Intravitreal Ranibizumab and Dexamethasone Implant in the Treatment of Macular Edema Secondary to Retinal Vein Occlusion: Six-month Results

Retinal Ven Tıkanıklığına Bağlı Maküler Ödem Tedavisinde İntravitreal Ranibizumab ve Dexamethasone İmplant: Altı Aylık Sonuçlar

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ABSTRACT

Objective: To assess and compare the efficacy of intravitreal ranibizumab (IR) and dexamethasone implant (IDI) in eyes with macular edema (ME) secondary to branch and central retinal vein occlusion (BRVO and CRVO).

Material and Methods: This is a retrospective study. Patients who had received IR 0.5mg/0.05mL or IDI 0.7mg for the treatment of ME due to BRVO or CRVO were included in the study. Efficacy outcomes were considered as the change from baseline in best-corrected visual acuity (BCVA) and central macular thickness (CMT).

Results: Forty three patients were included (24 BRVO, 19 CRVO) in the study. BCVA and CMT improved from baseline in all groups. In BRVO patients, increase of mean BCVA was significantly higher with IR in the 4th, 5th and 6th months, and decrease of mean CMT was significantly higher with IDI only in the 1st month. In CRVO patients, there were not significant differences in BCVA and CMT improvements compared to IR or IDI. The mean number of injections was 2.3 and 2.7 for BRVO and CRVO cases treated with IR, 1.4 and 1.3 for BRVO and CRVO cases treated with IDI in 6 months. Intraocular pressure (IOP) increase occurred in 3(33.3%) BRVO and 1(11.1%) CRVO patients treated with IDI.

Conclusion: Intravitreal ranibizumab and IDI provide significant benefits in visual acuity gain and anatomic improvement in eyes with ME secondary to BRVO and CRVO. Ranibizumab seems to be more effective in BCVA gain in BRVO patients. Increase in IOP can be observed in IDI treated patients.

Key Words: Branch retinal vein occlusion, central retinal vein occlusion, dexamethasone implant, ranibizumab, retinal vein occlusion.

ÖZ

Amaç: Santral retinal ven tıkanıklığı (SRVT) ve retinal ven dal tıkanıklığına (RVDT) bağlı maküla ödemi (MÖ) olan gözlerde intravitreal ranibizumab (İR) ve deksametazon implantın (İDİ) etkinliğini değerlendirmek ve karşılaştırmak.

Gereç ve Yöntemler: Bu çalışma retrospektif olarak yapıldı. SRVT veya RVDT'ye bağlı MÖ tedavisi için 0.5mg/0.05mL İR veya 0.7mg İDİ yapılan hastalar çalışmaya dahil edildi. En iyi düzeltilmiş görme keskinliği (EİDGK) ve santral maküla kalınlığındaki (SMK) başlangıca göre değişim etkinlik kriterleri olarak kabul edildi.

Bulgular: Kırk üç (24 RVDT, 19 SRVT) hasta çalışmaya dahil edildi. Tüm gruplarda EİDGK ve SMK başlangıca göre düzeldi. RVDT hastalarında, İR grubunda ortalama EİDGK artışı 4., 5. ve 6. aylarda istatistiksel olarak daha fazlayken, İDİ grubunda ortalama SMK azalması 1. ayda istatiksel olarak daha fazlaydı. SRVT hastalarında, EİDGK ve SMK'daki düzelme açısından İR ve İDİ grupları arasında istatistiksel olarak anlamlı fark yoktu. Altı ayda, ortalama enjeksiyon sayıları, İR ile tedavi edilen RVDT ve SRVT hastalarında 2.3 (1-4) ve 2.7 (2-4), İDİ ile tedavi edilen RVDT ve SRVT hastalarında 1.4 (1-2) ve 1.3 (1-2)'tü. İDİ ile tedavi edilen SRVT hastalarının 1 (%11.1)'inde, RVDT hastalarının 3 (%33.3)'ünde göz içi basınç (GİB) artışı görüldü.

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Sonuç: SRVT ve RVDT'ye bağlı maküla ödemli gözlerde İR ve İDİ görme keskinliği artışı ve anatomik düzelme sağlamaktadır. RVDT hastalarında İR'nin daha fazla EDGK artışı sağladığı görülmüştür. İDİ ile tedavi edilen hastalarda GİB artışı görülebilir.

