

## Treatment of Branch Retinal Vein Occlusion Induced Macular Edema in Treatment-naïve Cases with A Single Intravitreal Triamcinolone or Bevacizumab Injection

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**Background:** To evaluate the effects of a single intravitreal injection of triamcinolone acetonide (ivTA) or bevacizumab (ivBe) on visual acuity and central macular thickness (CMT) in cases of macular edema secondary to branch retinal vein occlusion (BRVO) for eyes that are treatment-naïve.

**Methods:** This consecutive, retrospective, nonrandomized, clinical interventional study included 83 patients (83 eyes) with macular edema secondary to BRVO who received single ivTA (25 patients) or ivBe (24 patients) injections, or no treatment (controls, 34). The main outcomes included CMT measurements using optical coherence tomography (OCT) and best-corrected visual acuity (BCVA).

**Results:** CMT decreased significantly from baseline at 4, 8, 12 and 24 weeks after treatment ( $p < 0.05$ ) in both the intravitreal groups and the control group. BCVA improved significantly from baseline at 4 and 8 weeks after treatment among the ivTA group ( $p < 0.05$ ) and at 4, 8 and 12 weeks after treatment among the ivBe group ( $p < 0.05$ ). Comparing CMT between the groups, significant differences were found between ivTA and control groups and ivBe and control groups at the 4- and 8- week checkpoints ( $p < 0.05$ ). Significant differences were found in BCVA only between ivBe and control groups at the 8-week checkpoint ( $p = 0.049$ ). No significant differences were found for CMT and BCVA between the ivBe and ivTA groups ( $p > 0.05$ ) at any checkpoint after treatment. No patient experienced immediate procedure-related complications or any obvious systemic adverse events in either the ivTA group or the ivBe group. Delayed complications included steroid induced ocular hypertension in eight eyes (32%) and development of posterior subcapsular cataracts in five eyes (28%) in the ivTA group.

**Conclusions:** Both the ivTA and ivBe therapies were beneficial short-term treatment options for the treatment of macular edema secondary to BRVO. However, the ivBe treatment appears to be safer and less prone to adverse side effects such as ocular hypertension and cataract compared with ivTA therapy.

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**Key words:** triamcinolone acetonide, bevacizumab, branch retinal vein occlusion, macular edema, optical coherence tomography

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The complications of branch retinal vein occlusion (BRVO), including capillary non-perfusion, macular edema, intraretinal hemorrhage, surface wrinkling retinopathy, and revascularization with resulting vitreous hemorrhage, have been described in the literature.<sup>(1-3)</sup> Visual acuity is affected by all of these conditions, but visual loss is frequently ascribed to macular edema.<sup>(4)</sup> Macular edema is a vision-threatening complication of retinal vein occlusion and a therapeutic challenge for the ophthalmologist.

Currently, the only proven therapy for macular edema secondary to BRVO is argon laser treatment of the macula.<sup>(5)</sup> Although this treatment results in a statistically significant improvement in vision, the clinical outcomes are often disappointing. Injection of intravitreal triamcinolone acetonide (ivTA) is currently being used successfully 'off-label' for the treatment of macular edema from various causes. Several investigators have reported encouraging results with ivTA in cases of macular edema secondary to refractory diabetic macular edema,<sup>(6,7)</sup> uveitis,<sup>(8)</sup> central retinal vein occlusion,<sup>(9,10)</sup> idiopathic juxtafoveal telangiectasis,<sup>(11)</sup> refractory pseudophakic macular edema,<sup>(12,13)</sup> and BRVO.<sup>(14-17)</sup>

Bevacizumab (Avastin; Genentech) is an agent that inhibits the effects of vascular endothelial growth factor (VEGF).<sup>(18)</sup> Originally approved by the US Food and Drug Administration for the treatment of colon cancer, bevacizumab has been used 'off-label' to treat a variety of ocular diseases including choroidal neovascularization secondary to age-related macular degeneration.<sup>(19-21)</sup> More recently, bevacizumab was offered as an alternative treatment for patients with retinal vein occlusion.<sup>(22-25)</sup> These studies indicated that there were anatomic (by ophthalmic examination, optical coherence tomography [OCT] and/or fluorescence angiography [FAG]) and visual acuity improvements with limited adverse side effects in short-term studies of RVO patients receiving intravitreal bevacizumab (ivBe).

In view of these promising preliminary results, a larger number of patients than in previous studies, including a control group were enrolled in our study.<sup>(14-17,22-25)</sup> Our study also enrolled BRVO treatment-naïve patients to evaluate whether a single ivTA or ivBe injection could be therapeutically useful in decreasing central macular thickness (CMT) and increasing visual acuity among patients with BRVO induced macular edema, as revealed by third

generation OCT.

