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Original Article

Bevacizumab versus Dexamethasone Implant Followed by Bevacizumab for the Treatment of Macula Edema Associated with Branch Retinal Vein Occlusion

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Purpose: To compare visual and anatomical outcomes of intravitreal injections of bevacizumab and dexamethasone implant (Ozurdex) treatment for macular edema associated with branch retinal vein occlusion (BRVO).

Methods: We retrospectively reviewed patients who underwent intravitreal bevacizumab administered monthly on a pro re nata (PRN) basis (26 eyes, IVB group) or an initial 700-μg dexamethasone implant followed by a bevacizumab PRN injection (20 eyes, IVD group) for treatment of macular edema associated with BRVO. We compared best-corrected visual acuity (BCVA) and central macular thickness (CMT). We also measured ellipsoid zone recovery rate and ganglion cell-inner plexiform layer volume within the center 6 mm zone. A linear mixed model analysis was performed to compare serial changes in BCVA and CMT.

Results: Both groups showed significant improvement in BCVA and significant reduction in CMT. However, BCVA in the first month was significantly better in the IVD group (logarithm of the minimum angle of resolution, IVD group 0.21 ± 0.26 vs. IVB group 0.39 ± 0.30, p = 0.038) and the 1-month CMT was thinner in the IVD group (IVD group 270.0 ± 62.0 μm vs. IVB group 338.9 ± 122.6 μm, p = 0.028), and these trends were maintained during the 6-month follow-up. The IVD group showed more rapid macular edema resolution (p = 0.049); however, there were no significant differences in ellipsoid zone recovery rate (p = 0.268) or ganglion cell-inner plexiform layer volume between the two groups (p = 0.459).

Conclusions: There were no significant differences in final visual or anatomical outcomes between the two groups; however, initial dexamethasone implant injection followed by bevacizumab PRN injection initially showed more rapid improvement in vision and BRVO-associated macular edema resolution compared to intravitreal bevacizumab administered monthly on a PRN basis.

Key Words: Bevacizumab, Dexamethasone, Macular edema, Retinal vein occlusion

Branch retinal vein occlusion (BRVO) is the second most common major retinal vascular disease after diabetic retinopathy [1]. Most vision-threatening complications are caused by macular edema, which is known to occur in 5% to 15% of eyes every year. Without treatment, BRVO patients can experience vision improvements over time, with one-third to three-quarters of them gaining two or more lines of vision, but fewer patients experience clinically significant improvements over 20 / 40 vision [2].

Previously, grid laser photocoagulation was the standard

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of care for BRVO, based on the results of the Branch Retinal Vein Occlusion study. However, in the era of anti-vascular endothelial growth factor (anti-VEGF), ranibizumab, bevacizumab, or aflibercept has been proven to be effective for macular edema treatment due to BRVO. The BRAVO study showed that intraocular injections of 0.3 or 0.5 mg ranibizumab provided rapid and effective treatment for BRVO-associated macular edema with fewer side effects [3]. Similarly, the efficacy of bevacizumab [4-7] or aflibercept [8,9] for BRVO-associated macular edema has been shown in many studies. Steroids have also been used to treat BRVO-associated macular edema. Although intravitreal triamcinolone injections were not found to have superior efficacy over the conventional grid laser [10], this approach could be beneficial in some refractory cases [11]. Recently, a sustained release, biodegradable dexamethasone implant (Ozurdex; Allergan, Irvine, CA, USA) has been shown to be an effective treatment for retinal vein occlusion-related macular edema [12].

Anti-VEGF agents and dexamethasone implants are the most commonly used treatment modalities in clinics for BRVO-associated macular edema. However, there is still a lack of randomized controlled trials that have compared the efficacy and safety of the two therapies. A few studies have compared clinical outcomes of anti-VEGF agents with dexamethasone implants and assessed macular edema treatment secondary to retinal vein occlusion. However, these studies differ in dosing regimens or treatment protocols, making the overall outcomes more difficult to understand [13-17]. In particular, current clinical experiences recognize that, to achieve satisfactory visual and anatomic results after dexamethasone implant injections, the retreatment interval should be significantly shorter than six months [18], while some previous studies did not allow retreatment in the dexamethasone group before six months [14,16,17].

