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RETINAL DISORDERS

Intravitreal triamcinolone acetonide versus bevacizumab therapy for macular edema associated with branch retinal vein occlusion

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Abstract
Purpose To compare visual outcomes after intravitreal triamcinolone acetonide (IVTA) injection and intravitreal bevacizumab (IVB) administration for treatment of macular edema associated with branch retinal vein occlusion (BRVO).
Methods A retrospective comparative case series of 134 consecutive patients that were treated with either IVTA or IVB for macular edema caused by BRVO. Visual acuity at baseline and 1, 3, 6, 9, and 12 months, and central macular thickness measured by OCT at baseline and 1, 3, 6, and 12 months. The time to recurrence of macular edema after treatment was also analyzed.
Results Visual acuity (Snellen equivalent) improved significantly from 0.87 logMAR (0.14) to 0.49 logMAR (0.33) in the IVTA group, and from 0.91 logMAR (0.13) to 0.45 logMAR (0.36) in the IVB group 12 months after injection ($p<0.001$). Central macular thickness decreased significantly from 491.0 μm to 255.8 μm in the IVTA group, and from 477.4 μm to 218.9 μm in the IVB group 12 months after injection ($p<0.001$). In between-group comparisons, neither visual acuity ($p=0.892$) nor macular thickness ($p=0.612$) improvements were statistically significantly different. In the IVTA-all group, recurrence of macular edema occurred in 7.6% of patients at a mean of 12.6 months postoperatively, and the average number of injections was 1.08. In the IVB-all group, 26.0% of patients suffered recurrences at a mean of 5.3 months after treatment, and received a mean of 1.89 injections. Recurrence was more frequent in the IVB group compared to the IVTA group (Kaplan–Meier survival analysis log-rank test, $p<0.0001$).
Conclusions IVTA and IVB injections were similarly effective for improving visual acuity in patients with macular edema secondary to BRVO. However, the IVTA group showed longer mean improvement duration and less disease recurrence, and required fewer injections than the IVB group.

Keywords Bevacizumab · Branch retinal vein occlusion · Triamcinolone acetonide

Introduction

Branch retinal vein occlusion (BRVO) is the second most frequent cause of blindness among disorders of the retinal vasculature, following diabetic retinopathy [1-3]. The most important factor in central visual loss resulting from BRVO is macular edema, which has been reported in 60% of patients [4, 5].

Until now, laser photocoagulation according to the Branch Vein Occlusion Study (BVOS) conducted in 1984 was the only evidence-based effective treatment strategy for macular edema in patients with BRVO [3]. According to the SCORE study comparing standard care to intravitreal injection of triamcinolone, there was no difference in visual acuity at 12 months between the standard care group and the triamcinolone group, and rates of adverse events were higher in the triamcinolone group [6]. Although grid laser photocoagulation is considered the standard care, a laser is not suitable if there is retinal hemorrhage. However, many

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patients with macular edema secondary to BRVO complain of a decrease in visual acuity and metamorphopsia prior to the clearing of retinal hemorrhage. Unlike the laser, injection of intravitreal triamcinolone acetonide (IVTA) or intravitreal bevacizumab (IVB) can be safely performed even in the state of retinal hemorrhage. Thus, IVTA and IVB injections have been widely used in the treatment of BRVO from the early stages. However, only a few comparative studies on IVTA and IVB treatment for this common disease have appeared to date [7, 8].

IVTA injection was previously widely used in the treatment of macular edema associated with BRVO, but IVB injection has largely displaced IVTA treatment from the time when IVB became popular as a treatment modality for age-related macular degeneration (AMD) [9, 10]. The biological activities of triamcinolone acetonide and bevacizumab in the vitreous differ [5, 10-13] and drug efficacies might thus also be distinct.

The purpose of our study was to compare visual acuities in patients with macular edema attributable to BRVO, treated with IVTA and IVB. In addition, we compared objective measurements of central macular edema, maintenance period, and recurrence incidence after treatment.

Materials and methods

Study population and inclusion criteria

We retrospectively reviewed the medical records of 191 eyes from 191 consecutive patients with macular edema secondary to BRVO who were treated at least one intravitreal injections of 4 mg of TA between 1 January 2004 and 31 June 2008, or 1.25 mg of bevacizumab between 1 November 2005 and 31 June 2008, and had at least 3 months of follow-up, at the Vitreoretinal Service Clinic of the Yonsei University Eye and ENT Hospital, Seoul, Korea.