## METHODS

All patients were evaluated and treated by five experienced retina specialists. The study inclusion criterion was the presence of recent-onset (within 3 months) macular edema associated with BRVO that caused visual impairment. The exclusion criteria were any prior retinal laser photocoagulation therapy (scatter retinal photocoagulation or grid photocoagulation), intravitreal injection or any vitreoretinal surgery. The diagnosis of BRVO was based on clinical examination and macular edema by OCT findings. The criterion for ischemic BRVO was an area of capillary non-perfusion that was more than five disc diameters, as visualized with FAG. Eyes with ocular hypertension, glaucoma, or retinal diseases other than BRVO were excluded from this study.

The possible treatment options for BRVO with macular edema were explained to potential study candidates and this was done in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. No institutional review board approval was required due to the retrospective study design. These options included macular grid laser therapy, ivTA therapy, ivBe therapy (since August 2006), and continued observation. The nature of the "off-label" use of bevacizumab and its potential side effects, particularly the possibility of thromboembolic events and uveitis, was extensively discussed with the patients prior to treatment. Patients with any recent history of myocardial infarction or cerebral vascular accident and uncontrolled hypertension were not offered bevacizumab. Patients receiving ivTA or ivBe treatment were specifically informed about the nature of the intravitreal injection treatment and the potential risk of endophthalmitis, uveitis, cataract, ocular hypertension, and retinal detachment. At this point, patients who chose macular grid laser therapy were excluded from the study.

This consecutive, retrospective, nonrandomized clinical interventional study took place from January 2005 through December 2007 at Chang Gung Memorial Hospital, Kaohsiung, Taiwan and included 83 patients (83 eyes) with unilateral BRVO that showed marked macular edema upon OCT examination (Model 3000, Carl-Zeiss Instruments, Dublin, CA, U.S.A.). A minimum of 24 weeks of follow-up

was required for inclusion in this case series. Twenty-five patients (25 eyes) were selected without randomization and placed in the ivTA group; they received one single intravitreal injection of 4 mg (0.1 ml) of crystalline triamcinolone acetonide (Kenacort-A). Another 24 patients (24 eyes), who received one single intravitreal injection of 2.5 mg (0.1 ml) of bevacizumab (Avastin 25 mg/ml; Genentech) as therapy, were placed in the ivBe group. The remaining 34 patients (34 eyes), who selected observation, did not receive any intravitreal therapy and were regarded as the control group.

During this trial, in order to obtain data on a longer duration of effectiveness for both the ivTA and ivBe therapies in terms of decreased central macular thickness, we only included those eyes where an intravitreal dose of 2.5 mg bevacizumab was used instead of the more commonly used dose of 1.25 mg. Meanwhile, all eyes included needed to match the following criteria. No further injections of ivTA or ivBe were given to the patients, even if they showed only a limited response to the first injection in terms of decreased retinal thickness or improvement in visual acuity. Neither were injections of ivTA or ivBe given to patients with recurrent edema and associated deterioration of visual acuity during the first 24-weeks follow-up periods for all three groups. However, after that period, further ivTA, ivBe or additional macular laser photocoagulation treatment was allowed if macular edema recurred and/or visual acuity deteriorated.

OCT was performed using a previously reported methodology for all patients in order to measure CMT using a manually assisted technique in conjunction with the OCT system software.<sup>(26,27)</sup> This was carried out at baseline (the time of first visit), 4, 8, 12, and 24 weeks after injection. Foveal fixation and landmark functions were used for every scan in the same macular region. In addition to the OCT studies, all patients underwent complete ophthalmological examinations including standardized visual acuity measurements using Landolt C-ring charts, slit-lamp biomicroscopy, Goldmann applanation tonometry, and ophthalmoscopy at baseline, 4, 8, 12, and 24-weeks after treatment. FAG was performed after any severe intraretinal hemorrhage has been resolved and a clearer view of the fundus allowed for identification of macular perfusion. The response to treatment was monitored anatomically by measuring CMT

using OCT, and, functionally, by best-corrected visual acuity (BCVA) assessments. Potential corticosteroid-induced and injection-related complications, if any, were also recorded. No patient in this study had ocular hypertension at baseline, and intraocular pressure (IOP) was recorded at every visit. Topical antiglaucomatous medication was given if the IOP was more than 21 mmHg at any subsequent follow-up IOP measurement.