In this retrospective case series, we compared visual and anatomical outcomes between intravitreal bevacizumab injections and dexamethasone implant injections in a real-world setting. Although Ozurdex is approved for BRVO macular edema and is covered by national health insurance, it is still more expensive than bevacizumab in Korea. Thus, in this study, we compared clinical outcomes of intravitreal bevacizumab administered monthly on a pro re nata (PRN) basis and initial dexamethasone implant injection followed by bevacizumab PRN injection in treatment-naïve BRVO macular edema patients.

Materials and Methods

We retrospectively reviewed medical records of patients who underwent intravitreal dexamethasone or bevacizumab injection for BRVO-associated macular edema at Kangdong Sacred Heart Hospital and Seoul National University Bundang Hospital between July 1, 2014 and November 30, 2015. This study was approved by the institutional review board of Kangdong Sacred Heart Hospital, Seoul, Korea (KANGDONG 2016-09-010) and Seoul National University Bundang Hospital, Seongnam, Korea. All study conduct adhered to the tenets of the Declaration of Helsinki. The board waived the need for informed consent for study participation.

Patients that underwent either intravitreal injection of 1.25-mg bevacizumab (Avastin; Genentech, San Francisco, CA, USA; IVB group) or intravitreal injection of 700-μg dexamethasone implant (Ozurdex, IVD group) for BRVO-associated macular edema and who were followed-up for at least 6 months after initial treatment were included in this study. Inclusion criteria were as follows: (1) center-involving macular edema secondary to BRVO; (2) central macular thickness (CMT) greater than 350 μm; (3) no previous laser or intravitreal injection treatments for macular edema (treatment naïve cases); and (4) no signs of macula ischemia, assessed by fluorescein angiography. Exclusion criteria were as follows: (1) preexisting macular pathology, such as age-related macular degeneration, macular hole, or macular pucker; (2) diabetic retinopathy; (3) advanced glaucoma; (4) a prior history of ocular trauma; (5) prior intraocular surgery except non-complicated cataract surgery; (6) uveitis; and (7) dense cataract.

All patients underwent a comprehensive ophthalmologic examination including best-corrected visual acuity (BCVA), slit-lamp examination, dilated fundus examination, and spectral domain optical coherent tomography (OCT; Heidelberg Engineering, Heidelberg, Germany) at baseline and at every postoperative visit. Visual acuities were measured with the Snellen chart and converted to the logarithm of minimal angle resolution (logMAR) for statistical evaluation.

After initial injection, each patient was observed monthly; if there was any sign of increase or no improvement in CMT, an intravitreal bevacizumab injection was administered on a PRN basis. Due to reimbursement issues, retreatment after initial dexamethasone implant injection

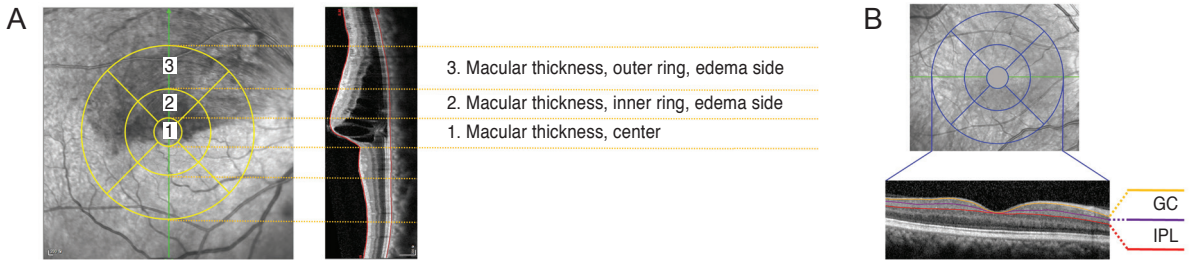


Fig. 1. Macular thickness and ganglion cell-inner plexiform layer complex (GCIPL) analysis (A) Macular thickness analysis. We measured center 1-mm average macular thickness (number 1), average macular thickness of edematous side of inner ring of Early Treatment Diabetic Retinopathy Study (ETDRS) grid (number 2), and average macular thickness of edematous side of outer ring of ETDRS grid (number 3). (B) GCIPL volume of 6-mm ETDRS grid were calculated. Area between yellow and purple line is ganglion cell (GC) and area between purple and red line is inner plexiform layer (IPL). GCIPL volume was calculated by adding the volume of GC and IPL.

was also performed with bevacizumab in the IVD group.

