• Clinical Research •

Efficacy of intravitreal conbercept injection on short- and long-term macular edema in branch retinal vein occlusion

Jing-Yi Bai[1], *Wen-Ying Wang*[1], *Zhi-Zhi Dou*[1], *Bo-Chao Geng*[1], *Xiao-Yan Xu*[1], *Yuan-Zhang Zhu*[1], *Shan-Yao Zhao*[1], *Min Liu*[2], *Shao-You Jia*[1], *Wen-Juan Luo*[1]

[1]Department of Ophthalmology, Qingdao University Affiliated Hospital, Qingdao 266003, Shandong Province, China
[2]The People's Hospital of Zoucheng City, Jining 272000, Shandong Province, China
Co-first authors: Jing-Yi Bai and Wen-Ying Wang
Correspondence to: Wen-Juan Luo. No.16 Jiangsu Road, Qingdao 266003, Shandong Province, China. luowenjuan@qduhospital.cn
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Abstract

● **AIM:** To observe the best-corrected visual acuity (BCVA) and central foveal thickness (CFT) repeatedly after the intravitreal injection of conbercept (IVC) for treating cystoid macular edema (CME) in branch retinal vein occlusion (BRVO) and explore the relationship between the duration of CME and visual outcome.

● **METHODS:** Subgroup analysis was performed to compare short-term (within 90d of CME onset) and long-term (over 90d of CME onset) macular edema in BRVO. After an initial IVC, a *pro re nata* (PRN) strategy was performed according to the recurrence of CFT or decrease of BCVA. Analysis of variance using repeated measurements, statistical analysis following indicators including BCVA and CFT collected at baseline and 1, 3, and 6mo after IVC.

● **RESULTS:** Among the 60 cases included in this retrospective study, 36 were short-term CME, and 24 were long-term CME. There were statistical significances between and within groups of the BCVAs at different time points (P<0.001). The interaction was found between group and time (P=0.006), indicating the difference in the speed of BCVA improvement between groups. In particular, the improvement speed of BCVA in the short-term CME group was faster than that in the long-term CME group. There were significant differences between and with groups of the CFT at different time points (P<0.001). However, the interaction between group and time in relation to CFT had no significant differences (P=0.59).

● **CONCLUSION:** IVC treatment for CME following BRVO is effective and safe. The duration of CME before treatment is a significant predictor of the visual outcomes of patients with BRVO. The improvement of vision might be faster with early IVC treatment than with delayed treatment.

● **KEYWORDS:** vascular endothelial growth factor; branch retinal vein occlusion; conbercept; best-corrected visual acuity; macular edema

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INTRODUCTION

In retinal vascular disease, the incidence of retinal vein occlusions (RVOs) ranks second in the world, of which include branch retinal vein occlusions (BRVOs), hemi-retinal vein occlusions, and central RVOs[1]. Generally, BRVOs were nearly 80% of all cases in RVOs[2] and often occur in arteriolar-venous junction at the proximal bitamporal proximal temporal side of the optic nerve. As such, RVO tends to leading to macular bleeding and fluid accumulation macular edema and decreased vision. The increasing level of vascular endothelial growth factor (VEGF) in the early stage of RVOs often attribute to the evolution and persistence of macular edema and hemorrhages[3].

Additionally, the high VEGF levels encourage the progression of retinal nonperfusion and ischemia, also further increasing VEGF levels[4]. Finally, macular edema and bleeding exacerbation result in visual disabilities.

In recent years, VEGF inhibitors, such as ranibizumab, bevacizumab, and aflibercept, have been widely used for treating macular edema caused by BRVO[5-9]. These studies have confirmed that anti-VEGF treatment significantly improves best-corrected visual acuity (BCVA) in BRVO.

As a fusion protein, conbercept (Lumitin; Chengdu Kang Hong Biotech Co., Ltd., Sichuan Province, China) consists of the extracellular domain 2 of VEGF receptor (VEGFR) 1 and extracellular domains 3 and 4 of VEGFR2. Conbercept plays its pharmacological effects by combing with the Fc portion

of human immunoglobulin G1. However, no studies have been applied to research the relationship of clinical outcome and duration of macular edema with conbercept treatment in BRVO.