Information regarding medical history (e.g., hypertension, diabetes, etc.) was obtained by chart review. The visual acuity measurements were converted to the logarithm of the minimum angle of resolution (log MAR) at baseline and at repeated intervals thereafter for statistical analysis.<sup>(28)</sup>

### **Surgical procedures**

The injection of ivTA or ivBe was performed under sterile conditions in the operating room using an operating microscope. Prior to the injection, topical povidone-iodine (5%) was applied to the periorbital skin and into the ocular surface. Anterior chamber paracentesis was performed to decrease the ocular volume. The injection of 4 mg of crystalline triamcinolone acetonide (Kenacort-A; ER Squibb & Sons, Inc., U.S.A.) in 0.1 ml of distilled water for patients in the ivTA group and 2.5 mg (0.1 ml) of commercially available bevacizumab (Avastin™, 25 mg/ml, Genentech, Inc., South San Francisco, CA, U.S.A.) in the ivBe group was performed using a sharp 27-gauge needle through the inferotemporal quadrant, at 3.5 or 4.0 mm posterior to the limbus in pseudophakic and phakic eyes respectively. The needle was carefully removed using a sterile cotton applicator to prevent reflux. After the injection, retinal artery perfusion was checked. Tobradex™ eye ointment (Alcon, tobramycin and dexamethasone) was immediately applied.

### **Statistical analysis**

The patients' baseline and follow-up variables were compared between the groups and within the groups. Chi-square and ANOVA were used to determine the statistical differences between the groups. Repeat measure ANOVA (RMANOVA) was used to evaluate the differences in the same group and different groups before treatment and at each follow-up point. The Bonferroni procedure was used as a post hoc test. All data were collected in an MS-Excel

2006 spreadsheet (Microsoft Corporation, Redmond, WA, U.S.A.) and analyzed using the Statistical Package for the Social Sciences software (version 10.0, SPSS Inc., Chicago, IL, U.S.A.) for Windows. A *p* value of less than 0.05 was considered statistically significant.

## RESULTS

Eighty-three eyes of 83 patients with macular edema secondary to BRVO (50 men and 33 women), between 38 and 79 years of age (mean age, 60.2 years), were included in the study. All 83 patients completed a minimum of 24 weeks of follow-up, and the mean follow-up duration was  $41.4 \pm 9.6$  weeks (24 to 72 weeks). The ivTA treatment group included 25 eyes of 25 patients (15 men and 10 women). The ages of these patients ranged from 46 to 79 (mean age, 60.8 years). The ivBe treatment group included 24 eyes of 24 patients (15 men and 9 women). The ages of these patients ranged from 42 to 78 (mean age, 60.7 years). The control group, who did not receive any intravitreal injection, consisted of 34 eyes of 34 patients (20 men and 14 women). The patient age of the control group ranged from 38 to 74 years (mean age, 59.4 years). Hypertension was noted in 9 patients (36%) from the ivTA group, 11 patients (45%) from the ivBe group and 13 patients (38%) from control group. Diabetes mellitus was noted in 5 patients (20%) in the ivTA group, 8 patients (33%) in the ivBe group and 8 patients (24%) in the control group. The duration to onset of treatment ranged from 0 to 12 weeks (mean, 6.4 weeks) in the ivTA group, 1 to 11 weeks (mean, 6.7 weeks) in the ivBe group and 1 to 12 weeks (mean, 6.5 weeks) in the control group. FAG examinations were performed on 19 eyes (76%), 18 eyes (75%) and 26 eyes (76%) in the ivTA, ivBe and control group, respectively. Parallel to this, macular non-perfusion, as identified by FAG, was found in 9 eyes (47% of eyes receiving FAG), 8 eyes (44% of eyes receiving FAG) and 11 eyes (42% of eyes receiving FAG) in the ivTA, ivBe and control groups respectively. The mean initial IOPs for the ivTA, ivBe and control groups were 14.1 mmHg (range 8 to 20 mmHg), 13.7 mmHg (range 9 to 19 mmHg) and 14.9 mmHg (range 9 to 21 mmHg), respectively. The lens status was phakia in 18 eyes (72%), 15 eyes (63%)

and 25 eyes (74%) in the ivTA, ivBe and control groups respectively. The lens status of the remaining eyes of each group was pseudophakia. The mean length of follow-up period in the ivTA, ivBe and control groups were 42.2 weeks (range 26 to 72 weeks), 41.4 weeks (range 24 to 66 weeks) and 40.8 weeks (range 28 to 69 weeks), respectively. The age, sex, numbers of patients with hypertension, diabetes mellitus, the durations of onset to treatment, the numbers of eyes receiving FAG examination, the macular perfusion on FAG, the initial IOPs, lens status (phakia or pseudophakia) and follow-up duration did not differ significantly across the three groups (*p* > 0.05 for all) (Table 1).