This retrospective study was approved by our Institutional Review Board. The potential risks and benefits were discussed with all patients before they received injections, and all patients read and signed informed consent forms.

Patients were included in the study if they had: (1) logMAR visual acuity (VA)≥0.3 (Snellen equivalent ≤20/40), (2) macular edema resulting from BRVO, as confirmed by diffuse fluorescein leakage on angiography (FA), or diffuse thickening of the retina on optical coherence tomography (OCT), with central macular thickness ≥250 μm, and (3) a minimum follow-up period of 3 months. The exclusion criteria were: (1) prior pars plana vitrectomy, (2) intraocular surgery, including and cataract extraction, within 6 months prior to the treatment; (3) laser treatment including sectorial scatter photocoagulation or grid macular photocoagulation within 6 months prior to treatment; (4) IVTA injection within 6 months prior to IVB treatment; (5) the presence of coexisting ocular disease causing macular edema (i.e., diabetic macular edema, central retinal vein occlusion, pseudophakic cystoid macular edema, or uveitis); or (6) the presence of comorbid ocular conditions that might affect VA.

To compare visual acuity (VA) and central macular thickness (CMT), 134 eyes from 134 consecutive patients who had at least 12 months of follow-up were included in this study. For Kaplan–Meier survival analysis of macula edema recurrence, all 191 eyes from 191 consecutive patients were included.

Baseline information included demographic data: (1) the duration of BRVO from onset of symptom to the date of first IVTA or IVT, history of cataract surgery, hypertension, sectorial scatter photocoagulation, or grid macular photocoagulation, (2) VA, (3) intraocular pressure, (4) central macular thickness, and (5) fluorescein angiographic evidence of capillary nonperfusion.

The main outcome measures included changes in VA, central macular thickness measured by OCT, and recurrence. Corrected VA was determined using the modified ETDRS chart by well-trained ophthalmic technicians with consistent methods. Ophthalmic examinations including 90+ diopter noncontact lens slit-lamp biomicroscopy, FA, color fundus photography, and third-generation OCT tests (OCT3 instrument; Stratus Zeiss Humphrey, San Leandro, CA, USA) were performed on all patients to evaluate macular edema. OCT scans were obtained using dilated pupils. Each macula was scanned along both horizontal and vertical meridians using the standard linear crosshair pattern, with scan lengths of 4 mm or 6 mm centered through the fovea. Central macular thickness (CMT) was measured manually in all scans, using the caliper tool of the OCT software, by a masked evaluator (YJB). The recurrence time was defined as the duration from the end date of previous injection to the date of relapse of macular edema with decreased visual acuity. Intraocular pressure (IOP) was assessed by Goldmann applanation tonometry.

Data on VA and IOP were collected at baseline and at 1, 3, 6, 9, and 12 months after treatment, and CMT data were collected at baseline and at 1, 3, 6, and 12 months.

Intravitreal injection

The IVTA patients received intravitreal injections of 4 mg/0.1 ml TA (40 mg/ml; Tamceton®; Hanall Pharmaceutical, Seoul, Korea) and the IVB group received intravitreal injections of 1.25 mg/0.05 ml bevacizumab. The TA was prepared by decanting. After removal of supernatant, we put BSS to make 0.1 ml solution containing 4 mg of TA. Injections were performed after application of 0.5% proparacaine drops (Alcaine®; Alcon Laboratories, Fort Worth, TX,

USA) under sterile conditions. Drugs were injected 3.5 mm posterior to the limbus through the inferotemporal pars plana using a 30-gauge needle. Correct intravitreal suspension localization and optic nerve head perfusion was confirmed by indirect ophthalmoscopy.

Patients were followed up at 1 week after injection, monthly for the first 3 months, and then every 3 months thereafter. Patients were retreated with the same drug, in the case that the increase in CMT≥100 μm measured by OCT was associated with a vision loss or symptomatic metamorphopsia. The same criteria of retreatment was used in both groups.