In this study, we quantitatively and qualitatively evaluated baseline and post-injection OCT findings and compared the results of the IVB and IVD groups. The average macular thickness was measured using built-in software. We measured average macular thickness of the center 1-mm Early Treatment Diabetic Retinopathy Study (ETDRS) grid area (CMT) and average macular thickness of the edematous side (either superior or inferior) of the inner (3 mm) and outer (6 mm) rings of the ETDRS grid (Fig. 1A). We also evaluated ganglion cell-inner plexiform layer complex (GCIPL) volume within the center 6 mm zone. The GCIPL volume was calculated at post-injection 6 months in eyes with complete macular edema resolution using built-in segmentation software that also manually readjusted for segmentation errors. The GCIPL volume was calculated by adding the volumes of the ganglion cell and inner plexiform layer (Fig. 1B). We evaluated the macular edema resolution rate and ellipsoid zone recovery rate. We also evaluated both horizontal and vertical scans crossing the fovea center and assessed whether retinal cystoid space or subretinal fluid was resolved and if the outer retinal ellipsoid zone was intact. We defined the ellipsoid zone as recovered when it was clearly visible without any discontinuity and the underlying interdigitation zone was discernible [19]. Two independent observers (SYM and YKK) measured and evaluated OCT parameters. When discrepancies arose, the two observers discussed their evaluations and came to an agreement.

Continuous variables were compared using Student's *t*-test, and categorical variables were compared using a chi-square or Fisher's exact test. Serial changes in visual outcome and CMT were compared between the IVB and IVD groups using a linear mixed model. In these models, study group and time were fixed effects, and patient identification number was used as the categorical random effect. The rates of macular edema resolution and ellipsoid zone recovery were compared between the two groups using log-rank tests. Statistical analyses were performed using statistical software (Stata ver. 13.0; Stata Corp., College Station, TX, USA), and statistical significance was defined as a $p < 0.05$.

Results

During the study period, 45 patients received intravitreal bevacizumab injections, and 36 patients underwent intravitreal dexamethasone implant injections for BRVO-associated macular edema. After excluding those with previous laser or intravitreal injection treatments (29 patients) and short follow-up period (6 patients), 46 eyes of 46 patients (26 in the IVB group and 20 in the IVD group) were finally included in this study. Baseline demographics and clinical characteristics of the patients are summarized in Table 1. There were no significant differences in terms of age, sex, underlying diabetes or hypertension, baseline BCVA, CMT, or ellipsoid zone status between the IVB and IVD groups.

Treatment with bevacizumab and dexamethasone implants both resulted in a significant improvement in BCVA and a significant reduction in CMT over the 6- month follow-up period (all $p < 0.001$, linear mixed modeling). However, BCVA improvement was much faster in the IVD group during the first month and after initial treatment (significant group × time interaction during the first month;

Table 1. Baseline demographics and clinical characteristics of patients with macular edema associated with BRVO treated with intravitreal bevacizumab or intravitreal dexamethasone implant

	Bevacizumab (n = 26)	Dexamethasone (n = 20)	*p*-value*
Age (yr)	60.7 ± 8.1	60.8 ± 10.1	0.950
Male	15 (58)	10 (50)	0.604
Diabetes mellitus	4 (15)	3 (15)	> 0.999
Hypertension	7 (27)	6 (30)	0.818
Pseudophakia	1 (4)	1 (5)	> 0.999
Follow up period (mon)	14.9 ± 5.7	12.6 ± 5.0	0.150
BRVO location			0.293
Superior	17 (65)	10 (50)	
Inferior	9 (35)	10 (50)	
Baseline BCVA (logMAR)	0.53 ± 0.34	0.60 ± 0.28	0.458
Baseline CMT (μm)	566.6 ± 221.8	500.3 ± 137.8	0.248
Baseline ellipsoid zone status†			0.293
Fair	9 (35)	10 (50)	
Poor	17 (65)	10 (50)	

