

Short-term effect of intravitreal conbercept injection on major and macular branch retinal vein occlusion

Journal of International Medical Research

2019, Vol. 47(3) 1202–1209

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DOI: 10.1177/0300060518819613

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Abstract

Objective: To evaluate the effectiveness of intravitreal conbercept injection on major and macular branch retinal vein occlusion (BRVO).

Methods: This retrospective analysis involved 43 patients with BRVO (major BRVO n = 24; macular BRVO, n = 19) who were diagnosed by fluorescein fundus angiography (FFA) and injected with intravitreal conbercept. The following outcomes were measured at baseline and follow-up (1-6 months): best-corrected visual acuity (BCVA), central foveal thickness (CFT), total retinal volume in a 6-mm diameter section of the macula, choroidal thickness under the central fovea of the macula, relative area of retinal hemorrhage, complications, and times when repeated injection was performed.

Results: There were significant differences between the two groups in terms of BCVA, CFT, and total retinal volume in a 6-mm diameter section of the macula at 6 months after treatment. Choroidal thickness under the central fovea of the macula and relative area of retinal hemorrhage showed no significant differences between the two groups at 6 months after treatment; however, they significantly differed from baseline measurements.

Conclusion: In general, intravitreal injection of conbercept may have a better short-term effect in patients with macular BRVO than in patients with major BRVO.

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Keywords

Conbercept, BRVO, macular BRVO, VEGF, visual acuity, central foveal thickness, retinal hemorrhage, choroidal thickness

Date received: 30 July 2018; accepted: 23 November 2018

Introduction

Retinal vein occlusion (RVO) is a common retinal vascular disease treated in ophthalmologic clinics,¹ which often leads to local instillation of drops in the retina, secondary cystoid macular edema (ME), retinal neovascularization, neovascular glaucoma, and other complications.² RVO is categorized as either central retinal vein occlusion (CRVO) or retinal branch vein occlusion (BRVO), according to its etiology.³ BRVO is categorized into major and macular branches⁴; major BRVO exhibits the highest incidence in venous occlusion, while macular BRVO occurs within the area of the venule of the drainage macular region.⁵ There are 2–3 retinal branch venules above and below the macula, with a drainage area of 5–6 disc-diameters; here, small vein obstruction comprises macular BRVO. In 1980, Joffe et al.⁶ reported a clinical study of 75 patients with macular BRVO, which contributed to gradual recognition of the differences between macular BRVO and major BRVO. For patients with macular BRVO, although venous reflux is completely blocked, the visual prognosis is better because of the small scope of retina involvement and fewer associated complications. In addition, because the ischemic area is relatively limited, neovascularization typically does not occur.

Increased levels of vascular endothelial growth factor (VEGF) early in RVO constitute a major contributor to the evolution and persistence of ME and hemorrhage.⁷

Therefore, anti-VEGF drugs are increasingly used to inhibit VEGF expression in the treatment of RVO.⁸ Conbercept, a novel anti-VEGF reagent, is a humanized, soluble, VEGF receptor (VEGFR) protein comprising extracellular domain-2 of VEGFR-1, and extracellular domains-3 and-4 of VEGFR-2. Clinical trials have demonstrated that conbercept is well-tolerated in the eye, with a low incidence of adverse effects similar to that of other anti-VEGF reagents.⁹ Furthermore, intravitreal injection of conbercept has been proven to be safe and effective for the treatment of ME secondary to BRVO.¹⁰ This study aimed to evaluate changes in best-corrected visual acuity (BCVA) and central fovea thickness (CFT) after treatment with conbercept in patients with major and macular BRVO, and to compare responses to treatment between both types of BRVO.

Methods

Patients

This retrospective study was approved by the administration of Qilu Hospital of Shandong University (KYL-2017-213) and informed consent was obtained from each patient. The study included eyes of BRVO patients with ME that received intravitreal conbercept injection between February 2011 and May 2016. The specific diagnostic criteria for major and macular BRVO were based on fluorescein fundus angiography (FFA): major BRVO was

defined as trunk obstruction of the superior or inferior temporal branches of the central retinal vein; macular BRVO referred to a lack of trunk obstruction of the superior or inferior temporal branches, accompanied by blockage of one or two small branches in the macular area. All patients were diagnosed by the same physician. The inclusion criteria were: normal blood pressure, negative urine protein, normal liver and kidney function, and normal electrocardiogram; no prior intravitreal injection, laser photocoagulation, or intake of blood-activating and stasis-removing drugs before operation. The exclusion criteria were: presence of chronic dacryocystitis, glaucoma, cataract, severe proliferative vitreoretinopathy or vitreous hemorrhage, macular epiretinal membrane or macular ischemia, diabetic retinopathy, age-related macular degeneration, ocular trauma, or other retinal/ocular diseases.