Statistical analysis

Baseline demographic and clinical parameters were compared using Student's *t*-tests for continuous variables and chi-square tests for categorical variables. Comparisons of differences between follow-up and baseline data within a treatment group at each follow-up timepoint and between-group comparisons at particular timepoints were performed using repeated measurement analysis. Normalized distributions of measured data were confirmed by Kolmogorov–Smirnov analysis. The time to recurrence of macular edema after treatment was analyzed by Kaplan–Meier survival analysis. Patients who received additional intravitreal injections of TA or bevacizumab, grid laser photocoagulation, cataract surgery, or who were lost to follow-up during the study period, were considered to be censored.

Statistical analyses utilized SAS®, version 9.13 (SAS, Cary, NC, USA). The level of statistical significance was set at $p<0.05$. For within-group comparisons, the significance level was adjusted to take into account the number of comparisons to baseline. The family-wise error rate was controlled.

Results

Baseline characteristics

This study included 191 eyes of 191 consecutive patients with macular edema secondary to BRVO (Table 1). Among these, 134 consecutive patients had been followed up more than 12 months, and 87 (64.9%) underwent IVTA (IVTA group) and 47 (35.1%) IVB injections (IVB group). The time between the onset of symptoms and the first injection averaged 3.57 months in the IVTA group and 3.44 months in the IVB group. No statistically significant difference in anatomical or functional outcomes was noted between the two groups, except in follow-up period and total number of injections. The mean follow-up period for the IVTA group was longer than that for the IVB group (23.2±10.0 months vs 17.1±5.3 months, $p=0.001$). In contrast, more injections were given to the IVB group than to those receiving IVTA (2.44±1.47 injections vs 1.09±0.28, $p=0.0001$).

To compare the recurrence of macular edema after treatment, all 191 patients were included for survival analysis, and the mean follow-up for the IVTA-all group was longer than that for the IVB-all group (19.3± 11.5 months vs 11.1±6.5 months, $p<0.001$).

Visual acuity

Comparisons of VA between baseline and at follow-up are presented in Fig. 1 and Table 2 for each treatment group. Within 1 month after the first injection, the VA logMAR (Snellen equivalent) improved in both groups (0.87±0.31 [0.14±0.17] to 0.50±0.39 [0.32±0.31] in the IVTA group vs 0.91±0.31 [0.13±0.17] to 0.54±0.39 [0.29±0.31] in the IVB group). These significant changes continued through the entire 12-month follow-up period. Thus, within each treatment group, paired comparisons revealed significant VA improvements at every follow-up visit (repeated measurement analysis, all $p<0.005$). Between-group comparisons revealed no significant difference in baseline VA or VA measurements at any follow-up visit (repeated measurement analysis, $p=0.892$).

Central macular thickness

CMT levels at baseline, and at 1, 3, 6 and 12 months, are shown in Fig. 2. After 12 months, in 62 eyes of IVTA group and 39 eyes of IVB group, an OCT test was performed. Significant CMT improvement was observed in both groups 1 month after the first injection (from 491.0±135.0 μm to 241.6±74.9 μm in the IVTA group, and from 477.4±212.6 μm to 245.4±103.1 μm in the IVB group). These significant changes continued throughout 12 months of follow-up (repeated measurement analysis, all p values<0.001 except p value=0.002 at 3 months in both group). Between-group comparisons revealed no difference in CMT as measured by OCT, either at baseline or at any follow-up visit (repeated measurement analysis, $p=0.612$).

Recurrence of macular edema

The mean ± SD follow-up duration was 19.3±11.5 months for the IVTA–all group and 11.1±6.5 months for the IVB-all group. After treatment, macular edema recurred in 7.6% of patients ($n=9$) in the IVTA-all group and in 26.0% ($n=19$) in the IVB-all group. The recurrence time from previous injection was a mean of 12.6±6.4 months in the IVTA-all group and 5.3±3.1 months in the IVB-all group (log-rank test, $p<0.0001$). Kaplan–Meier survival analysis of macular edema recurrence in the IVTA-all and IVB-all