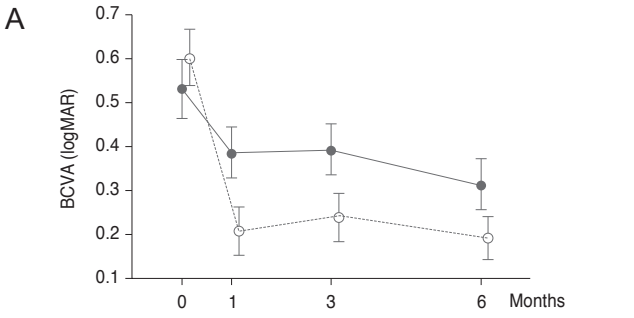
Values are presented as mean ± standard deviation or number (%).
BRVO = branch retinal vein occlusion; BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; CMT = central macular thickness.
*Student's *t*-test and chi-square test or Fisher's exact test used for continuous and categorical variables, respectively; †Ellipsoid zone status was fair when the ellipsoid zone was clearly visible, without any discontinuity, and the underlying interdigitation zone was discernible.

β-coefficient = -0.25; 95% confidence interval [CI], -0.36 to -0.14; $p < 0.001$) (Fig. 2A). The BCVA 1-month post-injection was significantly better in the IVD group compared to the IVB group (logMAR, IVD group 0.21 ± 0.26 vs. IVB group 0.39 ± 0.30, $p = 0.038$) (Table 2), and this trend was maintained during the 6-month follow-up (group difference after 1 month; β-coefficient = -0.19; 95% CI, -0.35 to -0.03; $p = 0.021$) (Fig. 2A). Similarly, the 1-month CMT was thinner in the IVD group (IVD group 270.0 ± 62.0 μm vs. IVB group 338.9 ± 122.6 μm, $p = 0.028$) (Table 2), and this trend was also maintained during the 6-month follow-up (group difference after 1 month; β-coefficient = -74.94; 95% CI, -139.20 to -10.67; $p = 0.022$) (Fig. 2B). However, there were no significant differences in final BCVA or CMT between the two groups 6 months post-injection (Table 2). The average macular thickness of the edematous side in the inner ETDRS 3-mm grid ring was thinner in the IVD group (group difference after 1 month; β-coefficient = -80.60; 95% CI, -145.89 to -15.31; $p = 0.016$) (Fig. 2C); however, there were no significant differences in average macular thickness of the edematous side in the ETDRS 6-mm grid outer ring between the two groups (group difference after 1 month; β-coefficient = -35.77; 95% CI, -90.06 to 18.52; $p = 0.197$) (Fig. 2D).

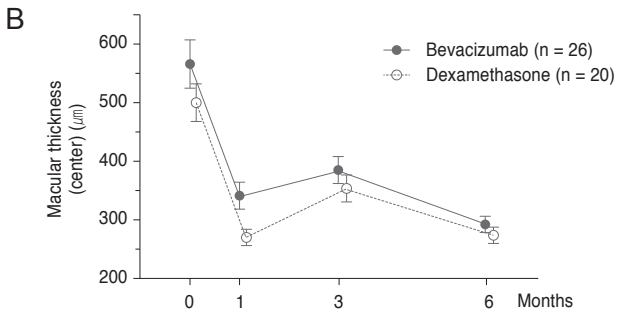
The IVD group showed more rapid macular edema resolution after treatment compared to the IVB group ($p = 0.049$, log-rank test) (Fig. 3A). The IVD group also showed a trend toward faster ellipsoid zone recovery by 6 months, with 15 of 20 patients (75%) in the IVD group and 14 of 26 patients (54%) in the IVB group showing ellipsoid zone recovery; however; there was no significant difference in overall ellipsoid zone recovery rate ($p = 0.373$, log-rank test) (Fig. 3B). On GCIPL volume analysis, there were no significant differences in average GCIPL volume in the center 6-mm zone between the two groups (Table 2).

During the 6 months of follow-up, the IVB group received a mean of 2.0 ± 1.2 additional injections, while the IVD group received a mean of 0.8 ± 0.7 additional injections ($p < 0.001$) (Table 2). The mean interval between the initial and second injections was 4.1 ± 0.8 months in the IVD group.

