ORIGINAL ARTICLE

Effectiveness of Ranibizumab and Aflibercept in Branch Retinal Vein Occlusion

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ABSTRACT

Purpose: To assess functional and anatomic effectiveness of intravitreal ranibizumab and aflibercept injection given to patients with macular edema secondary to branch retinal vein occlusion.

Method: We retrospectively reviewed files of 62 treatment-naive patients with macular edema due to branch retinal vein occlusion. The best-corrected visual acuity and optic coherence parameters were recorded on months 0, 1, 3, 6 and 12 in all patients. First 3 injections were performed in a monthly manner. Pro re nata (PRN) regimen was given during follow-up.

Findings: Baseline visual acuity was 50.7±7.6 letters in ranibizumab group and 49.2±6.7 letters in aflibercept group (p=0.403). No significant difference was detected in visual acuity on month 12 between groups (p=0.313). Again, no significant difference was detected in central foveal thickness on month 12 between groups (p=0.408). Mean number of intravitreal injection was 6.2±1.4 in ranibizumab group and 5.7±1.0 in aflibercept group (p=0.174). At the end of month 12, complete recovery in subretinal detachment was detected in 16 patients (88.8%) receiving ranibizumab and 15 patients receiving aflibercept (93.8%) (p=0.525).

Conclusion: In our study, no significant difference was detected in reduction of central foveal thickness, improvement in visual acuity and number of injections between two agents.

Key Words: Aflibercept, Macular edema, Ranibizumab, Branch retinal vein occlusion.

INTRODUCTION

The branch retinal vein occlusion (BRVO) is the second most common retinal vascular disease following diabetic retinopathy. The main cause for decreased vision is macular edema in BRVO.[1, 2] More retinal area is involved as branch retinal vein occlusion occurs more proximally. Occlusion generally develops at cross-over areas of artery and vein. In a previous study, it was proposed that occlusion occur due to platelet aggregation which is caused by intravenous turbulent flow and endothelial injury resulting from compression by thickened and stiffened artery wall.[3] However, the pathogenesis hasn't been fully elucidated in branch retinal vein occlusion. The risk factors include diabetes mellitus (DM), hypertension, hyperlipidemia, atherosclerosis, hypercoagulability and glaucoma.[4-6]

In the treatment, grid laser photocoagulation (LF), intravitreal (IV) steroid and anti-vascular endothelial growth factor (VEGF) agents are used.[7-9] It was shown that VEGF is an important factor in macular edema secondary to branch retinal vein occlusion.[10-12]

Ranibizumab is a monovalent fragment of monoclonal antibody (48-kDa in weight) which involves antigen-binding Fab domain but not Fc domain. It can bind to all VEGF-A isoforms specifically.

Aflibercept is a recombinant fusion protein (115 kDa in weight) containing VEGF receptors 1 and 2 fused to Fc fragment of human IgG. It binds VEGF-A, VEGF-B and placental growth factor (PIGF) with high affinity.

In our study, it was aimed to compare visual and anatomic outcomes when two agents were used in the treatment of macular edema secondary due to branch retinal vein occlusion.

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METHOD

In the study, we retrospectively reviewed files of 62 patients treated for macular edema secondary to RVBO at Retina Clinic of Diskapi Yildirim Beyazit Training and Research Hospital. The study was approved by Ethics Committee of Diskapi Yildirim Beyazit Training and Research Hospital. The study included patients with retinal macular thickening ≥300 micron on optic coherence tomography (OCT, RTVue-XR 100 Avanti software v.6.1, Optovue, Inc., Fremont, CA, USA) and focal or diffuse leakage on fluorescein angiography. The patients with previous history of IV injection, argon laser therapy, vitreoretinal surgery and those with diabetic retinopathy, glaucoma, vitreomacular traction and tractional retinal detachment were excluded.

The patients were informed about grid laser photocoagulation, IV steroid or anti-VEGF therapies as treatment options in macular edema secondary to RVBO. Informed consent was obtained in patients accepted intravitreal ant-VEGF therapy. Intravitreal ranibizumab (Lucentis® Novartis) and aflibercept injections (Eylea® Bayer) were administered to the patients. After topical anesthesia with 0.5% proparacaine, ocular surface was prepared with 5% povidone iodine (over 3 minutes). The ranibizumab or aflibercept (0.5 mg/o.05 ml) was injected to vitreal space from 3.5 mm posterior to limbus in pseudophakic patients and 4 mm posterior to limbus in phakic patients using 30 G needle. After injection 0.3% ofloxacin (eye drop; 4x1 over 5 days) was prescribed to all patients. In first 3 months, injections were administered monthly and PRN regimen was used thereafter. At follow-up, laser photocoagulation was performed in patients with neovascularization at iris and/or disc.