Table 1 Baseline characteristics of patients

Variable	IVTA group (n=87)	IVB group (n=47)	P value	IVTA-all (n=118)	IVB-all (n=73)	P value
Age, mean ± SD, years (range)	62.02±8.59 (45–81)	63.32±12.0 (38–89)	0.635[b]	61.37±8.56 (41–81)	63.28±12.04 (33–89)	0.371[b]
Gender no., male:female (%)	40:47 (34.8/65.2)	19:28 (40.4:59.6)	0.190[c]	39:79 (33.1/66.9)	28:45 (38.9:61.1)	0.623[c]
HTN (%)	42 (47.8)	19 (40.4)	0.401[c]	49 (41.5)	30 (41.1)	0.946[c]
Duration of BRVO (months)[a]	3.57±3.39	3.44±2.50	0.893[b]	2.60±2.28	2.95±1.38	0.573[b]
Lens no.			0.406[c]			0.610[c]
Phakic (%)	84 (95.7)	43 (91.5)		114 (96.6)	69 (94.5)	
Pseudophakic (%)	3 (4.3)	4 (8.5)		4 (3.4)	4 (5.5)	
Previous treatment Hx. no. (%)						
Grid laser photocoagulation	6 (6.9)	4 (8.5)	0.054[c]	6 (5.1)	4 (5.5)	0.921[c]
Sectorial scatter photocoagulation	6 (6.9)	4 (8.5)	0.054[c]	8 (6.8)	6 (8.2)	0.779[c]
IVTA injection	0 (0)	8 (17.0)		0 (0)	8 (11.0)	
Subtenon TA injection	2 (2.3)	0 (0)		2 (2.1))	0 (0)	
Baseline VA, mean ± SD, logMAR (range, median)	0.87±0.31 (0.3–2, 0.7)	0.91±0.31 (0.4–2, 0.8)	0.512[b]	0.83±0.52 (0.3–2, 0.7)	1.0±0.71 (0.4–2, 0.9)	0.121[b]
Baseline IOP, mean ± SD, mmHg	14.3±2.9	14.7±4.3	0.750[b]	14.4±2.7	14.5±3.7	0.823[b]
Baseline CMT, mean ± SD, μm (range, median)	491.0±135.0 (275–739, 480)	477.4±212.6 (250–876, 419)	0.827[b]	522.9±160.7 (275–739, 489)	483.3±169.2 (250–876, 421)	0.305[b]
Macula perfusion status			0.628[c]			0.290[c]
Ischemic (%)	5 (5.7))	6 (12.8)		5 (4.2)	7 (9.6)	
Non-ischemic (%)	82 (94.3)	41 (87.3)		113 (95.8)	66 (90.4)	
Mean follow-up, months, mean ± SD (range)	23.2±10.0 (12–51)	17.1±5.3 (12–29)	0.001[b]	19.3±11.5 (3–51)	11.1±6.5 (3–29)	<0.001[b]
Total no. of injections, mean ± SD (range)	1.09±0.28 (1–2)	2.44±1.47 (1–6)	0.0001[b]	1.08±0.28 (1–2)	1.89±0.98 (1–6)	<0.001[b]
Subtype of FA			0.792			0.631
Ischemic (%)	45 (51.7)	23 (48.9)		60 (51.1)	34 (45.7)	
Exudative (%)	42 (48.3)	24 (51.1)		58 (48.9)	39 (54.3)	

SD=standard deviation; HTN=hypertension; VA=visual acuity; BRVO: branch retinal vein occlusion; CMT=central macular thickness; IOP=intraocular pressure; IVB=intravitreal bevacizumab; IVTA=intravitreal triamcinolone acetonide