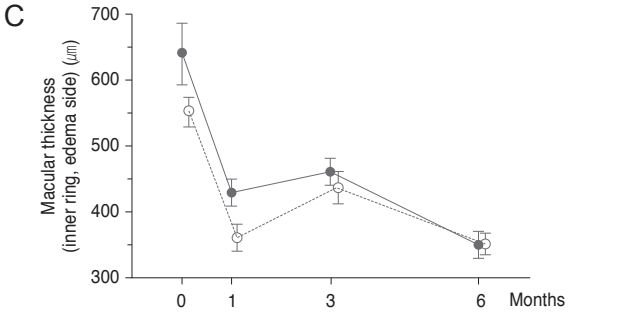
There were no cases of severe adverse events such as endophthalmitis, retinal breaks, or retinal detachment during the study period. There were also no significant changes in intraocular pressure or severe cataract progression that led to cataract surgery.



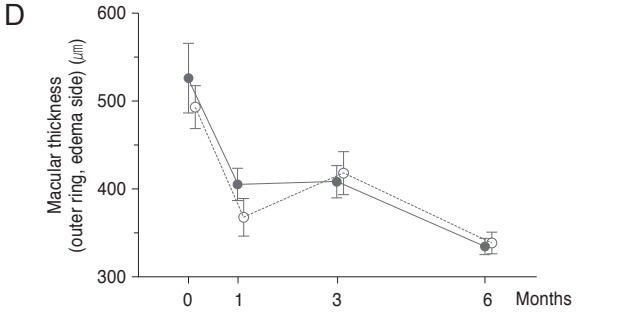
Overall	Coef.	*p*-value	Before 1 mon	Coef.	*p*-value	After 1 mon	Coef.	*p*-value
Group	-0.04	0.561	Group	0.07	0.417	Group	-0.19	**0.021**
Time	-0.03	**< 0.001**	Time	-0.14	**< 0.001**	Time	-0.02	**0.024**
Group × time	-0.02	0.089	Group × time	-0.25	**< 0.001**	Group × time	0.01	0.284



Overall	Coef.	*p*-value	Before 1 mon	Coef.	*p*-value	After 1 mon	Coef.	*p*-value
Group	-73.14	**0.028**	Group	-66.28	0.136	Group	-74.94	**0.022**
Time	-34.58	**< 0.001**	Time	-226.77	**< 0.001**	Time	-11.65	**0.020**
Group × time	9.63	0.271	Group × time	-3.58	0.950	Group × time	10.17	0.177



Overall	Coef.	*p*-value	Before 1 mon	Coef.	*p*-value	After 1 mon	Coef.	*p*-value
Group	-85.89	**0.008**	Group	-86.01	-0.060	Group	-80.60	**0.016**
Time	-38.21	**< 0.001**	Time	-207.34	**< 0.001**	Time	-18.43	**< 0.001**
Group × time	15.54	0.078	Group × time	-14.99	0.796	Group × time	14.51	0.061



Overall	Coef.	*p*-value	Before 1 mon	Coef.	*p*-value	After 1 mon	Coef.	*p*-value
Group	-35.63	0.220	Group	-32.92	0.425	Group	-35.77	0.197
Time	-26.56	**< 0.001**	Time	-119.53	**< 0.001**	Time	-15.64	**0.001**
Group × time	7.85	0.220	Group × time	-4.87	0.906	Group × time	7.95	0.179

Fig. 2. Comparison of serial changes of (A) best-corrected visual acuity (BCVA) and (B) center, (C) inner ring, and (D) outer ring macular thickness. between bevacizumab and dexamethasone implant treatment groups and the results of linear mixed model analysis. Tables underlying the graphs represent the results of linear mixed modeling, which was performed three times, overall, during the first month after first injection and between 1 and 6 months after first injection (group and time were fixed effects, patient identification number was a categorical random effect). Significant group and time interaction (group × time) imply different rates of change between the groups. Coef. = β coefficient.

Discussion

In this study, we compared visual and anatomical outcomes between bevacizumab and dexamethasone implant injections for BRVO-associated macular edema. Both groups achieved significant improvement in BCVA and CMT reduction. However, the IVD group achieved more rapid improvement in BCVA and CMT than the IVB group and showed significantly better BCVA and thinner CMT at 1 month post-injection compared to the IVB group. This better early visual and anatomical outcome tendency in the IVD group was maintained at 1 month and through 6 months post-injection.