Intravitreal conbercept injection

Before injection, patients instilled 5 g/L levofloxacin hydrochloride eye drops, four times per day for 3 days. Ocular surface anesthesia was performed by oxybuprocaine hydrochloride after regular disinfection. The eyeball was disinfected by application of 50 g/L povidone iodine for 90 s; the conjunctival sac was then washed with saline. Subsequently, 0.05 mL (0.5 mg) conbercept (Chengdu Kanghong Biotechnologies Co., Ltd.; Chengdu, Sichuang, China) was slowly injected into the vitreous using a 1-mL empty needle. Pressure was applied to the wound with an aseptic wet cotton swab for 1–2 min after removing the needle. All injected eyes were bandaged with levofloxacin eye ointment. All patients showed no obvious discomfort in the operating room for 0.5 h after injection.

Evaluation of the therapeutic effect of intravitreal conbercept injection over time

All patients were followed-up for 6 months. If recurrent ME was detected, the 1+PRN (pro re nata) regimen was adopted. Recurrent ME was defined as a 100- μ m increase in foveal thickness (FT) relative to the previous measurement.¹¹ FT and BCVA were measured before injection (baseline) and at least every 1 month for 6 months after injection. Snellen distant visual acuity (VA), assessed with a Landolt chart, was converted to logarithm of the minimum angle of resolution (logMAR).⁸ When Snellen distant VA was below 0.1, counting fingers was designated as logMAR 2.2, hand motion was designated as logMAR 2.3, and light perception was designated as logMAR 2.5. CFT and the total retinal volume in a 6-mm diameter section of the macula were measured by optical coherence tomography (OCT). On the basis of routine OCT, the enhanced depth imaging mode was selected to measure choroidal thickness. The relative area of retinal hemorrhage (a/A) was measured using Photoshop CS6 software (Adobe, Inc.; San Jose, CA, USA) through color fundus photography of (a) the area of bleeding and (A) the optic disc area under equal magnification.¹² Complications and the total number of conbercept injections were recorded during follow-up.

Statistical analysis

Data analysis was performed by SPSS 16.0 software (SPSS, Inc.; Chicago, IL, USA). All values are expressed as the mean \pm standard deviation. The enumeration data were compared by chi-squared analysis. Comparisons between groups were performed by one-way analysis of variance; the test level was $\alpha = 0.05$. $P < 0.05$ was considered statistically significant.

Results

Patient characteristics

The study included 43 eyes of 43 BRVO patients with ME (20 males and 23 females, aged 46–83 years) that received intravitreal conbercept injection between February 2011 and May 2016. According to FFA, the patients comprised major BRVO and macular BRVO groups (Table 1). There were no significant differences regarding sex, age, and onset time between the two groups. All patients had single-eye disease, and all showed poor central vision. Indirect ophthalmoscopy showed that the macular area exhibited cystic or diffuse edema, while the branch of the retinal vein was dilated with hemorrhage. OCT analysis showed eminence of the macular region and edematous thickening.

Baseline and follow-up BCVA and CFT

Before treatment, BCVA did not significantly differ between major BRVO and macular BRVO patients (0.61 ± 0.12 vs. 0.58 ± 0.14). As shown in Figure 1a, BCVA significantly improved after conbercept treatment, compared with BCVA at baseline ($P < 0.05$). In addition, there were significant differences between the two groups after 4–6 months of follow-up ($P < 0.05$). Baseline CFT was $567.4 \pm 121.7 \mu\text{m}$ in major BRVO patients, whereas it was $533.2 \pm 124.3 \mu\text{m}$ in macular

BRVO patients; these measurements were not significantly different. As shown in Figure 1b, CFT significantly decreased after treatment with conbercept, compared with CFT at baseline ($P < 0.05$); there were significant differences between major BRVO and macular BRVO patients after 5–6 months of follow-up ($P < 0.05$).

Baseline and follow-up total retinal volume in a 6-mm diameter section of the macula

The baseline total retinal volume in a 6-mm diameter section of the macula was $11.37 \pm 1.18 \text{ mm}^3$ in major BRVO patients and $10.98 \pm 1.13 \text{ mm}^3$ in macular BRVO patients; these measurements were not significantly different. As shown in Figure 1c, the total retinal volume in a 6-mm diameter section of the macula was significantly smaller after treatment with conbercept, compared with the volume at baseline ($P < 0.05$); there were significant differences between the two groups after 4–6 months of follow-up ($P < 0.05$).