[a] from onset of symptom to the date of first IVTA or IVB

[b] Student's t-test; [c] Chi-square test

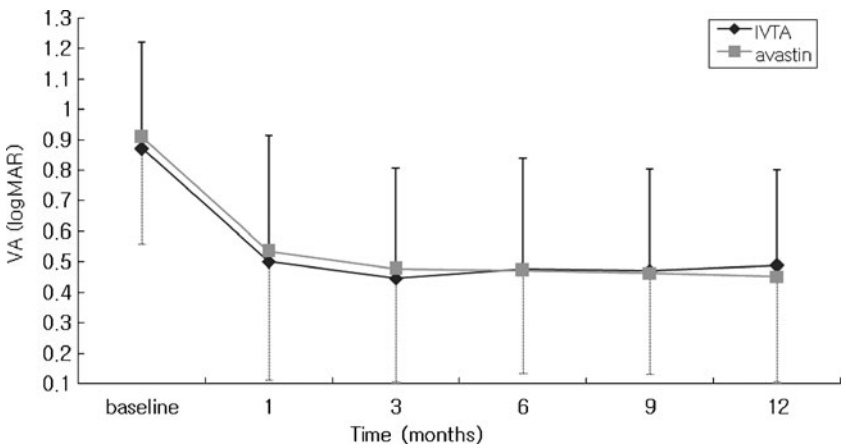

Fig. 1 Change in logMAR visual acuity (VA) of all patients after treatment. Significant improvements in logMAR VA were noted in both the intravitreal triamcinolone acetonide (IVTA) and intravitreal bevacizumab (IVB) groups at every follow-up visit (repeated measurement analysis, all p values<0.005). Between-group comparisons revealed no difference in VA from baseline at any follow-up visit after treatment (repeated measurement analysis, p=0.892)

Table 2 Change in logMAR visual acuities of all patients

	IVTA group (n=87)		IVB group (n=47)		P value
Time (months)	Mean ± SD	P value[a]	Mean ± SD	P value[a]	0.892[b]
Baseline	0.87±0.31		0.91±0.31		
1	0.50±0.43	0.002	0.54±0.38	0.029	
3	0.45±0.34	<0.001	0.48±0.33	0.001	
6	0.48±0.34	<0.001	0.47±0.37	0.002	
9	0.47±0.34	<0.001	0.46±0.34	0.001	
12	0.49±0.42	0.0036	0.45±0.35	0.002	

IVB=intravitreal bevacizumab; IVTA=intravitreal triamcinolone acetonide; SD=standard deviation

[a] Baseline vs follow-up measures within a group; repeated measurement analysis; significance level 0.05

[b] IVTA group vs IVB group; repeated measurement analysis; significance level 0.05

groups showed a consistently higher recurrence incidence in the IVB group than in the IVTA group (log-rank test, $p<$ 0.0001; Fig. 3).

Of nine patients exhibiting recurrent macular edema of IVTA-all group, two patients refused re-injection despite documented recurrence at 11 months and 19 months respectively, and were not treated further. Seven patients who received re-injection were followed-up for 5.3 months (3–10 months) after the last recorded re-injection, and macular edema was healed in these patients by the time of the last follow-up.

All 19 patients exhibiting recurrent macular edema of IVB-all group received re-injections; follow-up duration was 8.5 months (3-21 months) after the last recorded re-injection, and macular edema was healed by the time of the last follow-up. The mean interval to recurrence after 1st, 2nd, and 3rd re-injection was 3.86 months (2–5 months), 6 months (4–8 months), and 5.5 months (5–6 months) respectively. The proportion of eyes exhibiting recurrent macular edema decreased with every re-injection. In 34 eyes which received a single injection, 12 eyes (35.3%) showed recurrent macular edema. In 13 eyes which received two injections, four eyes (30.8%) showed recurrent macular edema. In eight eyes which received three injections, two eyes (25.0%) showed recurrent macular edema. In five eyes which received four injections, one eye (20.0%) showed recurrent macular edema.

Complications

In the present study, none of the possible complications (pseudo-endophthalmitis, endophthalmitis, central artery occlusion, or retinal detachment) were observed.

Comparisons of IOP between baseline and at follow-up were investigated for each treatment group. No statistically significant difference in IOP was noted between the two groups. At 1 month after the first injection, the IOP increased in the IVTA group (14.33±2.90 mmHg to 15.82±