Although several studies have compared clinical outcomes of intravitreal anti-VEGF and dexamethasone implant injections for BRVO-associated macular edema, there is a lack of randomized controlled clinical trial evidence that compares the efficacy and safety of the two treatments. Furthermore, different dosing regimens or treatment protocols make it more difficult to interpret the results of different studies. In studies that did not allow re-treatment before 6 months in dexamethasone implant in-

jection groups, clinical outcomes tended to be worse in the dexamethasone groups compared to anti-VEGF groups. Kim et al. [16] reported that the IVB group showed a trend toward greater BCVA gain and a significant central foveal thickness decrease at 6 months compared to the IVD group. The central foveal thickness of the IVD group began to deteriorate after 5 months in the IVD group. In a recent randomized clinical trial that compared ranibizumab and dexamethasone implant injections for central retinal vein occlusion-associated macular edema, the ranibizumab group maintained its efficacy, while that of the dexamethasone implant group decreased from month 3. The dexamethasone group received only a single treatment during the 6-month study [17].

In comparison, early clinical outcomes tended to be better in studies that allowed dexamethasone injection groups to undergo retreatment before 6 months. Chiquet et al. [15] compared visual and anatomical outcomes in treatment-naïve patients with retinal vein occlusion-associated macular edema, and they concluded that early visual acuity recovery was better in the dexamethasone group, although there were no significant differences in CMT changes or long-term visual and anatomical outcomes. In their study, retreatment was allowed in the dexamethasone group after 4 months. This group included both central retinal vein occlusion and BRVO cases, and this could be a reason for the different early anatomical outcomes compared to our results. In another small, prospective pilot study that allowed retreatment in the dexamethasone group after 4 months, the dexamethasone group showed more rapid functional and anatomical improvement compared to the bevacizumab group, while no significant difference was found between the two groups at the 6-month follow-up visit, which is similar to our results [13]. In our study, the mean interval between initial and second injections in the IVD group was 4.1 months. In the BEVORDEX study, the CMT peaked at 4 and 8 months after initial injection [20]; based on these results, the efficacy of the dexamethasone implant injection does not appear to last for more than 6 months; therefore, close follow-up and retreatment should be considered before 4 to 5 months after initial treatment in dexamethasone-treated patients. In this study, we did not perform the initial three monthly injections in the IVB group, and this might have been associated with inferior initial efficacy in the IVB group. However, the IVD group showed better initial clinical outcomes 1 month after initial treatment, and the mean total injection number in the IVB group during the 6 months was 3.0 ± 1.2, which was not significantly different from other studies [13,16]. Further prospective studies that compare the efficacy of anti-VEGF and dexamethasone injections for BRVO-associated macular edema and that allows early re-

Table 2. Clinical and anatomical outcome comparisons between bevacizumab and dexamethasone implant treatment groups

	Bevacizumab (n = 26)	Dexamethasone (n = 20)	*p*-value*
BCVA (logMAR)			
1 mon	0.39 ± 0.30	0.21 ± 0.26	0.038
3 mon	0.39 ± 0.30	0.24 ± 0.25	0.074
6 mon	0.31 ± 0.29	0.19 ± 0.22	0.123
Central macular thickness (μm)			
1 mon	338.9 ± 122.6	270.0 ± 62.0	0.028
3 mon	383.7 ± 120.4	351.6 ± 115.8	0.367
6 mon	282.0 ± 66.9	273.1 ± 66.2	0.346
6-mon-macular edema resolution rate	21 (81)	18 (90)	0.446
6-mon-ellipsoid zone recovery rate	14 (54)	15 (75)	0.141
GCIPL volume (6-mm ETDRS grid, mm^3)	1.93 ± 0.18 (n = 19)	1.88 ± 0.20 (n = 15)	0.459
No. of additional injections within 6 mon	2.0 ± 1.2	0.8 ± 0.7	< 0.001

Values are presented as mean ± standard deviation or number (%).
BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution; GCIPL = ganglion cell-inner plexiform layer complex; ETDRS = Early Treatment Diabetic Retinopathy Study.
*Student's *t*-test and chi-square test or Fisher's exact test used for continuous and categorical variables, respectively.