### Retinal thickness

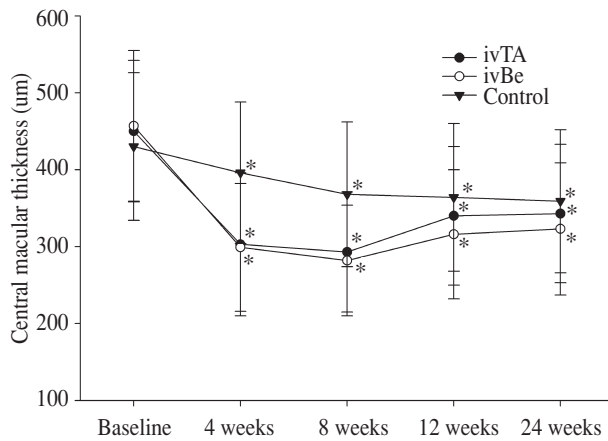
OCT imaging demonstrated that the CMT (mean  $\pm$  SD) was decreased significantly from  $450 \pm 92$   $\mu$ m at baseline to  $303 \pm 93$   $\mu$ m,  $293 \pm 78$   $\mu$ m,  $340 \pm 90$   $\mu$ m and  $343 \pm 90$   $\mu$ m at 4, 8, 12 and 24 weeks respectively after ivTA therapy (RMANOVA, *p* < 0.05 for all four values). In the ivBe group, CMT (mean  $\pm$  SD) also was decreased significantly from  $457 \pm 98$   $\mu$ m at baseline to  $299 \pm 83$   $\mu$ m,  $282 \pm 72$   $\mu$ m,  $316 \pm 84$   $\mu$ m and  $323 \pm 86$   $\mu$ m respectively at 4, 8, 12 and 24 weeks after treatment (RMANOVA, *p* < 0.05 for all). However, CMT (mean  $\pm$  SD) in the control group also decreased significantly from  $430 \pm 96$   $\mu$ m at baseline to  $396 \pm 92$   $\mu$ m,  $368 \pm 94$   $\mu$ m,  $364 \pm 96$   $\mu$ m and  $359 \pm 93$   $\mu$ m at 4, 8, 12 and 24 weeks respectively (RMANOVA, *p* < 0.05 for all) (Fig. 1).

On comparing the difference in CMT among the ivTA, ivBe and control groups at the different follow-up times, it was observed that the CMT differed significantly only at 4 and 8 weeks after treatment (RMANOVA, *p* < 0.0001 and = 0.0002) and that the CMT difference was not significantly different at baseline, 12 and 24 weeks after treatment (RMANOVA, *p* > 0.05 for all) (Table 2). Furthermore, the CMT differed significantly between the ivTA and the control group at 4 and 8 weeks after treatment (The Bonferroni procedure, *p* = 0.0004 and 0.003) and significantly between ivBe and control group at 4 and 8 weeks after treatment (*p* = 0.0003 and 0.0007). However, CMT did not differ significantly between ivTA and ivBe groups at the 4 and 8 week check-points (*p* = 1.0 for two values) (Table 3).

**Table 1.** Patient Characteristics

	IvTA group	IvBe group	Control group	<i>p</i> value
Number (patients/eyes)	25/25	24/24	34/34	1.000
Age, year (mean)	46-79 (60.8)	42-78 (60.7)	38-74 (59.4)	0.882
Sex (male/female)	15/10	15/9	20/14	0.961
Hypertension, patients (%)	9 (36)	11 (45)	13 (38)	0.786
Diabetes mellitus, patients (%)	5 (20)	8 (33)	8 (24)	0.412
Duration of onset to treatment, weeks (mean)	0~12 (6.4)	1~11 (6.7)	1~12 (6.5)	0.953
FAG received, eyes (%)	19 (76)	18 (75)	23 (67)	0.792
Macular perfusion, number (% of eyes receiving FAG)				0.859
Non-ischemic	10 (53)	10 (56)	14 (60)	
Ischemic	9 (47)	8 (44)	9 (40)	
Mean initial IOP/mmHg (range)	14.1 (8~20)	13.7 (9~19)	14.9 (9~21)	0.342
Lens status, number of eyes %				0.641
Phakia	18 (72)	15 (63)	25 (74)	
Pseudophakia	7 (28)	9 (37)	9 (26)	
IOP > 21 mmHg during follow-up period, number of eyes (%)	8 (32)	0(0)	1 (3)	0.0002
Cataract formation or progression, number of eyes (% of phakic eyes)	5 (28)	0(0)	0 (0)	
Follow-up period/weeks (mean)	26~72 (42.2)	24~66 (41.4)	28~69 (40.8)	0.907

**Abbreviations:** ivTA: intravitreal triamcinolone acetate; ivBe: intravitreal bevacizumab; FAG: fluorescein angiography; IOP: intraocular pressure.



