumab group, and 2.2±1.1 in aflibercept group (P=0.03). Seven (30%) eyes in ranibizumab group required no additional injection except the baseline injections as 10 (45.4%) eyes in aflibercept group required no additional injection except the baseline injections. Mean number of baseline injections per eye was 2.65±0.48 in

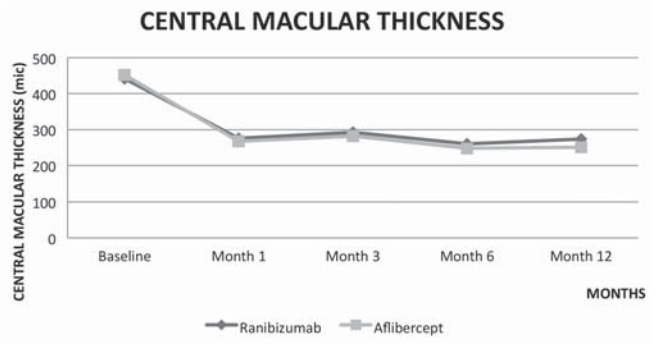

Figure 1: *Average central macular thickness during study period.*

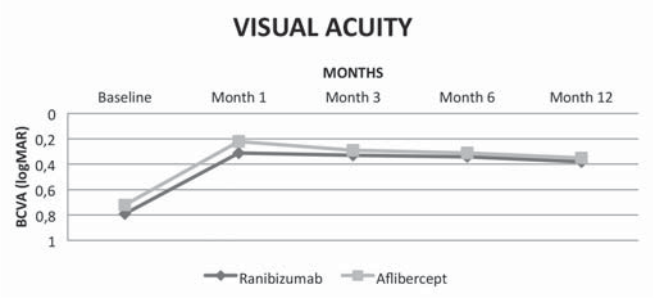

Figure 2: *Average visual acuity during study period.*

Table 1: *Demographic and clinical properties at baseline.*

	Ranibizumab (n=23)	Aflibercept (n=22)	P value
Age (years) mean ± SD	67.6 ± 8.2	65.5 ± 6.3	0.23[a]
Sex (M/F)	13/10	12/10	0.21[b]
Duration of macular edema (days)	23.4 ±5.4	26.3 ±7.4	0.25[a]
BCVA (logmar) mean±SD	0.79 ± 0.35	0.72 ± 0.44	0.24[a]
Phacic/Pseudophacic	14/9	14/8	0.18[b]
Central macular thickness (micron) mean±SD	442.4 ± 86.5	452.4 ± 72.1	0.15[a]
Intraocular pressure (mmHg)	16.2 ± 0.3	15.3 ± 0.4	0.18[a]
a: unpaired t-test b: Fisher's exact test			

Table 2: *Comparison of clinical datas between aflibercept and ranibizumab groups at month 12.*

	Ranibizumab (n=23)	Aflibercept (n=22)	P value
Final BCVA (logMAR)	0.38±0.35	0.35±0.28	0.22[a]
Change in BCVA from baseline at month 12 (logMAR)	-0.41±044	-0.37±0.38	0.35[a]
Final BCVA≥ 20/40	13/23	14/22	0.26[b]
Final CMT (mic)	273.7±79.3	251.2±69.3	0.21[a]
Change in CMT from baseline at month 12 (mic)	-168.7±78.6	-201.2±66.8	0.15[a]
Number of injection	3.4±1.2	2.2±1.1	0.03[a]
a:Mann-Whitney rank sum test b: Fisher's exact test			

ranibizumab group, and 1.68±0.40 in aflibercept group (P=0.04). Mean number of injections required after baseline injections during one year follow was 1.3±0.47 in ranibizumab group and 1.1±0.38 in aflibercept group (p=0.05). 3 eyes in aflibercept group and 4 eyes in ranibizumab group with resistant macular edema, despite 3 monthly consecutive injections, were applied grid laser photocoagulation (p>0.05).

Complications such as; uveitis, endophthalmitis, retinal detachment, vitreous hemorrhage, elevated intraocular pressure or thromboembolic events did not developed in any eye. Any acute complication related to the injection was not observed. The most common side effect was local hyperemia or subconjunctival hemorrhage at the site of injection. No systemic adverse events were occurred.

DISCUSSION

Macular grid laser was the standard treatment modality of macular edema in perfused BRVO. But the visual improvement after macular laser was limited with mean improvement of 1.33 lines of vision [13]. Intravitreal injection of anti-VEGF agents has been showed to be a promising treatment modality which presents anatomical and functional improvement. In BRVO cases, blood flow diminishes in the affected area which causes reduced availability of nutrients and oxygen. Production of VEGF is stimulated by hypoxia and it induces vessel permeability and new vessel growth. Simultaneously increased venous and capillary pressure promotes to water flow from the vessel into the tissue in accordance with Starling's law. Inhibition of VEGF and decreasing of venous congestion and the high hydrostatic pressure can reverse macular edema [14]. Several injection patterns have been applied in the studies such as two or three injections as a starting dose and a flexible injection scheme depending on visual acuity and CMT [15,16] or a scheme with reinjections until macular edema resolves completely [17]. Our treatment scheme was similar to the first one. After monthly injections until CMT decreased to <300 µm, retreatment was based on findings at monthly examinations of optical coherence tomography including CMT more than 300 µm or findings including persistent or recurrent macular cysts or submacular fluid that affected the visual acuity even if CMT is less than 300 µm.