There are high affinities between conbercept and VEGF (A, B, C) and placental growth factor (PGF). Several evidences have indicated that the ranibizumab and conbercept treatment by intravitreal injection can improve visual acuity and central foveal thickness (CFT) in macular edema secondary to BRVO[5,10].

In the current study, the efficacy and safety were investigated for intravitreal injection of conbercept (IVC) in cystoid macular edema (CME) caused by BRVO. The relationship between the duration of CME and visual outcomes was evaluated and compared in short- and long-term CME groups.

SUBJECTS AND METHODS

Ethical Approval This study was performed according to the Declaration of Helsinki. All patients signed informed consent before treatment.

The study retrospectively included 60 eyes from 60 patients who were adopted 10 mg/mL IVC with total 0.5 mg as the sole treatment for macular edema due to BRVO between January 2017 and December 2020. All the subjects were assigned into two groups on the basis of the CME duration: short-term CME (≤90d from onset to injection) and long-term CME groups (>90d from onset to injection). After an initial IVC, a *pro re nata* (PRN) strategy was performed according to the prespecified anatomic criteria with a monthly post-injection follow-up for 6mo. The following parameters were evaluated at the time of baseline and the first, third, sixth months, after injection: BCVA in accordance with the protocol of the Early Treatment Of Diabetic Retinopathy Study (ETDRS); intraocular pressure (IOP) *via* Goldmann applanation tonometry; and CFT *via* spectral-domain optical coherence tomography (Stratus OCT™; Carl Zeiss Meditec Inc., Dublin, CA, USA) and fluorescein angiography (HRA-II Heidelberg, German). Two researchers measured and collected the data independently and carefully.

Patients Patients were included in the analysis if they met all of the inclusion criteria as following: 1) aged over 18y; 2) BCVA worse than 20/40 (equivalent to 70 letters in ETDRS); 3) CFT on optical coherence tomography (OCT) ≥250 μm. Subjects were out of this study if they satisfied the exclusion criteria: 1) the IOP level was over 21 mm Hg; 2) iris neovascularization; 3) past intraocular operation history; 4) treatment history for other ophthalmic diseases by using grid photocoagulation or anti-VEGF therapy. According to the PRN scheme, the retreatment criteria were: 1) vision loss of ≥10 ETDRS letters compared with BCVA in the previous month; 2) increase of CFT (OCT) ≥50 μm; 3) CFT (OCT) >250 μm; 4) presence of intraretinal fluid, intraretinal cyst or subretinal fluid macular edema.

Intraocular Injections All patients were treated with IVC (0.5 mg, total volume was 0.05 mL) monthly (total 6mo) in accordance with the following procedures. In brief, after given topical anesthetic drops, the eye was firstly inserted a lid speculum. After administered superficial oxybuprocaine anesthesia, 5% povidone iodine was used for cleaning the injection site. Then, using one 30-gauge needle inserted through the pars plana, injecting 50 μL conbercept. Within 30min after the injection, the researchers measured IOP.

Outcome Measures At months 1, 2, 6 from baseline, the mean BCVA changes was considered as the primary end point, the mean CFT changes was considered as the second outcome measures. The percentage of subjects gaining over fifteen BCVA letters at 6th month was also set as the second outcome measures. The incidence and severity of adverse events (AEs) and serious adverse events (SAEs) in ocular and nonocular were used for evaluating safety outcomes.

Statistical Analysis All the patients were divided into short- and long-term CME treatment groups according to the duration from the onset of CME to the first IVC treatment. Assessment indicators, including BCVA and CFT, were evaluated through repeated measures ANOVA. A 2-sided significance level of 0.05 was set for the general linear model (GLM) of repeated measures for continuous variable data. When the test of sphericity was disobeyed, the degrees of the averaged significance tests was adjusted by using Greenhouse-Geisser. Taking Chi-square test to analyze the differences in the proportions of those eyes gained over fifteen ETDRS letters.