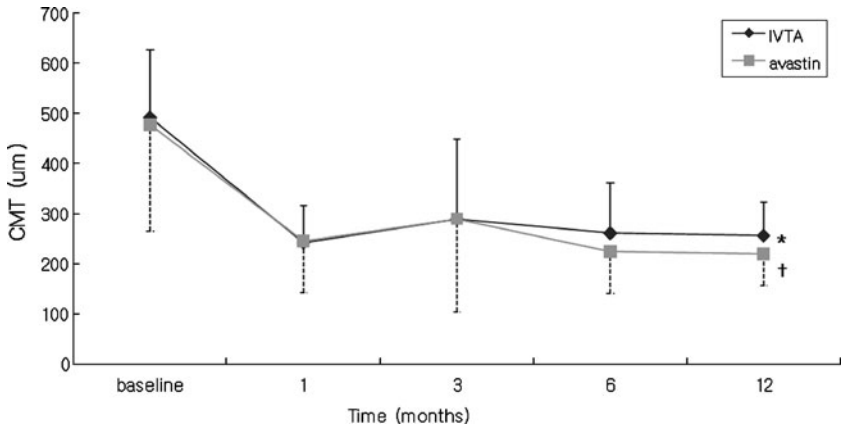

Fig. 2 Change in central macular thickness (CMT) after treatment. A significant CMT improvement was observed at every follow-up visit in both groups (repeated measurement analysis, all p values<0.001 except p value=0.002 at 3 month in both groups). Between-group comparisons revealed no difference in CMT from baseline at any follow-up visit (repeated measurement analysis, p=0.612).The asterisk (*) indicates the data of 62 eyes, and the cross(†) indicates the data of 39 eyes

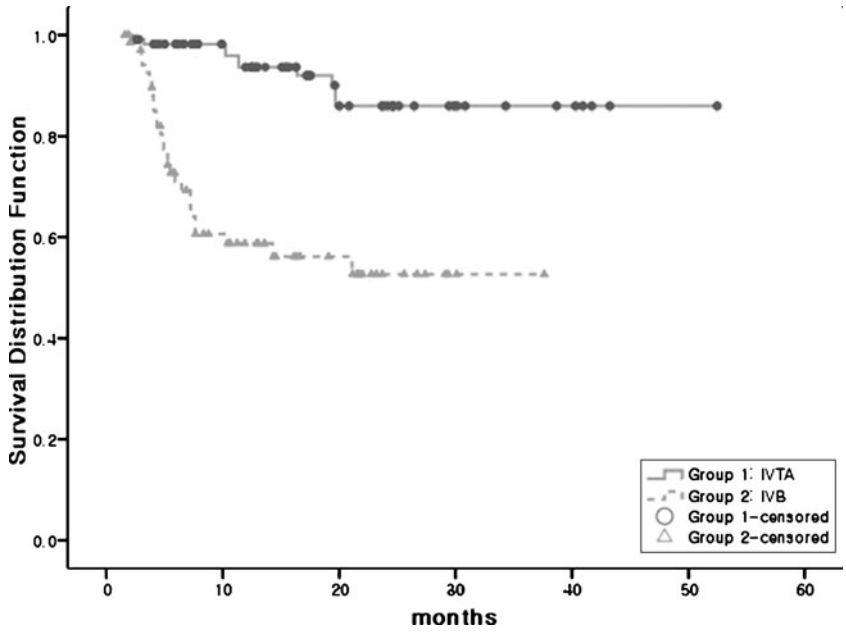

Fig. 3 Kaplan–Meier survival analysis of macular edema recurrence. Kaplan–Meier survival curves of IVTA-treated patients and those receiving IVB, showing the cumulative proportions of dry macula at various time intervals. The between-curve difference was statistically significant by the log-rank test ($p<0.0001$)

3.82 mmHg, repeated measurement analysis $p=0.03$) in the IVTA group. IOP rose above 25 mmHg in three eyes (3.4%) 1 week following IVTA treatment, but was well-controlled by anti-glaucoma drugs.

Three patients (3.4%) underwent cataract surgery because of aggravated lens opacity after IVTA treatment and had VA improvement. One of them underwent cataract surgery at 6 months after treatment, and was excluded from the study for comparing VA and CMT. However, two patients underwent cataract surgery more than 1 year after treatment, and were included in the study.

Discussion

Since IVTA and IVB injections have been widely used in the treatment of BRVO, a comparison of these two treatment modalities is very informative and meaningful to the clinician. Most studies, however, have not directly compared the two drugs, had a limited patient follow-up period, and long-term treatment efficacy remained unclear. The present study was designed to directly compare the long-term efficacy of IVTA and IVB injections for treatment of macular edema secondary to BRVO.