Ranibizumab is a humanized anti-VEGF antibodyfragment that can bind all forms of VEGF-A [18,19]. Rouvas et al presented that repeated intravitreal injections of ranibizumab had showed promising short term results in visual acuity improvement and a decrease in CMT in patients with macular edema due to BRVO [9]. Risard found that monthly regimen of intravitreal ranibizumab injection presented greater reduction in macular edema and improvement in visual acuity than quarterly regimen [20]. Pieramici concluded that mean BCVA improved and mean CMT decreased after ranibizumab treatment [21].

Aflibercept is a soluble decoy consisting of components of both VEGF receptor 1 and VEGF receptor 2 fused to the Fc domain of IgG1, as ranibizumab does not have the Fc domain [22,23]. Ranibizumab blocks the receptor-binding domain of all VEGF-A isoforms as aflibercept also binds to all VEGF-B isoforms and the plasental growth factor. Aflibercept has a stronger binding affinity for VEGF-A and a longer intravitreal half-life when compared with ranibizumab, which explains the differences in the neutralizing ability against VEGF and duration of action [24,25]. Intravitreal aflibercept was noted to lower the intraocular VEGF levels in patients with neovascular age-related macular degeneration [10]. The VIBRANT study showed the efficacy of aflibercept over the macular grid laser for macular edema secondary to BRVO [11]. Gain in BCVA and decrease of CMT was significantly higher in aflibercept group than laser group. In Wang's study efficacy of aflibercept and bevacizumab in macular edema due to BRVO was compared and there was no significant difference between two agents in CMT and BCVA difference from baseline during 12 months follow-up period [26]. Tagami[27] and Wirth [28] found no significant improvement in BCVA and decrease in CMT after switching therapy from ranibizumab to aflibercept in treatment resistant patients with BRVO. But they gained significant prolonged intravitreal injection intervals after switching from ranibizumab to aflibercept. On the other hand Pfau[29] and Cohen [30] showed significant improvement in BCVA, decrease in CMT and prolonged injection interval, after switcing therapy from ranibizumab to aflibercept.

Our study is one of the rare publication comparing clinical outcomes of aflibercept and ranibizumab for patients with macular edema due to BRVO. We found, aflibercept had similar efficacy and safety with ranibizumab for patients with macular edema associated with BRVO. Significant improvement in BCVA and decrease in CMT were obtained by intravitreal apply of aflibercept and ranibizumab.

Number of injections was significantly lesser in aflibercept group. On the other hand; it was reported that, about 18–40% of cases with macular edema at baseline resolve spontaneously over time [13,31]. As, we immediately treated all of the cases at the first diagnosis of BRVO, spontaneous remission of the disease can not be eliminated. The prolonged intravitreal injection interval in aflibercept group may be caused by spontaneous remission of the disease. But it must be considered that, the same possibility is valid for ranibizumab group too.

There were limitations of our study. It was a retrospective study with a short follow-up period. A large prospective randomized study, in longer follow-up period can confirm further data about this issue. In summary, intravitreal afliber-

cept had similar efficacy with ranibizumab with less number of injections in treatment for macular edema associated with BRVO during 12-months period. No serious systemic or ocular adverse events were noted.