RESULTS

Baseline Characteristics and Patient Disposition In this study, 36 subjects were included in the short-term CME group (the interval between the first visit and the first injection is less than 90d), and 24 subjects were included in the long-term CME group (the interval between the first visit and the first injection is more than 90d). Table 1 summarizes and compares patient demographics and baseline ocular characteristics. In the short-term CME group, 44.4% were male, the mean duration from the onset of CME to IVC treatment was 1.049mo the mean BCVA letter score at baseline was 45.944 letters, the mean baseline CFT was 571.833 μm, and the average number of conbercept injected during a period of six months were 2.56. In the long-term CME group, 33.3% were male, the mean duration from the onset of CME to IVC treatment was 3.5mo, the average of baseline BCVA scores was 43.708 letters, and the mean baseline CFT was 610.042 μm, and the average number of conbercept injected during a period of six months were 2.38. Two-sample *t* test revealed that the BCVA (t=0.476, P=0.636) and CFT (t=-0.692, P=0.492) had no

significant difference between the short- and long-term CME groups at baseline. Therefore, the two groups were statistically comparable.

Functional Outcomes from Baseline to Month 6 According to the BCVA changes from baseline to 6mo, the primary efficacy outcome was evaluated. In Table 2, the interaction between group and time on BCVA was statistically significant (F=4.637, P=0.006). This result suggested that the two groups had different vision improvement speeds. In Figure 1, compared with the long-term CME group, the increase in vision was faster in the group of short-term CME. On the 6th month, BCVA changed from 45.944±19.555 to 68.667±13.249 letters for the short-term CME, and the average increase was 22.723 letters. By comparison, the BCVA changed from 43.708±14.760 to 51.083±14.136 letters in the long-term CME group, and the mean increase was 7.375 letters. The BCVA was significantly different between the two groups at different time points (F=21.713, P<0.001).

Anatomic Outcomes from Baseline to Month 6 From baseline to 6th month, the CFT changes in the two groups reduced rapidly and dramatically after IVC, similar to the improvement in BCVA. In Table 3, the interaction between group and time in relation to CFT had no significant differences (F=0.644, P=0.59). This result suggested that the reduction speed of CFT had no difference between the two groups. Figure 2 presents the mean CFT at different time points in the two groups. On the 6th month, CFT changed from 571.883±194.73 μm to 229.08±54.228 μm in the short-term CME group, and the mean change was -342.803 μm. By comparison, CFT changed from 610.042±230.485 μm to 262.62±143.072 μm in the long-term CME group, and the mean change was -347.422 μm. The mean CFT change from baseline was statical significance between the two groups (t=11.543, P<0.001).

Proportion of Patients with Early Treatment Diabetic Retinopathy Gaining More Than Fifteen Letters Score At the 6th month, 77.8% of the patients in the short-term CME group gained more than fifteen BCVA letters score while those of 25% of the subjects in the long-term CME group (P<0.05). This result indicated significant differences (Figure 3).

Safety Outcomes from Baseline to Month 6 The subjects received IVC were evaluated for safety. Just similar to previously confirmed findings, almost all the AEs were evaluated as common and mild, like conjunctival hemorrhage, vitreous opacity, temporary elevated IOP, and decreased visual sensitivity[7,9,11]. From baseline to month 6, no SAE was observed in all the patients.

Table 1 Patient demographics and baseline characteristics mean±SD

Parameters	Early treatment group	Delay treatment group
Gender (M:F)	16:20	8:16
Mean BCVA (ETDRS letters)	45.944±19.555	43.708±14.760
Mean CFT (μm)	571.833±194.373	610.042±230.485
Mean duration (mo)	1.049±0.56	3.500±0.96
Mean number of IVC (times)	2.56±0.773	2.38±0.711

BCVA: Best corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; CFT: Central foveal thickness; SD: Standard deviation.

Table 2 Repeated measurement of ANOVA for BCVA in two groups mean±SD

Time	Early treatment group (n=36)	Delay treatment group (n=24)
Baseline	45.944±19.555	43.708±14.760
1mo	68.194±12.480	51.917±14.885
3mo	69.083±13.441	52.958±12.596
6mo	68.667±13.249	51.083±14.136
F (time×group)	4.637	
P	0.006	

BCVA: Best corrected visual acuity; SD: Standard deviation.

Table 3 Repeated measurement of ANOVA for CFT in two groups mean±SD

Time	Early treatment group (n=36)	Delay treatment group (n=24)
Baseline	571.883±194.73	610.042±230.485
1mo	231.28±58.324	244.54±103.386
3mo	230.53±44.805	279.46±153.676
6mo	229.08±54.228	262.62±143.072
F (time×group)	0.644	
P	0.59	

CFT: Central foveal thickness; SD: Standard deviation.