Baseline and follow-up choroidal thickness under the central fovea of the macula

Baseline choroidal thicknesses under the central fovea of the macula were $325.12 \pm 33.27 \mu\text{m}$ and $321.97 \pm 34.58 \mu\text{m}$ in major BRVO and macular BRVO patients; these measurements were not significantly different. As shown in Figure 1d, choroidal

Table 1. Characteristics of patients.

| Characteristic | Major BRVO (n = 24) | Macular BRVO (n = 19) | t, χ^2 | P |
|---------------------|------------------------|--------------------------|-------------|--------|
| Age | 59.35 ± 10.21 | 62.13 ± 9.18 | 0.9265 | 0.3596 |
| Sex | | | 0.0031 | 0.9559 |
| Male | 11 (45.8%) | 9 (47.3%) | | |
| Female | 13 (54.2%) | 10 (52.7%) | | |
| Onset time (months) | 4.6 ± 2.5 | 5.1 ± 2.1 | 0.6980 | 0.4891 |

BRVO, branch retinal vein occlusion.

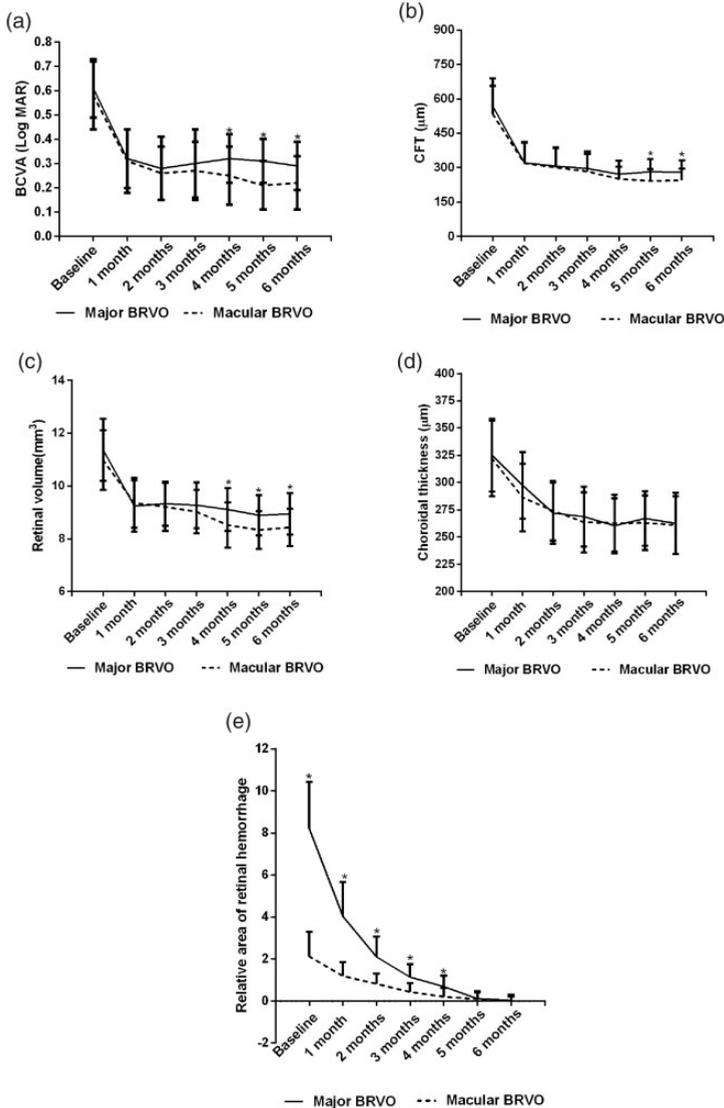


Figure 1. Time course of evaluation of the therapeutic effect of intravitreal conbercept injection at baseline and each follow-up evaluation of branch retinal vein occlusion (BRVO) group and macular BRVO group. Mean changes in (a) best-corrected visual acuity (BCVA) logarithm of the minimum angle of resolution (logMAR), (b) central foveal thickness (CFT), (c) total retinal volume in a 6-mm diameter section of the macula, (d) choroidal thickness under the central fovea of the macula, (e) relative area of retinal hemorrhage. Values are expressed as mean \pm standard deviation. * $P < 0.05$.

thickness under the central fovea of the macula significantly decreased after treatment with conbercept ($P < 0.05$). However, there were no significant differences between the two groups during follow-up.