**Fig. 1** Differences in central macular thickness (CMT) between the baseline and follow-up periods for the intravitreal triamcinolone acetate (ivTA), intravitreal bevacizumab (ivBe) and control groups, \*: Significant different from baseline data.

**Visual acuity**

After ivTA injection, there was a statistically significant improvement in the visual acuity in log MAR units (mean ± SD) from 0.967 ± 0.347 at baseline to 0.797 ± 0.348 and 0.743 ± 0.377 at 4 and 8 weeks after treatment (RMANOVA, *p* = 0.003 and < 0.0001, respectively), but not at 12 and 24 weeks (visual acuity 0.817 ± 0.362 and 0.844 ± 0.361, *p* = 0.109 and 0.199, respectively). In the ivBe treated group, there was a statistically significant improvement in visual acuity in log MAR units (mean ± SD) from 0.959 ± 0.319 at baseline to 0.808 ± 0.316, 0.623 ± 0.281 and 0.799 ± 0.329 at 4, 8 and 12 weeks respectively after treatment (RMANOVA, *p* = 0.016, < 0.0001 and 0.026), but not at 24 weeks (visual acuity 0.833 ± 0.310, *p* = 0.178). However, the visual acuity in log MAR units in the control group also improved slightly in a gradual manner but did not differ significantly from base-

**Table 2.** Differences in Central Macular Thickness (CMT) and Logarithm of the Minimum Angle of Resolution Visual Acuity (Log MAR VA) between Each Group at Baseline and Follow-up Periods

	ivTA group	ivBe group	control group	<i>p</i> value
<b>CMT (um)</b>				
Baseline	450 ± 92	457 ± 98	430 ± 96	0.561
4 weeks	303 ± 93	299 ± 83	396 ± 92	< 0.001
8 weeks	293 ± 78	282 ± 72	368 ± 94	0.0002
12 weeks	340 ± 90	316 ± 84	364 ± 96	0.126
24 weeks	343 ± 90	323 ± 86	359 ± 93	0.306
<b>Log MAR VA</b>				
Baseline	0.967 ± 0.347	0.959 ± 0.319	0.956 ± 0.473	0.994
4 weeks	0.797 ± 0.348	0.808 ± 0.316	0.935 ± 0.442	0.404
8 weeks	0.743 ± 0.377	0.623 ± 0.281	0.921 ± 0.472	0.049
12 weeks	0.817 ± 0.362	0.799 ± 0.329	0.900 ± 0.484	0.674
24 weeks	0.844 ± 0.361	0.833 ± 0.310	0.887 ± 0.472	0.891

**Table 3.** The Post Hoc Test Showed Differences in Central Macular Thickness (CMT) and Logarithm of the Minimum Angle of Resolution Visual Acuity (Log MAR VA) between Each Group

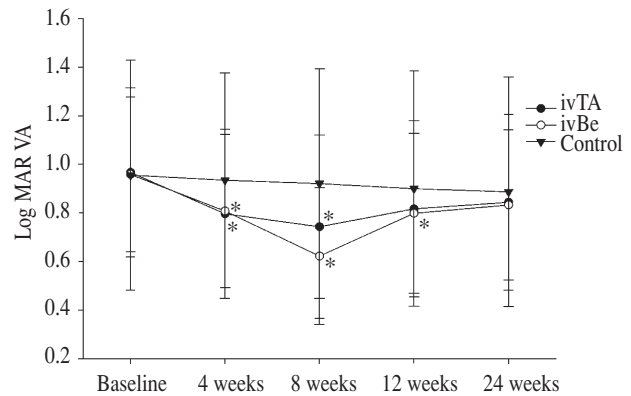
	<i>p</i> value (ivTA vs ivBe)	<i>p</i> value (ivTA vs control)	<i>p</i> value (ivBe vs control)
<b>CMT</b>			
4 weeks	1.000	0.004	0.0003
8 weeks	1.000	0.003	0.001
<b>Log MAR VA</b>			
8 weeks	1.000	0.426	0.049

**Abbreviations:** ivTA: intravitreal triamcinolone acetonide; ivBe: intravitreal bevacizumab.

The Bonferroni procedure was performed as the post hoc test.

line over the study period (RMANOVA, *p* > 0.05 for all) (Fig. 2).