Anahtar Sözcükler: Deksametazon implant, ranibizumab, retinal ven dal tıkanıklığı, santral retinal ven tıkanıklığı, retinal ven tıkanıklığı.

INTRODUCTION

Retinal vein occlusions (RVOs) are the second most common cause of retinal vascular disease after diabetic retinopathy. Retinal vein occlusions are classified as either branch RVO (BRVO) or central RVO (CRVO), depending on the location of the occlusion. Major causes of vision loss include macular edema (ME) and neovascularization with secondary vitreous hemorrhage and neovascular glaucoma in patients with RVO.[1,2]

Laser photocoagulation has been, for many years, the standard therapy for patients with ME secondary to BRVO.[3] However, laser treatment was not found to be beneficial to those with ME secondary to CRVO.[4] Recently, several studies have demonstrated the benefit of antivascular endothelial growth factor (anti-VEGF) therapies and steroids for the management of patients with ME secondary to RVO. Corticosteroids, such as triamcinolone acetonide, dexamethasone and fluocinolone have had potential to reduce edema of the macula in RVO. Anti-VEGF treatments, such as bevacizumab, ranibizumab, aflibercept and pegaptanib, inhibit VEGF-A and reduce the ME.[5,6] In BRAVO and CRUISE studies,[7,8] in the treatment of ME due to BRVO and CRVO, intravitreal ranibizumab (IR) 0.5 mg produced greater improvements in best-corrected visual acuity (BCVA) than sham in 6 months. In VIBRANT study,[9] monthly intravitreal injection of aflibercept 2 mg provided significantly greater visual benefit and reduction in central macular thickness (CMT) than grid laser photocoagulation in 6 months in eyes with ME due to BRVO. In COPERNICUS study,[10] monthly intravitreal injection of aflibercept 2 mg improved visual acuity and CMT in 6 months in eyes with ME due CRVO.

Nowadays, IR and intravitreal dexamethasone implant (IDI) are being used in the treatment of ME due to RVO. This study was conducted to assess and compare the efficacy of IR and IDI in eyes with ME secondary to BRVO and CRVO.

MATERIALS AND METHODS

We conducted a retrospective study of patients who received IR 0.5 mg/0.05 mL (Lucentis; Novartis Pharmaceuticals, Frimley, Camberley, Surrey, UK) and IDI 0.7 mg (Ozurdex; Allergan, Irvine, California, USA) for the treatment of ME due to RVO at 19 Mayıs University Hospital during the year 2013, with at least 6 months of follow-up. This study was approved by the local Research Ethics Committee and was performed according to the principles outlined in the Declaration of Helsinki.

Patients were included in the study if they received an IR or IDI for the treatment of ME due to non-ischemic BRVO or CRVO with a BCVA of ≥0.05 Snellen Line and had at least 6 months follow-up period without any treatment change. Patients were excluded if they had less than 6 months of follow-up after their first injection and had ischemia in fluorescein angiography. Baseline and follow-up visits included measurement of BCVA, slit-lamp biomicroscopy, dilated fundoscopy, intraocular pressure (IOP) measurement and measurement of the CMT with spectral-domain optical coherence tomography (SD-OCT) (Zeiss Stratus 3; Carl Zeiss Meditec, Inc., Dublin, CA). Efficacy outcomes were considered as the mean change from baseline in BCVA and the mean change from baseline in CMT. Patients were divided into 4 groups as group 1: BRVO cases treated with IR (n = 15), group 2: CRVO cases treated with IR (n = 10), group 3: BRVO cases treated with IDI (n = 9), group 4: CRVO cases treated with IDI (n = 9). Ranibizumab injections were applied as needed and if the macula was dry on OCT, re-injection was not applied. Second injection was not applied in the first 3 months after IDI even if ME was present. In BRVO patients, macular focal laser was applied to appropriate patients with persistent ME despite at least 3 IR or IDI.

To compare the changes over time in the value of CMT and BCVA, Friedman test and Wilcoxon sign test with a Bonferroni correction were used in each group. For these tests, p values <0.05 and <0.002 respectively were considered as statistically significant. While IR and IDI effects on BCVA and CMT were individually compared with each other for CRVO and BRVO: if the data was normally distributed, Student's t-test, if not, Mann-Whitney U test were used and a p value <0.05 was considered as statistically significant.