Baseline and follow-up relative area of retinal hemorrhage

At baseline, the relative areas of retinal hemorrhage were $8.23 \pm 2.21\%$ and

$2.13 \pm 1.17\%$ in major BRVO and macular BRVO patients; major BRVO patients showed a significantly larger relative area of retinal hemorrhage than macular BRVO patients ($P < 0.05$). As shown in Figure 1e, after treatment with conbercept, the relative area of retinal hemorrhage was significantly reduced compared with the area at baseline ($P < 0.05$); there was a significant difference between the two groups after 1–4 months of follow-up ($P < 0.05$).

Complications and repeated injections during follow-up

During follow-up, only six patients developed a transient increase in intraocular pressure, including three patients with major BRVO and three patients with macular BRVO; however, there was no significant difference between the two groups. No visible eye events occurred, such as endophthalmitis, uveitis, cataract progression, or long-term ocular hypertension. Twenty-seven patients were administered repeated injection: 19 patients in the major BRVO group and eight patients in the macular BRVO group; there was a significant difference between the two groups ($\chi^2 = 6.2344$, $P = 0.0125$). In addition, the average number of conbercept doses administered to major BRVO patients was 2.89 ± 0.74 doses, while it was 2.25 ± 0.46 doses for macular BRVO patients; the difference between the two groups was statistically significant ($t = 2.2764$, $P = 0.0316$).

Discussion

It has been reported that 60% of BRVO patients exhibit visual loss due to ME. Because of the increased intravascular pressure after vein occlusion, retinal tissue edema can occur. The edematous tissue causes compaction of blood vessels, thus forming a vicious cycle. In addition, edema and degeneration of the central

fovea caused by prolonged edema can result in the disappearance of central fibers and cystoid edema. The level of VEGF in the vitreous cavity significantly increases after RVO. Overexpression of VEGF and its receptors has been closely related to serum protein exudation, retinal thickening, and the presence of ME.¹³ Therefore, treatment with a VEGF antagonist can be used as treatment of ME secondary to BRVO. Previous studies have shown that the application of anti-VEGF therapy improves visual acuity of BRVO patients and promotes re-absorption of the area of ME.^{14,15} Our study aimed to investigate the effectiveness of intravitreal conbercept injection on major BRVO and macular BRVO.

Conbercept is an anti-VEGF drug, which can specifically bind to the human VEGF receptor, thus inhibiting the interaction of VEGF and its receptor; this blocks the onset of neovascularization and decreases vascular permeability, thereby reducing internal fluid infiltration in the retina and diminishing the extent of ME.^{16,17} In macular BRVO patients, the scope of drainage and the extent of obstruction are small; moreover, there are three layers of capillaries in the posterior pole, all of which are rich in blood vessels and not vulnerable to ischemia. Therefore, the degree of retinal ischemia is less than that present in major BRVO, and the blood vessel damage is relatively minimal. This might explain the enhanced response to conbercept and reduced number of injections in patients with macular BRVO.

In this study, we found that macular BRVO patients have a more pronounced response to conbercept treatment, compared with major BRVO patients. We speculate that, due to the minimal retinal involvement in macular BRVO, the amount of VEGF produced is likely to be lower; this may result in a lower concentration of receptors, which can more easily be

inhibited by an antagonist treatment. In addition, ischemia of local retinal tissue after RVO can increase VEGF in the retinal pigment epithelium, pericytes, and microvascular endothelial cells. VEGF causes blood vessels to expand and increases blood flow, as well as increasing permeability through enhanced production of nitric oxide; this leads to the accumulation of liquid, thus increasing choroidal thickness.¹⁸ The present study found that choroidal thickness under the central fovea of the macula was reduced after treatment with conbercept, compared with baseline, confirming that choroidal vessels the exhibited normal permeability after anti-VEGF treatment; thus, choroidal thickness decreased. We also found no significant differences in complications between the two groups, indicating that the treatment has similar safety in both macular BRVO and major BRVO.

Conclusion

In general, intravitreal injection of conbercept may have a better short-term effect on macular BRVO than on major BRVO. However, our study had limitations, in that it was nonrandomized, retrospective, and performed at a single center. A larger sample size and longer follow-up period are needed to validate our results.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Funding

The study was supported by a grant from Science and Technology Development Planning of Shandong Province, China (2012GSF11853).

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