REFERENCES / KAYNAKLAR

1. Hahn P, Fekrat S. Best practices for treatment of retinal vein occlusion. Curr Opin Ophthalmol 2012;23(3):175-81
2. The EyeDisease Case Control Study Group. Risk factors for central and branch retinal vein occlusion. Am J Ophthalmol 1993;116:286-96
3. H Noma, H Funatsu, M Yamasaki et al. Aqueous humour levels of cytokines are correlated to vitreous levels and severity of macular oedema in branch retinal vein occlusion. Eye 2008;22:42-8
4. Noma H, Funatsu H, Yamasaki M et al. Pathogenesis of macular edema with branch retinal vein occlusion and intraocular levels of vascular endothelial growth factor and interleukin-6. Am J Ophthalmol 2005;140(2):256-61
5. Noma H, Minamoto A, Funatsu H et al. Intravitreal levels of vascular endothelial growth factor and interleukin-6 are correlated with macular edema in branch retinal vein occlusion. Graefes Arch Clin Exp Ophthalmol 2006;244(3):309-15
6. Keck PJ, Hauser SD, Krivi G, et al. Vascular permeability factor, an endothelial cell mitogen related to PDGF. Science 1989;246(4935):1309-12
7. Leung DW, Cachianes G, Kuang WJ, et al. Vascular endothelial growth factor is a secreted angiogenic mitogen. Science 1989;246(4935):1306-9
8. Campochiaro PA, Hafiz G, Shah SM, et al.Ranibizumab for macular edema due to retinal vein occlusions: implication of VEGF as a critical stimulator. Mol Ther 2008;16(4):791-9
9. Rouvas A, Petrou P, Ntouraki A, et al. Intravitreal ranibizumab (Lucentis) for branch retinal vein occlusion-induced macular edema: nine-month results of a prospective study. Retina 2010;30(6):893-902
10. Fauser S, Schwabecker V, Muether PS. Suppression of intraocular vascular endothelial growth factor during aflibercept treatment of age-related macular degeneration. Am J Ophthalmol 2014;158(3):532-6
11. Campochiaro PA, Clark WL, Boyer DS, et al. Intravitreal aflibercept for macular edema following branch retinal vein occlusion: the 24-week results of the VIBRANT study. Ophthalmology 2005;122(3):538-44
12. Yuan A, Ahmad BU, Xu D, et al. Comparison of intravitreal ranibizumab and bevacizumab for the treatment of macular edema secondary to retinal vein occlusion. Int J Ophthalmol 2014;18;7(1):86-91
13. The Branch Vein Occlusion Study Group. Argon laser photocoagulation for macular edema in branch vein occlusion. Am J Ophthalmol 1984;98(3):271-82
14. Stefánsson E.Treatment of branch retinal vein occlusion. Acta Ophthalmol 2008;86:122-3
15. Kriechbaum K, Michels S, Prager F, et al. Intravitreal Avastin for macular oedema secondary to retinal vein occlusion: A prospective study. Br J Ophthalmol 2008;92:518-22
16. Kreutzer TC, Wolf AH, Kook D, et al. Intravitreal bevacizumab for the treatment of macular oedema secondary to branch retinal vein occlusion. Br J Ophthalmol 2008;92:351-5
17. Rabena MD, Pieramici DJ, Castellarin AA, et al. Intravitreal bevacizumab (Avastin) in the treatment of macular edema secondary to branch retinal vein occlusion. Retina 2007;27: 419-25
18. Fung AE, Lalwani GA, Rosenfeld PJ, et al. An optical coherence tomography-guided, variable dosing regimen with intravitreal ranibizumab (Lucentis) for neovascular age-related macular degeneration. Am J Ophthalmol 2007;143(4):566-83
19. Ferrara N, Damico L, Shams N, et al. Development of ranibizumab, an anti-vascular endothelial growth factor antigen binding fragment, as therapy for neovascular age-related macular degeneration. Retina 2006;26(8):859-70
20. Risard SM, Pieramici DJ, Rabena MD, et al. Intravitreal ranibizumab for macular edema secondary to central retinal vein occlusion. Retina 2011;31(6):1060-7
21. Pieramici DJ, Rabena M, Castellarin AA, et al. Ranibizumab for the treatment of macular edema associated with perfused central retinal vein occlusions. Ophthalmology 2008;115(10):e47-54
22. Julien S, Biesemeier A, Taubitz T, et al. Different effects of intravitreally injected ranibizumab and aflibercept on retinal and choroidal tissues of monkey eyes. Br J Ophthalmol 2014;98(6):813-25
23. Browning DJ, Kaiser PK, Rosenfeld PJ, et al. Aflibercept for age-related macular degeneration: A game-changer or quiet addition? Am J Ophthalmol 2012;154(2):222-6
24. Stewart MW, Rosenfeld PJ. Predicted biological activity of intravitreal VEGF Trap. Br J Ophthalmol 2008;92(5):667-8
25. Papadopoulos N, Martin J, Ruan Q, et al. Binding and neutralization of vascular endothelial growth factor (VEGF) and related ligands by VEGF Trap, ranibizumab and bevacizumab. Angiogenesis 2012;15(2):171-85
26. Wang JK, Su PY, Hsu YR, et al. Comparison of the efficacy of intravitreal Aflibercept and Bevacizumab for macular edema secondary to Branch Retinal Vein Occlusion. Journal of Ophthalmology 2016;(1):1-5
27. Tagami M, Sai R, Fukuda M, et al. Prolongation of injection interval after switching therapy from ranibizumab to aflibercept in Japanese patients with macular edema secondary to branch retinal vein occlusion. Clin Ophthalmol 2017;22;11:403-8
28. Wirth MA, Becker MD, Graf N, et al. Aflibercept in branch retinal vein occlusion as second line therapy: clinical outcome 12 months after changing treatment from bevacizumab/ranibizumab-a pilot study. J Retina Vitreous 2016;23(2):20
29. Pfau M, Fassnacht-Riederle H, Becker MD, et al. Clinical outcome after switching therapy from ranibizumab and/or bevacizumab to aflibercept in central retinal vein occlusion. Ophthalmic Res 2015;54(3):150-6
30. Cohen MN, Houston SK, Juhn A, et al. Effect of aflibercept on refractory macular edema associated with central retinal vein occlusion. Can J Ophthalmol 2016;51(5):342-7
31. Rogers SL, McIntosh RL, Lim L, et al. Natural history of branch retinal vein occlusion: An evidence-based systematic review. Ophthalmology 2010;117 (6):1094-101