RESULTS

Twenty five (58.1%) males and 18 (41.9%) females with a mean age of 58.67±10.7 (38-80) years were included in the study. The groups did not differ in terms of demographic characteristics of the patients. Mean duration of ME before treatment was 2.2±0.4 (1-5), 3.9±1.2 (1-12), 11.4±3.1 (1-30) and 10.3±2.2 (1-21) months in group 1, 2, 3 and 4 respectively. Mean number of injections was 2.3 (1-4), 2.7 (2-4), 1.4 (1-2) and 1.3 (1-2) in group 1, 2, 3 and 4 respectively in six-month follow-up period.

Mean BCVA values increased after treatment in all groups (p <0.05). Pre-treatment mean BCVA was compared with the post-treatment each month's values , only in group 1, the difference of mean BCVA between the baseline and the 2nd, 3rd,

4th, 5th, 6th months were statistically significant (p <0.002). Average CMT values decreased significantly in all groups after treatment (p <0.05). Pre-treatment and post-treatment each month's values of mean CMT were compared: only in group 1, reduction of mean CMT from baseline in every month except month 2, was found statistically significant (p <0.002). The average BCVA values in group 1 were significantly higher than in group 3 in 4th, 5th and 6th months (p <0.05), but there was no difference between groups 2 and 4 (Table 1). The average CMT values in group 3 were higher than group 1 only in the 1st month (p <0.05), but there was no difference between groups 2 and 4 (Table 2).

The rate of patients who gained three lines or more BCVA from baseline in groups 1, 2, 3 and 4 were 60%, 40%, 33.3%, 44.4% respectively. Three patients in group 1 and 3 in group 3 received macular focal laser therapy. Laser was performed to the area of leakage and thickening on the macula with a grid photocoagulation dose. Four patients in group 3 and three patients in group 4 received second IDI. The average second IDI application time was 5.25±0.9 (4-6) and 4.6±0.6 (4-5) months in group 3 and 4, respectively.

A rise in intraocular pressure to >25 mmHg was seen in 3 (%33.3) and 1 (11.1%) patients in group 3 and 4 respectively from the first to fourth weeks after their IDI application. In these eyes, the mean IOP was 27.5±1.7 (26-30) mmHg which was managed with topical IOP-lowering medication. IOP rise was not observed in any eye treated with IR. One eye in group 2, 3, 4 were pseudophakic, the other eyes were phakic. In phakic eyes, new lens opacities were not seen in six-month follow-up period. No other ocular or systemic side effects were observed.

Table 1. *Mean best-corrected visual acuity values (Snellen Line).*

	Ranibizumab		Dexamethasone implant			
Month	**BRVO** (n=15) Mean±SD	**CRVO** (n=10) Mean±SD	**BRVO** (n=9) Mean±SD	**CRVO** (n=9) Mean±SD	**p^1**	**p^2**
0	0.25±0.05	0.24±0.07	0.20±0.04	0.13±0.04	0.51	0.18
1	0.40±0.08	0.38±0.08	0.37±0.07	0.23±0.08	0.86	0.16
2	0.41±0.08	0.36±0.06	0.34±0.05	0.23±0.07	0.42	0.21
3	0.49±0.08	0.42±0.07	0.31±0.04	0.29±0.09	0.38	0.28
4	0.53±0.08	0.47±0.09	0.31±0.05	0.30±0.1	0.03*	0.25
5	0.55±0.09	0.39±0.06	0.28±0.05	0.29±0.1	0.01*	0.38
6	0.54±0.08	0.40±0.08	0.33±0.09	0.29±0.09	0.04*	0.39

Abbreviations: BRVO = Branch retinal vein occlusion; CRVO = Central retinal vein occlusion; p1 = Wilcoxon sign test with a Bonferroni correction. Significance of comparison between ranibizumab and dexamethasone implant in BRVO patients; p2 = Wilcoxon sign test with a Bonferroni correction. Significance of comparison between ranibizumab and dexamethasone implant in CRVO patients; * = Statistically significant result.