The control visits were scheduled in monthly basis. In all control visits, best-corrected visual acuity was assessed using Snellen charts and transformed into logMAR. In addition, comprehensive ophthalmologic examination including SD-OCT and fundus imaging was performed. Intravitreal ranibizumab or aflibercept was administered when ≥1 line decline was detected in visual acuity or in case of central foveal thickness ≥ 300 µ. Visual acuity and central foveal thickness at baseline and on months 3, 6, 9 and 12, subretinal detachment, macular edema type (cystoid or diffuse), branch retinal vein occlusion type (ischemic or non-ischemic), demographic data and comorbid diseases (DM, hypertension) were recorded. The number of injections was also recorded.

Data were analyzed using SPSS version 20.0. Normal distribution was assessed by Kolmogorov-Smirnov test. Mean values were assessed using t test or Mann Whitney U tests. Categorical variables were assessed using Chi-square test. A p value<0.05 was considered as statistically significant.

RESULTS

No significant difference was detected in age, gender, DM, hypertension, duration and type of edema and presence of ischemia between groups (p>0.05) (Table 1). Baseline visual acuity was 50.7±7.6 letters (38-69) in ranibizumab group and 49.2±6.7 letters (35-56) in aflibercept group (p=0.403). When visual acuity at baseline and control visits

Table 1. *Demographic data.*

	Ranibizumab	Aflibercept	P value
Age	62.3±4.2	61.8±3.8	0.711
Gender Male n (%) Female n (%)	19 (59.4) 13 (40.6)	20 (60) 10 (40)	0.606
Best-corrected visual acuity, mean, (min-max) (letter)	50.7±7.6 (38-69)	49.2±6.7 (35-66)	0.264
Central foveal thickness, mean, (min-max)(micron)	506.4±39.1 (439-568)	512.9±28.9 (430-534)	0.460
Duration of macular edema, mean, (min-max) (month)	1.8±0.9 (0.5-4)	1.9±1.0 (1-4)	0.467
Hypertension n (%)	20 (62.5)	21(70)	0.598
Diabetes mellitus n (%)	7 (21.9)	8 (26.7)	0.770
Ischemic type n (%)	10 (31.2)	8 (26.7)	0.783
Subretinal detachment n (%)	18 (56.2)	16 (53.3)	0.459
Cystoid macular edema n (%)	24 (75)	24 (80)	0.764
Diffuse macular edema n (%)	8 (25)	6 (20)	

were compared, a significant improvement was detected in groups (p<0.0001) (Figure 1).

Mean visual acuity on month 12 was 69.2±6.5 letters (50-78) in ranibizumab group and 70.7±5.4 letters (48-79) in aflibercept group (p=0.313). Baseline central foveal thickness was 506.4±39.1 µm (439-568) in ranibizumab group and 512.9±28.9 µm (430-534) in aflibercept group (p=0.460).

In all control visits, a significant decrease was detected in central foveal thickness in groups (p<0.0001)(Figure 2). The central foveal thickness on month 12 was 278.8±25.4 µm (220-300) in ranibizumab group and 284±24.8 µm (230-294) in aflibercept group (p=0.408).

On month 12, visual acuity gain was 18.4 letters in ranibizumab group and 21.5 letters in aflibercept group (p=0.151). The central foveal thickness change was 227.5.±28.1 in ranibizumab group and 228.7±26.4 in aflibercept group (p=0.863).

On month 12, complete resolution in macular edema was detected in 17 patients (53.1%) in ranibizumab group and 18 patients (60%) in aflibercept group.

At baseline, there was subretinal detachment in 34 patients (54.8%). Mean visual acuity was 47.7±4.3 (38-50) in patients with subretinal detachment at baseline and 52.4±8.8 (38-69) in those without subretinal detachment (p=0.013). Central foveal thickness was 530±8.6 in patients with subretinal detachment whereas 487.7±38.0 (3439-525) in those without subretinal detachment at baseline (p<0.001). In patients with subretinal detachment, baseline visual acuity was poorer while central foveal thickness was higher. However, no significant differences were detected between group on month 12 (Table 2). When patients with central retinal detachment were compared, no significant difference was detected on month 12 between agents used (Table 3).

Mean number of intravitreal injection was 6.2±1.4 in ranibizumab group and 5.7±1.0 in aflibercept group (p=0.174).