Comparing BCVA in the ivTA, ivBe and control groups at baseline and over the follow-up period, the only significant difference was found at the 8-week checkpoint (RMANOVA, *p* = 0.049) (Table 2). The BCVA at the remaining time checkpoints, baseline, 4, 12 and 24 weeks, did not differ significantly



**Fig. 2** Differences in logarithm of the minimum angle of resolution (log MAR) visual acuity between baseline and follow-up periods for the intravitreal triamcinolone acetonide (ivTA), intravitreal bevacizumab (ivBe) and control groups, \*: Significant different from baseline data.

(RMANOVA, *p* > 0.05 for all). Furthermore, BCVA differed significantly between ivBe and the control group only at 8 weeks after treatment (The Bonferroni procedure, *p* = 0.049). However, BCVA did not differ significantly between the ivTA and the ivBe group and the ivTA and control group at the 8 weeks checkpoint (*p* = 1.0 and 0.426) (Table 3).

### Complications

The intravitreal injections appeared to be well tolerated by all patients. No patient experienced immediate procedure-related complications or any obvious systemic adverse event in either the ivTA or ivBe group. Delayed complications consisted of steroid induced ocular hypertension in eight patients (8 eyes, 32%) in the ivTA group, which was controlled by topical medication. In addition, one eye (3%) in the control group developed ocular hypertension during the follow-up period, which was also well controlled by topical anti-glaucoma medication. Posterior subcapsular cataracts developed or progressed in five eyes (28% of phakic eyes) in the ivTA group during follow-up. One of these was noted at the 24-week follow-up; three more were noted at the 36-week follow-up, and one more at the 48-week follow-up. No patient underwent cataract extraction during the follow-up period. However, it should be noted that the above complications (ocular hypertension and cataract development) occurred in the ivTA group, but not in any eyes in the ivBe group. No other late complications, such as retinal detachment, vitreous hemorrhage, sterile endophthalmitis, or infectious endophthalmitis, occurred in either the ivTA or the ivBe group.

## DISCUSSION

Macular edema and fluid accumulation after venous occlusion occurs rapidly after the breakdown of normal circulation. Visual acuity depends mainly on the state of the remaining circulation or on the speed of its regeneration.<sup>(29,30)</sup> Furthermore, visual acuity declines fast in most cases of macular edema secondary to BRVO.

As far as we are aware and based on a Medline search, our study is the first trial to compare the efficacy of a single intravitreal injection of triamcinolone or bevacizumab with a control group in treatment naive patients with BRVO and macular edema. In order to evaluate the true benefit of a single intravitreal injection of bevacizumab or triamcinolone, central macular thickness and visual acuity outcome after injection need to be compared with the natural course of BRVO. In this trial, CMT in both the intravitreal injection groups and the control group appeared to reduce significantly at 4, 8, 12 and 24 weeks after treatment compared to baseline; how-

ever, the CMT reduction in the control group was much less than that in either intravitreal injection groups. Meanwhile, comparing the difference in CMT between each group, we found that both the ivTA and the ivBe group exhibited a significant reduction compared to the control group at the 4 and 8 weeks checkpoints.

In the ivTA group, a maximum decrease in CMT was observed at 8 weeks after treatment and then the CMT started to increase gradually after the 8-week checkpoint. This finding is similar to a previous report indicating that CMT again began to increase about 2 months after ivTA.<sup>(14)</sup> Nonetheless, the patients showed visual improvement over the initial 24 weeks after ivTA therapy and gained peak visual acuity at 8 weeks after ivTA injection. However, between week 8 and 12, and weeks 12 and 24, a trend towards decreased visual acuity was observed. Therefore, our study reveals that ivTA therapy leads to a marked decrease in macular edema and an improvement in visual acuity during the first 24 weeks and agrees with earlier studies that the maximal effect occurs at 8 weeks after treatment on patients with retinal vein occlusion.<sup>(9,10)</sup> This limited duration of the ivTA effect is most likely due to elimination of the drug by diffusion. The long therapeutic window of triamcinolone acetonide is due to its low water solubility. In a pharmacokinetic study of ivTA (4 mg) in nonvitrectomized human eyes, the mean half-life was 18.6 days, and a measurable concentration lasted for 3 months.<sup>(31,32)</sup>