In the current study, patients treated with IVTA or IVB injections for macular edema secondary to BRVO between 1 January 2004 and 31 June 2008 were categorized into two groups. At our institute, IVTA injection had been performed until November 2005, and after that date IVB injection became the usual treatment for macular edema secondary to branch retinal vein occlusion. As a result, the present study was comparative even though the work was retrospective and nonrandomized in design.

The work shows that IVTA and IVB injections demonstrate similar efficacy in terms of visual outcomes in patients with macular edema secondary to BRVO. However, the mean number of re-injections was 1.08 in the IVTA-all group and 1.89 in the IVB-all group. Therefore, multiple injections of IVB should be considered to maintain efficacy. Moreover, IVTA treatment resulted in less recurrence and longer-term improvement.

It has been known that IVTA injections present more side-effects, such as increases in IOP and cataract aggravation, than IVB injections [14-16]. Because aggravating lens opacity during follow-up is a drawback of IVTA compared to IVB, we did not exclude two patients who underwent cataract surgery more than 1 year after treatment when between-group comparisons were made. These patients were censored after cataract surgery on the Kaplan–Meier survival analysis. Only a few cases showed side-effects, and they were managed. Therefore, IVTA injections can be performed safely with attention paid to side-effects.

In this study, logMAR VA (Snellen equivalent) improved significantly from 0.87 (0.14) to 0.49 (0.33) in the IVTA group, and from 0.91 (0.13) to 0.45 (0.36) in the IVB group, 12 months after injection. These results are in line with previous studies. Ozkiris et al. [17] found an improvement from 1.01 to 0.62 when IVTA injections were used to treat BRVO, and Lihteh et al. [18] reported that the logMAR VA fell from 1.1 to 0.59 when IVB injections were used. Although both Avitable et al. [19] and Oh et al. [20] reported much better VA improvement using IVTA than in the present study (logMAR VA changes from 0.82 to 0.23 and 1.07 to 0.3, respectively), the cited studies had short follow-up periods.

Prager et al. [21] reported that a mean of eight injections were required to diminish macular edema secondary to

BRVO in their recent prospective study. In contrast to their report, patients achieved similar improvements of visual acuities with only 2.44 injections in our current study (0.2 to 0.4 vs 0.13 to 0.36). The difference of injection rate between the two studies is about 3 times. In their trial, all patients received initial three injections at monthly intervals. We did not perform the three initial monthly injections, because we believe that macular edema secondary to retinal vascular disorders such as branch retinal vein occlusion or diabetes should be treated with different protocols from those used for AMD. Since we did not routinely perform the initial three injections, two of the initial injections were not necessary in our treatment strategy. There are still, on average, three less injections in our study than their study. We think this discrepancy is caused by a different re-injection criteria between the two studies. They repeated injections if OCT showed evidence of intraretinal or subretinal fluid. Our retreatment criteria were based on treating surgeons′ discretion, but it has been very consistent.

We further investigated a subgroup of patients with angiographically perfused macula, as pre-existing macular ischemia may affect treatment efficacy.[18] Before treatment, five eyes (5.7%) in the IVTA group and six (12.8%) in the IVB group showed macular ischemia by FA. After excluding these eyes, between-group comparisons continued to show no significant VA difference from baseline at any follow-up visit (repeated measurement analysis, $p=0.796$).

Some eyes in our study were previously treated with other modalities for macular edema secondary to BRVO. In the IVTA group, 12 eyes (13.8%) had received grid or sectorial photocoagulation and two had been treated with subtenon TA injections before IVTA use. In the IVB group, eight eyes (17.0%) received grid or sectorial scatter photocoagulation and eight (17.0%) had been treated with IVTA injections before the first IVB injection. Thus, we further investigated the subgroup of patients who had received IVTA or IVB as initial treatments. In this subgroup, there was again no between-group VA difference (repeated measurement analysis, $p=0.591$). Furthermore, we compared the visual acuity outcome and CMT thickness at 12 months for the subgroups of IVTA pretreated eyes and naïve eyes in IVB groups (47 eyes). The significant VA logMAR improvement was observed in both IVTA pretreated eyes and naïve eyes 12 months after the first injection [from 0.93±0.23 to 0.47±0.25 ($p<0.001$) in IVTA pretreated eyes vs 0.90±0.31 to 0.44±0.29 ($p<0.001$) in naïve eyes]. Between-group comparisons revealed no significant difference in baseline VA or VA measurements at any follow-up visit (repeated measurement analysis, $p=0.561$). The CMT improvement was also observed in both groups 12 months after the first injection (from 411±125.0 μm to 234.7±76.3 μm in the IVTA pretreated eyes vs 491.4±201.6 μm to 215.4±103.1 μm in naïve eyes). There was again no between-group CMT thickness difference (repeated measurement analysis, $p=0.898$).