DISCUSSION

In the current study, the mean duration of macular edema was 1.049mo in the group of short-term CME, and 3.500mo in the group of long-term CME. At the 6th month from baseline, the mean BCVA improvement was 22.723 letters in the short-term CME group and 7.375 letters in the long-term CME group. The interaction between group and time in relation to BCVA was significantly different (F=4.637, P=0.006). This result suggested that the two groups had different vision improvement speeds. In particular, the increase in vision was faster in the short-term CME group than in the long-term CME group. Therefore, early treatment was beneficial to visual outcomes up to the 6th month of follow-up. On the 6th month, 77.8% of the patients in the short-term CME group gained more than 15 letters in BCVA, whereas 25.0% of the patients in the long-term CME group achieved the same outcome (P<0.05). At the 6th month from baseline, the mean CFT change was -42.803 μm in the short-term CME group and -47.422 μm in the long-term CME group. However, the interaction between

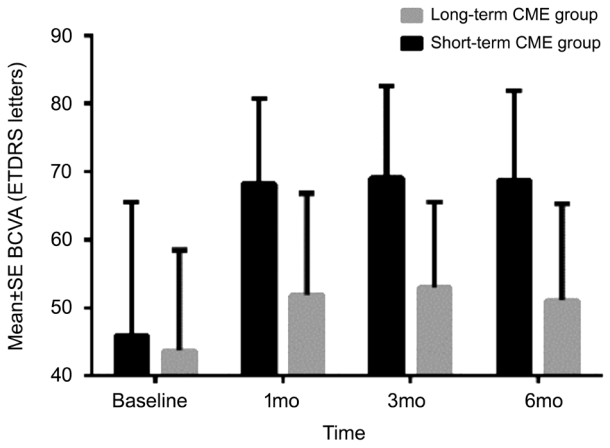

Figure 1 Mean BCVA from baseline to month 6.

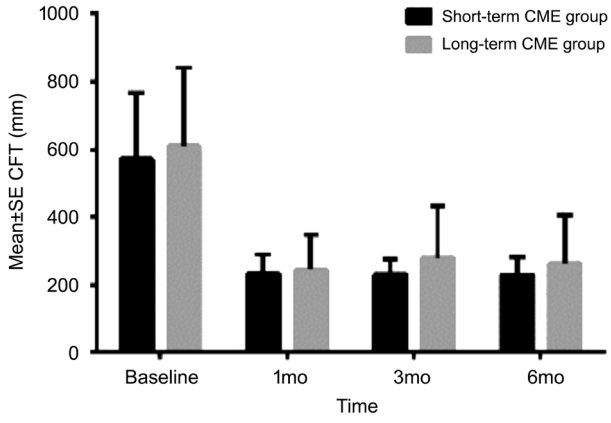

Figure 2 Mean CFT from baseline to month 6.

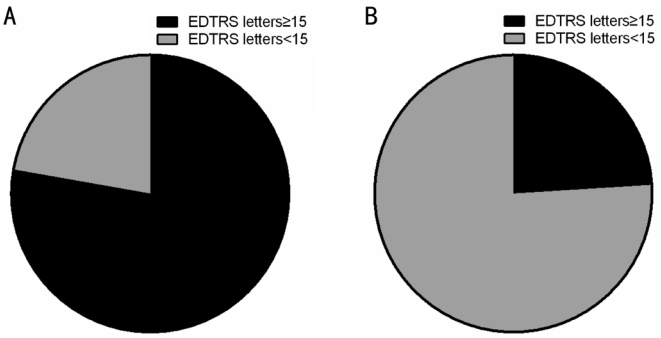

Figure 3 Proportion of patients with early treatment diabetic retinopathy gaining more than fifteen letters score A: Short-term CME group (n=36); B: Long-term CME group (n=24).

group and time in relation to CFT did not significantly differ (F=0.644, P=0.59). Thus, the reduction speed of CFT had no difference between the groups of long- and short-term CME, but the mean baseline CFT change was significantly different between the two groups at different time points (F=48.825; P<0.001).