Intraocular administration of corticosteroids has the benefit of delivering a high concentration without systemic toxic effects. Prior animal studies and human clinical trials support the safety of ivTA.<sup>(33,34)</sup> Nonetheless, ivTA injections are not without potential complications. Recent reports suggest that ivTA treatment is associated with vitreous hemorrhage, progressive cataract formation,<sup>(16,35)</sup> endophthalmitis,<sup>(36,37)</sup> sterile pseudo-endophthalmitis of uncertain etiology,<sup>(38,39)</sup> and secondary ocular hypertension.<sup>(40,41)</sup> The actual reasons for many of these complications are unknown and therefore careful patient selection for ivTA therapy is warranted. Posterior subcapsular cataracts developed in five patients (28%) during the first 12 months of follow-up. It has been reported in a previous study that 44% of patients developed subcapsular cataracts.<sup>(16)</sup> None of the patients in the present study underwent cataract surgery. Nonetheless,

cataract progression is still of particular concern because the need for subsequent cataract surgery is associated with a risk of aggravating macular edema. A steroid-induced rise in IOP is another side effect that occurred in eight eyes (32%) in the ivTA treatment group and this was medically controlled in all patients. This side effect occurred at almost the same frequency as in previous studies (30% to 70%).<sup>(40,41)</sup>

Intravitreal bevacizumab therapy provides a new treatment option for early intervention against formation of macular edema. Using ivBe, we observed a positive biological effect on the macular edema in patients with BRVO disease. VEGF, a key mediator of intraocular neovascularization and macular edema, is triggered by hypoxia and is found in the eyes of animal models with central retinal vein occlusion.<sup>(42,43)</sup> Therefore, inhibition of VEGF should theoretically offer a therapeutic advantage. The observed decrease in macular edema could be secondary to the reduction in vascular permeability that is caused by inhibiting VEGF. In the current study, the CMT decreased significantly from baseline over the first 24-week follow-up period and reached a minimum at 8 weeks checkpoint. The CMT began to increase gradually again after the 8-week checkpoint. The BCVA improved significantly at 4, 8 and 12 weeks after treatment compared with baseline after ivBe injection and reached a peak also at 8-weeks. However, a significant difference in BCVA between the ivBe and control group could only be observed at the 8-week checkpoint. Therefore, our study reveals that the effect of intraocular ivBe on central macular thickness reduction seems to last for 12 weeks, which is similar to earlier studies on patients with retinal vein occlusion who were treated with bevacizumab injection.<sup>(22,24,25)</sup> However, the real duration of the effect may be only up to 8 weeks, after which time there was partial macular edema resolution and BCVA improvement continued by natural progression.

In cases of BRVO with severe intraretinal hemorrhages, an obstructed view of the fundus does not allow for immediate laser treatment. Intravitreal bevacizumab treatment can be initiated immediately while waiting for the hemorrhage to clear before initiating laser treatment. In a previous study, bevacizumab prevented the development of neovascularization.<sup>(44)</sup> Meanwhile, bevacizumab also offers the advantage of helping the rapid clearance of retinal

hemorrhages,<sup>(45,46)</sup> which may help to explain the beneficial effects of ivBe over ivTA therapy, where no beneficial effect was noted between the ivTA group and control group, with respect to changes in BCVA observed at 8 weeks after injection.

A single intravitreal bevacizumab injection appears to improve the visual acuity of BRVO patients with macular edema within the first 12 weeks of treatment. This effect is probably due to a reduction of blood vessel permeability, a similar effect to ivTA; this improves visual acuity and show a maximum efficacy at 8 weeks. Nonetheless, the use of ivBe for BRVO offers significant advantages over triamcinolone because increases in IOP and cataract formation were not observed in patients treated with ivBe. The results compare favorably with previous reports.<sup>(19,24,25)</sup> For this reason, ivBe injection is a particularly attractive treatment option for steroid-responders and phakic patients. In the present study, no other possible complications, such as conjunctival ulceration, infectious or noninfectious endophthalmitis, central retinal artery occlusion, or retinal detachment, were observed in patients treated with ivBe injection. In addition, systemic adverse events due to ivBe injection have, thus far, been reported include deregulation of blood pressure in hypertensive patients.<sup>(47)</sup> This is important particularly if multiple treatments of ivBe are necessary for some patients. Our results suggest that, even though an average of 12 weeks duration for the effects of bevacizumab on BCVA and retinal thickening were observed, its real effective duration might be only up to 8 to 12 weeks after subtracting the natural progression factor. This duration is similar to that found in previous studies where a recurrence of macular edema was detected at a mean of 2.1 to 3 months after ivBe has been reported.<sup>(24,48)</sup>

In this trial, the effective period of ivBe and of ivTA compared to the control group was short and there were no differences in CMT or BCVA across the three groups at 24 weeks. It is possible that these drugs are not effective anymore at 24 weeks or, alternatively, the drugs have been metabolized, in which case repeated injections might be necessary. However, the results over more than 24 weeks and with repeated injections need to be further investigated.