In our present study, recurrent macular edema developed in 7.6% of patients, and the average time to recurrence after treatment was 12.6 months in the IVTA-all group. In contrast, 26.0% of the IVB-all group suffered recurrence of macular edema, and the mean recurrence time was 5.3 months.

Previous studies have shown that the half-life of intravitreal TA (4 mg) was 18.6 days in nonvitrectomized eyes, and the mean retention time of TA in the vitreous of BRVO patients was 3–5 months [12, 22, 23]. On the other hand, the aqueous half-life of 1.5 mg intravitreally injected IVB in nonvitrectomized eyes was only 9.82 days [24]. To treat age-related macular degeneration, three consecutive monthly IVB injections are usually given because of the short IVB half-life [25, 26].

The brief duration of IVB therapeutic effects and the frequent recurrence of macular edema created a need for repeated bevacizumab injections. The problem with such injections is that they not only expose patients to a cumulative risk of injection-related complications such as endophthalmitis, intraocular hemorrhage, retinal detachment, and glaucoma, but also make treatment more expensive compared to IVTA.

Patel et al. [27] reported that although IVTA was effective to improve VA and reduce macular edema in patients with retinal vein occlusion, the drug provided only temporary benefits, and no sustained visual improvement was seen after 12 months of follow-up. However, our Kaplan–Meier analysis of macular edema recurrence indicates that the IVTA maintenance period for macular edema secondary to BRVO may be over 3 years. With IVB, the response is only temporary in many patients, necessitating re-injections [13, 18]. Recurrence of macular edema at an average of 2.1 months has been reported, [10] and Stahl et al. [28] also found early recurrence after IVB treatments, recommending that reinjection should be considered 6 weeks after initial injection, based on OCT and VA data. Our Kaplan–Meier survival analysis also revealed shorter maintenance periods and higher recurrence rates in the IVB-all group than in the IVTA-all group (log-rank test, $p<0.0001$).

Our results show that the two drugs are of equal efficacy in VA treatment and decrease CMT to 1 year of follow-up, but IVTA injections are superior in efficacy when the risks and cost burden of repeated injections are considered.

Recently, Cheng et al. [8] also reported that the therapeutic effects of IVTA showed no significant differences compared with IVB with regard to anatomical and functional outcomes.

We further investigated subgroup analysis of visual acuity outcome at 12 months by the state of involving

fovea, the subtype of FA (ischemic or exudative), and the type of macular edema (cystoid or diffuse). Between-subgroup comparisons revealed no significant difference in baseline VA and VA at 12 months (data not shown).

We acknowledge the shortcomings of this nonrandomized retrospective study.

FA images were not available for many patients during the follow-up or at the time of remission; therefore, the leakage change during the follow-up was not included in our measured outcome. This could be one of the limitations of retrospective design.

However, as explained above, IVTA injections were performed only until November 2005; IVB injections have been the treatment of choice in our Institute since that time. This naturally randomized the two groups, and we were able to compare the efficacies of IVTA and IVB injections, despite the retrospective nature of the study. Furthermore, we were able to minimize the effects of confounding factors, by subgroup analysis excluding patients with ischemic macular conditions or who had received previous treatment.

In conclusion, our results suggest that IVTA may be more efficacious than IVB when economic benefits and potential risks are considered, although both IVTA and IVB injections are effective and safe treatment options for improvement of VA and to decrease macular thickness in patients with macular edema secondary to BRVO. Moreover, according to the SCORE study, there was no difference in visual acuity at 12 months between the standard care versus IVTA [6]. Therefore, we may conclude that grid laser photocoagulation remains the gold treatment for BRVO until now.

A randomized, prospective, comparative clinical trial of IVTA and IVB for treatment of macular edema secondary to BRVO is required to accurately compare the two treatment modalities.

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