No ocular or systemic adverse event was observed. Argon

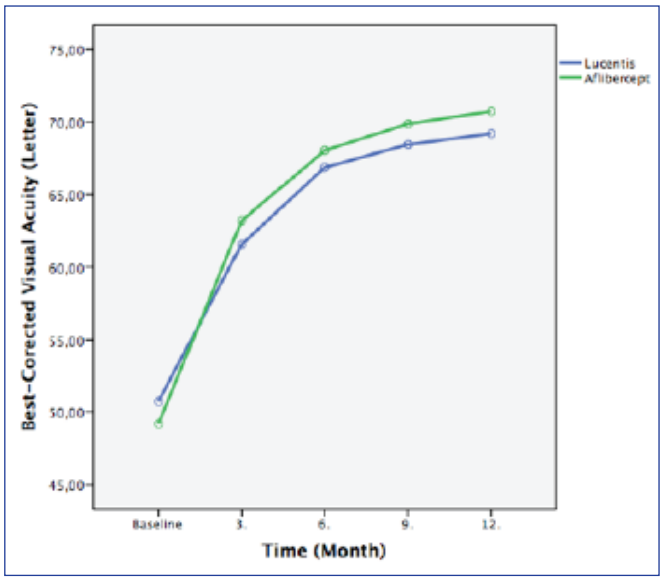

Figure 1. *Change in visual acuity according to groups.*

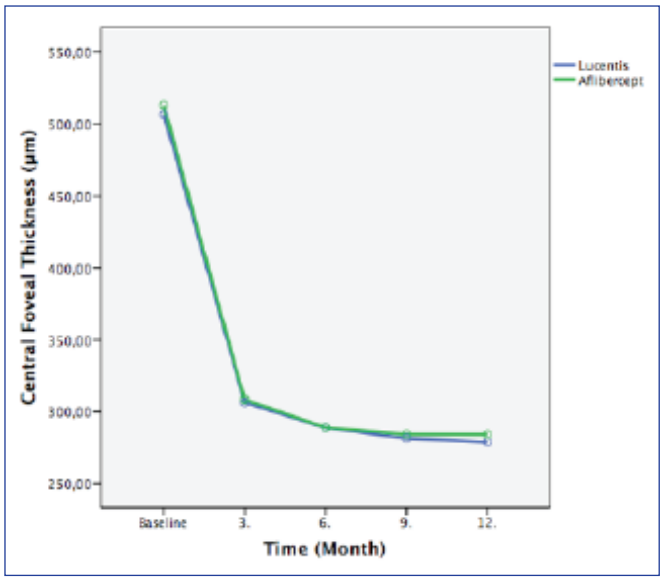

Figure 2. *Change in central foveal thickness according to groups.*

Table 2. *Patients characteristics according to presence of subretinal detachment.*

	Patients with subretinal detachment (n=34)	Patients without subretinal detachment (n=28)	P value
Visual acuity at baseline (letter)	47.7±4.3	52.4±8.8	***0.013***
Visual acuity on month 12 (letter)	71.1±3.5	68.6±7.6	0.109
Central foveal thickness at baseline (micron)	530±8.6	487.7±38	***<0.001***
Central foveal thickness on month 12 (micron)	286.4±20	276.1±28	0.111

Table 3. *Characteristics of patients with subretinal detachment.*

	Ranibizumab (n=18)	Aflibercept (n=16)	P value
Baseline visual acuity (letter)	47.8±4.1	47.6±4.6	0.889
Visual acuity on month 12 (letter)	70.6±3.7	71.6±3.4	0.419
Baseline central foveal thickness (micron)	533.3±11.1	527.1±3.7	0.054
Central foveal thickness on month 12 (micron)	285.4±19.5	287.3±22.1	0.799
Recovery in subretinal detachment on month 12 n (%)	16 (88.8)	15 (93.8)	0.525

laser therapy was used due to retinal neovascularization in 3 patients from ranibizumab group and 2 patients from aflibercept group (p=0.531). Vitrectomy due to vitreous hemorrhage was performed in a patient (ranibizumab group) not attending controls over 3 months. The patient was excluded from analysis.

DISCUSSION

The branch retinal vein occlusion (BRVO) is the second most common retinal vascular disease following diabetic retinopathy.[1,2] The main cause for decreased vision is macular edema in RVBO.[2] VEGF is the primary mediator involved in the pathogenesis of macular edema.[7] In our study, we aimed to compare effectiveness of ranibizumab and aflibercept in the treatment of macular edema secondary to branch retinal vein occlusion. During 12-months follow-up, significant improvement was detected in both ranibizumab and aflibercept group when compared to baseline.

In our study, visual gain was 18.5 letters in ranibizumab group and 21.5 letters in aflibercept group over 12-months period. In the BRAVO study, first study investigating effectiveness of ranibizumab in the treatment of macular edema secondary to branch retinal vein occlusion, visual acuity gain was 16.6 and 18.3 letters in 0.3 and 0.5 mg ranibizumab groups while it was 7.3 letters in sham injection group when results were compared on month 6.[13] Based on these results, 0.3 mg ranibizumab was introduced into treatment of RVBO.