In BRVO, due to luminal pressure increases caused by exist distal obstruction, the transudation of blood and plasma are increased, which further increase interstitial fluid pressure and reduce capillary perfusion finally causing retinal ischemia. VEGF, which released by the ischemic retina, mediates neovascular responses and induce vascular permeability excessively[11-12]. Thus, macular edema likely attribute to VEGF releasing. As an anti-VEGF drug, conbercept can specifically bind to retinal VEGFR to inhibit the interaction between VEGF and its receptor[13]. Compared with leizumab and bevacizumab, conbercept has a structure similar to that of aftercept, which binds to all subtypes of VEGF-A, VEGF-B, and PIGF, and has a higher affinity for VEGF due to the addition of the fourth IG like domain of VEGFR-2 in Fab fragment[13]. Several studies have confirmed that conbercept can quickly improve macular edema secondary to BRVO and improve vision[14-16]. The latest research results of optical coherence tomography angiography (OCTA) show that after treatment with conbercept, the whole retinal thickness decreases, the area of non-perfusion area of retina decreases, and the blood circulation of choroid is significantly improved[17-19].

Many cytokines and inflammatory factors are considered to be associated with macular edema secondary to BRVO. BRVO causes retinal hypoxia, resulting in the up regulation of the expression of VEGF and a variety of inflammatory factors. VEGF can play a role in leukocyte recruitment by activating VEGFR-1 or increase vascular permeability and up regulate the expression of inflammatory cytokines by activating VEGFR-2. Both pathways produce a positive feedback loop, which further aggravates retinal hypoxia. With the extension of macular edema time, its pathological mechanism becomes more complex, and the effect of inflammation also increases[20]. Many experiments have verified this mechanism[8,21-27]. Noma *et al*[24] found that vitreous fluid levels of soluble VEGFR-2, VEGF, soluble intercellular adhesion molecule 1, interleukin 6 (IL-6), monocyte chemotactic protein 1, pentraxin 3, and pigment epithelium-derived factor are strongly correlated with retinal vascular permeability and the severity of macular edema in patients with BRVO. A foreign study showed that IL-6 and IL-8 were significantly increased in the aqueous humor of BRVO patients compared with the control group[25]. We speculate that inflammatory factors may be an important reason for the poor response of long-term macular edema to conbercept in patients with BRVO.

According to the Guidelines for the Management of Retinal Vein Occlusion by the European Society of Retina Specialists (EURETINA), the duration of non-perfusion is a crucial prognostic factor requiring timely therapeutic intervention[28]. Moon *et al*[29] Evaluated the predictors of refractory macular edema in patients with BRVO after multiple injections of bevacizumab. The results showed that delayed treatment initiation more than 3mo is significantly associated with the development of refractory macular edema. They said that recurrent and persistent macular edema may lead to irreversible photoreceptor damage, so that visual function is still poor

after multiple anti-VEGF treatments. Yeh *et al*[30] evaluated the relationship between me duration and treatment outcome during initial intravitreal dexamethasone implant (IVD). The results showed that the effect of macular edema duration on outcome was stronger and statistically significant in BRVO patients[30]. A trial by Do *et al*[31] compared the correlation between intravitreal bevacizumab (IVB) or IVD according to the duration of macular edema of BRVO. The results showed that IVD may be more suitable for patients with longer macular edema duration. However, macular edema duration was associated with final BCVA in both IVB and IVD groups.

Guidelines for me anti-VEGF treatment after BRVO have not been established. Chen *et al*[32] compared the efficacy and safety of 1+PRN and 3+PRN in 60 patients with BRVO treated with conbercept. The results showed that the 3+PRN regimen do not lead to better functional outcomes or lower treatment needs in clinical practice as compared to the 1+PRN regimen. Similarly, a study by Miwa *et al*[33] showed that in IVR treatment for macular edema after BRVO, 1+PRN and 3+PRN regimens achieved similar 12-month functional outcomes. In this current study, 1+PRN strategy was applied to reduce the financial burden and risk of infection of the patients. The functional outcomes were comparable with those of previous findings.

This research had few limitations. First, the study selected 30 pairs of eyes, a relatively small number. Second, long-term therapeutic effects were not detected because the observation period was only 6mo. Other therapies, such as retinal laser photocoagulation, should be applied in the long run. Third, edema subsided spontaneously in some of the patients with short-term CME, and their vision improved.

In conclusion, this study suggested that IVC for CME following BRVO was effective and safe. The duration of CME before treatment was a significant predictor of the visual outcomes of patients with BRVO. The improvement of vision might be faster with early IVC treatment than with delayed treatment.

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