There were two reasons why we included two intravitreal treatment groups and an observation only



control group rather than included a macular laser treatment group. Firstly, this study was aimed at purely comparing the short-term (within 12 weeks) and mid-term (24 weeks) effect of ivTA and ivBe on decreasing macular edema induced by BRVO and the monitoring of change in macular edema over the 24-weeks study period. The obvious control for these groups is to compare them with patients without any treatment who undergo the natural course of BRVO with macular edema. Secondly, according to the Branch Vein Occlusion Study (BVOS) group guidelines,<sup>(5)</sup> macular laser is the standard treatment for vision loss attributed to macular edema in patients with BRVO of at least 3 months duration and with a visual acuity of 20/40 or worse. Importantly, in this study, the durations of onset to treatment in all cases were less than 3 months and therefore these patients do not fit the above guidelines. Finally, macular laser performed by different surgeons could lead to different effects in terms of macular edema resolution; this would result in a selection bias that is not encountered in the intravitreal treatment and control groups of this study.

Most studies on triamcinolone or bevacizumab injection have included only a very limited number of patients, have involved a large number of injections to individual patients, or are where the injections serve mainly as an adjuvant treatment.<sup>(14,16,17,24,25)</sup> The strengths of the present study are the relatively large number of treatment naïve BRVO patients, the presence of an appropriate control group, the use of a single intravitreal injection of triamcinolone or bevacizumab as primary treatment for all eyes and the long follow-up duration. The shortcomings of this study are its retrospective nature and the lack of randomization.

In summary, we showed that a single ivTA or a single ivBe injection is an effective and relatively safe treatment for macular edema secondary to BRVO and that the treatment was effective for twenty-four weeks with both treatments reaching a maximum efficacy at eight weeks. Since we did not observe increases in IOP and cataract formation in patients who underwent ivBe injection, we suggest bevacizumab treatment for patients with BRVO with macular edema, in particular for steroid-responders and phakic patients. Such treatment should be carried out under close postoperative observation. The results support the need for a large, prospective, ran-

domized trial to clarify the modes of action of ivTA and ivBe treatment for BRVO with macular edema.

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# 玻璃體內單一注射 triamcinolone 或 bevacizumab 治療視網膜分支靜脈阻塞引起的黃斑水腫

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- 背景：** 評估以單一玻璃體內注射 triamcinolone 或 bevacizumab 治療視網膜分支靜脈阻塞引起的黃斑水腫，對視力和黃斑中央厚度的影響。
- 方法：** 這項連續、追溯性的臨床研究包括 83 例病患 (83 眼) 罹患視網膜分支靜脈阻塞繼發之黃斑水腫，以單一玻璃體內注射 triamcinolone (ivTA 組，25 例) 或注射 bevacizumab (ivBe 組，24 例)，或者不接受任何治療 (對照組，34 例)。主要結果評估包括使用光學同調斷層掃描術測量黃斑中央厚度和最佳矯正視力。
- 結果：** 在注射組與對照組中，黃斑中央厚度在 4、8、12 和 24 週後皆比治療基期有顯著性下降。在 ivTA 組，其最佳矯正視力在 4 和 8 週後以及 ivBe 組在 4、8 和 12 週後皆比治療基期有顯著性上升。比較各組之間的黃斑中央厚度，ivTA 和對照組及 ivBe 和對照組之間在治療 4 和 8 週後有顯著性差異。最佳矯正視力顯著性差異發生在治療 8 週後的 ivBe 組與對照組之間。在 ivBe 組和 ivTA 組之間，黃斑中央厚度和最佳矯正視力在治療後任何期間皆無顯著差異。在 ivTA 組或 ivBe 組皆無病患發生與注射有關的併發症或任何明顯的全身性不良反應事件。延遲的併發症包括類固醇引起的高眼壓 8 眼 (32%) 和後囊性白內障 5 眼 (28%) 在 ivTA 組。
- 結論：** 對視網膜分支靜脈阻塞引起的黃斑水腫而言，ivTA 和 ivBe 療法皆是短期有效的治療方法。然而，ivBe 治療似乎比 ivTA 治療更安全和較少引發不良的副作用，如高眼壓症和白內障。  
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**關鍵詞：** triamcinolone acetone, bevacizumab, 視網膜分支靜脈阻塞, 黃斑水腫, 光學同調斷層掃描術