In the VIBRANT study on aflibercept in RVBO aflibercept and laser groups were assessed during 52-weeks period. The patients in aflibercept group received 6 injections by 4-weeks intervals followed by intravitreal injections by8-weeks interval. In laser group, aflibercept was initiated at week 24 as salvage therapy. Based on results of first 24 weeks, rate of visual acuity gain≥15 letters was found to be 52.7% in aflibercept group and 26.7% in laser group. On week 52, these figures were 57.1% and 41.1% in laser and aflibercept groups, respectively.[14,15]

In a recent meta-analysis including 1743 patients, 8 randomized, controlled studies on ranibizumab and aflibercept was reviewed.[16] The rate of visual acuity gain≥15 letters was 39% in aflibercept group and 35% in ranibizumab group (p>0.05). In consistent with our study, it was found that both VEGF agents had marked effect on visual outcomes in the treatment of macular edema secondary to branch retinal vein occlusion. There was no significant difference between groups.

In our study, at the end of 12-months follow-up, mean reduction in central foveal thickness was 227 micron in ranibizumab group and 228 micron in aflibercept group (p=0.862). When foveal thicknesses on month 3, 6, 9 and 12 were compared, no significant difference was detected between ranibizumab and aflibercept. In a study comparing ranibizumab and aflibercept in the treatment of macular edema secondary to central retinal vein occlusion, Chatziralli et al. found a significant decrease in central foveal thickness on month 1 and subsequent months. They also found there was no significant difference between groups at baseline and on month 18.[17] In a study by Kaldırım et al., no significant difference was found in central foveal thickness at the end of month 6 between ranibizumab and aflibercept groups.[18] These findings are consistent with our study. On month 12, complete resolution in macular edema was detected in 17 patients (53.1%) in ranibizumab group and 18 patients (60%) in aflibercept group. In a study on central retinal vein occlusion, complete resolution rate was 50% in ranibizumab and 42.9% in aflibercept groups.[17]

In our study, we found that baseline central foveal thickness was greater and visual acuity was poorer in patients with subretinal detachment when patients with macular edema secondary to RVBO were stratified according to presence of subretinal detachment. However, on month 12, there was no significant difference in visual acuity and central foveal thickness between patients with and without subretinal detachment. There are a few studies on subretinal detachment in macular edema secondary to RVBO. In their study, Pinazo et al. assessed patients with macular edema secondary to branch retinal vein occlusion

who were treated with intravitreal ranibizumab.[19] When classified patients according to presence of serous macular detachment, authors found that patients with serous macular detachment had significantly poorer visual outcomes at the end of month 12 despite lack of marked difference in OCT parameters. They suggested that serous macular detachment could a criterion for poor prognosis. In our study, patients with subretinal detachment at baseline had poorer visual acuity and higher central foveal thickness. However, following 12-months of anti-VEGF therapy, no significant difference was detected in visual acuity and central foveal thickness between patients with or without subretinal detachment. In study using bevacizumab, Poon et al. found that baseline visual acuity was comparable but central foveal thickness was higher in patients with subretinal detachment.[20] Authors found that there was no significant difference in ceentral foveal thickness on month 6 but visual acuity was better in patients with subretinal detachment. Authors suggested that visual potential can be preserved if retinal architecture can be restored immediately before onset of mechanical photoreceptor damage secondary to fluid.

In a real-life study comparing ranibizumab and aflibercept in the treatment of macular edema secondary to central retinal vein occlusion, number of injections was found as 6.8±1.3 in ranibizumab group and 6.1±2.0 in aflibercept group during 18-months study period ($p>0.05$).[9] In the study comparing two anti-VEGF agents in the treatment of macular edema secondary to branch retinal vein occlusion, Kaldirim et al. found that mean number of injection was 3..64±0.49 in ranibizumab and 3.35±0.49 in aflibercept group during 6-months study period. Authors found no significant difference in number of injections between groups.[18] In a meta-analysis by Regnier et al., number of injections during first 6 months was 5.7 for aflibercept in VIBRANT study,[14] 4.8 in BRIGHTER study,[21] 4.9 in COMPARE-B study[22] and 5.7 in BRAVO study[16] for ranibizumab. In agreement with literature, mean number of injections was 6.2±1.4 in ranibizumab group and 5.7±1.0 in aflibercept group over one-year of follow-up in our study, indicating no significant difference.

CONCLUSION

The reductions in central foveal thickness, improvement in visual acuity and number of injections were found to be comparable between ranibizumab and aflibercept which showed marked anatomic and functional effectiveness in macular edema secondary to branch retinal vein occlusion. Both agents could be effectively used in the treatment.

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