Table 2. *Mean central macular thickness values (μm).*

	Ranibizumab		Dexamethasone implant			
Month	**BRVO** (n=15) Mean±SD	**CRVO** (n=10) Mean±SD	**BRVO** (n=9) Mean±SD	**CRVO** (n=9) Mean±SD	**p^1**	**p^2**
0	573.5±55.3	592.6±43.0	616.1±86.8	628.8±56.8	0.89	0.61
1	337.3±36.8	253.6±9.4	250.8±15.9	330.4±65.9	0.04*	0.90
2	366.7±52.8	338.8±53.7	267.6±30.8	355.7±56.8	0.35	0.97
3	291.6±36.9	360.6±43.9	316.3±60.4	371.3±73.9	0.61	0.57
4	273.3±22.9	330.6±63.2	323.1±52.2	347.6±80.9	0.33	0.71
5	267.1±21.3	360.5±50.0	338.7±53.4	446.3±86.0	0.16	0.71
6	274.3±24.4	449.2±61.8	345.6±64.1	420.4±59.1	0.59	0.37

Abbreviations: BRVO = Branch retinal vein occlusion; CRVO = Central retinal vein occlusion; p^1 = Wilcoxon sign test with a Bonferroni correction. Significance of comparison between ranibizumab and dexamethasone implant in BRVO patients; p^2 = Wilcoxon sign test with a Bonferroni correction. Significance of comparison between ranibizumab and dexamethasone implant in CRVO patients; * = Statistically significant result.

CONCLUSION

Macular edema is a major cause of vision loss in patients with RVO. Chronic ME can lead to pigmentary degeneration and photoreceptor loss with a permanent central scotoma.[1,2] Untreated BRVO can be associated with sustained loss of vision. Visual acuity of 20/200 is seen in 23% of untreated eyes at three years and 17% may lose two or more lines of visual acuity following the initial event. Results from the Branch Vein Occlusion Study showed that some patients with BRVO benefit from laser photocoagulation for ME.[3] Complications that have been associated with grid pattern laser treatment for ME include choroidal neovascularization, subretinal fibrosis, and visual field loss.[2,3] Grid pattern photocoagulation reduced the angiographic ME, but had no beneficial effect on visual acuity and is not recommended for treatment of ME due to CRVO.[4] Therefore, alternative treatments for ME have been searched.

The results of the SCORE study[11] demonstrated that there was no difference in visual acuity between eyes treated with intravitreal TA or grid pattern laser in 12 months in ME due to BRVO. SCORE study report 5[12] revealed that intravitreal TA was superior to observation for treating vision loss associated with ME secondary to CRVO. But TA has an increased rate of side effects, particularly increased IOP and cataract formation, endophthalmitis and retinal detachment.[11,12] Corticosteroids reduce vascular permeability and stabilize the blood-retina barrier. The mechanism for these effects involves inhibition of the production of inflammatory mediators and vascular permeability factors as well as stabilization of vascular endothelial cell tight junctions.[13,14]

Ozurdex received FDA approval for treatment of ME secondary to BRVO and CRVO in 2009. The GENEVA study[15] reported that IDI 0.7 mg induced significant improvements in mean BCVA in 6 months in patients with BRVO, although the difference was not significant in patients with CRVO. There was no significant difference between groups for the proportion of patients gaining at least 15 letters in 6 months. However, significant differences for this endpoint were demonstrated at months 1, 2 and 3 in patients with BRVO, and in months 1 and 2 for patients with CRVO. Joshi et al.[16] reported the peak response of IDI for BRVO and CRVO at 4 weeks, with a gain of 11 and 17 letters, respectively. The median time for the relapse of ME in these patients was 17 weeks for patients with BRVO and 18 weeks for patients with CRVO. A rise in IOP to >25 mmHg was seen in 27% eyes following their first IDI. Querques et al.[17] evaluated 33 eyes and reported that retreatment was required after 4.7±1.1 months from the first and 5.1±1.5 months from the second IDI. Twelve eyes developed a transient IOP increase between 1 and 4 months after each injection, which was successfully managed with topical IOP lowering medication. Meyer et al.[18] reported that 69% of patients treated with IDI 0.7 mg had an IOP increase of at least 5 mmHg and 50% of patients had an increase of ≥10 mmHg during the study period. Studies suggest that the optimum retreatment interval for IDI should be <6 months. In our study, retreatment was required after 5.25±0.9 months in BRVO and 4.6±0.6 months in CRVO patients. In addition, 33.3% of BRVO and 11.1% of CRVO patients treated with IDI required topical IOP lowering medication. This ratio is slightly lower than that in the literature.