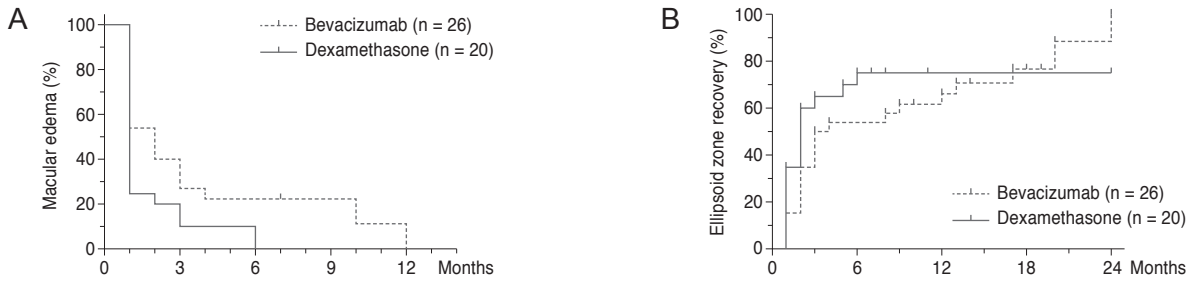


Fig. 3. Comparison of macular edema resolution and ellipsoid zone recovery rate between bevacizumab and dexamethasone implant treatment groups. (A) Macular edema resolution rate. Dexamethasone group showed significantly rapid resolution of macular edema ($p = 0.049$, log-rank test). (B) Ellipsoid zone recovery rate. There were no significant differences in ellipsoid zone recovery rate between two groups ($p = 0.373$, log-rank test).

treatment in the IVD group are needed.

In the GENEVA study, the improvement in visual acuity outcomes persisted longer than the reduction in retinal thickness in the retinal vein occlusion patients treated with dexamethasone implants [21]. In the BEVORDEX study, additional reduction of CMT in dexamethasone implant-treated eyes did not translate to better visual outcomes in diabetic macular edema patients [20]. These results suggest that anatomical parameters other than macular thickness might be associated with visual outcomes. In this study, we evaluated ellipsoid zone status, which is known to be associated with visual outcomes after retinal vein occlusion treatment [22,23]. The IVD group showed a greater rapid macular edema resolution rate and a trend of faster ellipsoid zone recovery compared to the IVB group. However, there was no statistically significant difference in overall ellipsoid zone recovery rate between the two groups. Although this was a retrospective study, and some of the ellipsoid zone recovery time points might have been inaccurate due to irregular follow-up intervals, especially after 12 months, it seems that the two treatments did not have significantly different results regarding photoreceptor recovery rate after macular edema resolution. We also assessed GCIPL volume of the patients, which is known to be thinner in BRVO eyes, especially in ischemic BRVO cases [24,25]. In our study, there was no significant difference in the center 6 mm zone GCIPL volume between the IVB and IVD groups. Therefore, there were no significant differences in neuronal toxicity of bevacizumab or dexamethasone treatment. However, we evaluated GCIPL volume 6 months after initial treatment, when macular edema was resolved, to ensure valid retinal layer segmentation; thus, the number of patients included in this analysis was small.

There was no significant intraocular pressure elevation or cataract formation in the IVD group during the study period. Due to reimbursement issues, we performed retreatment with bevacizumab in the IVD group. The average number of retreatment in the IVD group was less than one, and it seems that bevacizumab also worked well to maintain early visual and anatomical improvements following dexamethasone treatment. Initial dexamethasone injection followed by PRN anti-VEGF retreatment could provide a good treatment option to alleviate dexamethasone-related ocular complications. However, steroid-related cataract generally appears in the second year after initial treatment; thus, additional long-term follow-up study is needed to evaluate steroid-related ocular adverse events [26].

This study was limited by its retrospective design, small case numbers, and short follow-up period. However, we compared two drugs in a real-world setting, such that retreatment was allowed in the IVD group without injection interval limitation, and retreatment was also performed with bevacizumab in the IVD group with consideration of national reimbursement issues. We also performed a comprehensive analysis of anatomical outcomes in patients, including ellipsoid zone recovery rate, GCIPL volume, and CMT, which are known to be associated with visual outcomes in BRVO patients.

In conclusion, both bevacizumab and dexamethasone implant injections showed good visual and anatomical outcomes in patients with BRVO-associated macular edema. Although there were no significant differences in final visual or anatomical outcomes, initial dexamethasone implant injection followed by bevacizumab PRN injection

initially showed more rapid improvement in vision and macular edema resolution compared to intravitreal bevacizumab administered monthly on a PRN basis. Further long-term studies with adequate prospective design and a large number of patients are needed to confirm the results of this study.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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