VEGF plays a key role in the pathophysiology of CRVO and its sequelae. Several anti-VEGF treatments have been developed to decrease VEGF and block vascular permeability and angiogenic activity (e.g., bevacizumab, ranibizumab, pegaptanib).[2] Several retrospective and prospective case series have reported decreased retinal thickness and improved visual acuity after intravitreal treatment with bevacizumab in RVO eyes with ME.[19,20,21] But, the lack of randomized clinical trials limits the safety profile data on bevacizumab because, intravitreal use of bevacizumab is off-label.[2] In BRAVO study, in the treatment of ME due to BRVO, IR 0.5 mg produced greater improvements in BCVA than sham at 6 months and the difference was statistically and clinically significant.[7] In CRUISE[8] and ROCC[22] study, in the treatment of ME due to CRVO, IR 0.5 mg produced greater improvements in BCVA than did sham in 6 months; the difference between ranibizumab and sham was clinically and statistically significant for CRUISE but not for ROCC study. According to 12-month outcomes of BRAVO and CRUISE studies, a significant reduction in CMT and improvement in BCVA were seen in the sham group receiving IR injections after the 6th months, but improvement was not to the extent of that in the ranibizumab group.[23,24] In HORIZON trial,[25] patients who completed BRAVO and CRUISE studies were examined at least every 3 months and given an IR if they met prespecified retreatment criteria. Results of study showed a decline in vision in CRVO patients, but stable vision in BRVO patients. Results suggest that during the second year of ranibizumab treatment of RVO patients, follow-up and injections should be individualized and, CRVO patients may require more frequent follow-up than every 3 months.

In our study, when we evaluated IR and IDI separately, both caused improvement in BCVA and CMT in RVO patients. Only in patients with BRVO who were treated with IR, BCVA and CMT continued to improve after the first month. In the comparison of IR and IDI, in BRVO patients, improvement in BCVA in the 4th, 5th and 6th months and reduction in CMT in the 1st month were more prominent with IR. Efficacy of IR and IDI were similar in CRVO groups. The rate of three lines or more BCVA gain: in BRVO patients treated with IR, was 61.1% which was compatible with 60% in BRAVO study,[7] in CRVO patients treated with IR, was 40% which was similar to 47.7% in CRUISE study,[8] in BRVO and CRVO patients treated with IDI, were 33.3% and 44.4% respectively which were higher than 23% and 18% in GENEVA study.[15] Three lines or more BCVA gain was more

pronounced in patients receiving IR for BRVO and IDI for CRVO. Yumusak et al.[26] evaluated the short-term efficacy and safety of IDI, IR, and intravitreal TA in 32 eyes with ME secondary to BRVO. They found a significant improvement in BCVA in all groups. But in contrast to our results, IDI and intravitreal TA reduced CMT more than IR. In COMRADE-B study, the mean average change in BCVA was superior with IR compared to IDI from baseline to month 1 through month 6. Similarly, in our study, improvement in BCVA in the 4th, 5th and 6th months was more prominent with IR in BRVO patients. (Efficacy and safety of ranibizumab 0.5 mg versus dexamethasone 0.7 mg in branch retinal vein occlusion: 6-month results of the COMRADE-B study. By: Eter, Nicole Group Author(s): COMRADE-B. Conference: Annual Meeting of the Association-for-Research-in-Vision-and-Ophthalmology (ARVO) Location: Denver. CO Date: May 03-07, 2015 Investigative Ophthalmology & Visual Science Volume:56 Issue:7 Meeting Abstract: 5806 Published: Jun 2015). In COMRADE-C study,[27] similar efficacy was observed for IR and IDI in the months 1 and 2 in patients with ME due to CRVO. Ranibizumab maintained its efficacy throughout the study, whereas IDI declined from month 3 onward. But in this study, IDI group received only a single treatment during the 6-month study. Similar to our results, elevated IOP was reported for 5.6% of patients in the IR group and 31.9% of patients in the IDI group.

This study needs to be viewed in the light of the following limitations: it is not a prospective study, durations of ME before treatment in IR and IDI groups were different and we have a relatively small number of patients included in the study.

In conclusion, IR and IDI provide significant benefits in visual acuity gain and anatomic improvement in eyes with ME secondary to BRVO and CRVO. Ranibizumab seems to be more effective in BCVA gain in BRVO patients. Efficacy of IR and IDI implant is similar in patients with ME secondary to CRVO. Increase in IOP can be observed in IDI treated patients. Ranibizumab is safer than IDI regarding side effects.

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