

# Comparison of intravitreal injection of conbercept and triamcinolone acetonide for macular edema secondary to branch retinal vein occlusion

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## Abstract

• **AIM:** To compare the safety and efficacy of the intravitreal injection of conbercept (IVC) and triamcinolone acetonide (IVTA) for macular edema (ME) secondary to branch retinal vein occlusion (BRVO).

• **METHODS:** A prospective, randomized clinical study. Patients with ME secondary to BRVO were randomly assigned to either IVC group or IVTA group at a ratio of 2:1 and a 12-month follow-up was performed. The efficacy outcome measures included the mean changes and differences in best corrected visual acuity (BCVA) and the central retinal thickness (CRT). The safety profiles and the mean retreatment intervals were also compared.

• **RESULTS:** There was no statistically significant difference of baseline between the two groups (IVC group,  $n=36$ ; IVTA group,  $n=17$ ). At 12mo, the BCVA letters improved by  $27.31\pm 18.36$  in the IVC group, and  $13.53\pm 11.37$  in the IVTA group ( $P=0.0004$ ). CRT reduction was  $253.33\pm 163.69$  and  $150.24\pm 134.32$   $\mu\text{m}$ , respectively ( $P=0.0034$ ). The mean BCVA in the IVC group was superior to that of the IVTA group for months 6-12 ( $P<0.01$ ). The mean CRT at 9 and 12mo were thinner in the IVC group compared to the IVTA group ( $P<0.01$ ). The mean retreatment interval in the IVC group was longer than that in the IVTA group ( $97.40\pm 36.27\text{d}$  vs  $68.71\pm 36.38\text{d}$ ,  $P=0.0030$ ). One eye in the IVC group and seven eyes in the IVTA group developed elevated intraocular pressure (IOP;  $P=0.0012$ ). The proportion of eyes with cataract new-onset or progression were 19.44% in the IVC group and 64.71% in the IVTA group ( $P=0.0012$ ).

• **CONCLUSION:** IVC could maintain or improve BCVA and reduce CRT for a longer time and have longer retreatment

interval than IVTA. In addition, patients treated with IVTA are more susceptible to IOP elevation and cataract progression.

• **KEYWORDS:** conbercept; triamcinolone acetonide; branch retinal vein occlusion; macular edema

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## INTRODUCTION

Retinal vein occlusion (RVO) remains second only to diabetic retinopathy (DR) as the main driver of retinal vascular blindness, and can be classified as branch retinal vein occlusion (BRVO), hemiretinal vein occlusion (HRVO) and central retinal vein occlusion (CRVO). RVO rates reportedly range from 0.4%-4.6%<sup>[1]</sup>. BRVO is more common than CRVO. Macular edema (ME) is the most frequent driver of impaired vision in BRVO.

Although progress has been made, the pathogenesis of ME secondary to BRVO (BRVO-ME) remains unclear. Inflammatory compounds and vascular endothelial growth factor (VEGF) which increase the permeability of the macula and the blood-retinal barrier are thought to contribute to ME. Anti-VEGF and anti-inflammatory therapies therefore represent promising strategies for BRVO-ME.

Conbercept (also named KH902 or Lumitin; 143 kDa) was developed through the fusion of the vascular endothelial growth factor receptor 1 (VEGFR1) extracellular domain 2 and VEGFR2 extracellular domains 3&4 to a human IgG1 Fc region<sup>[2]</sup>. In preclinical assessments<sup>[3]</sup>, conbercept showed high binding affinity for placental growth factor (PlGF) and VEGF, and could modulate endothelial cell chemotaxis, cell proliferation, and permeability. Clinical trials have shown that intravitreal conbercept injections (IVC) display high efficacy and tolerability profiles for ME treatment in wet age-related macular degeneration (wAMD) patients<sup>[4]</sup> and those with RVO<sup>[5]</sup>. Triamcinolone acetonide (TA) is a multipotent drug with anti-angiogenic and anti-inflammatory properties. Furthermore, it

**Table 1 Inclusion and exclusion criteria**

Inclusion criteria

- Macular edema due to non-ischemia BRVO
- Foveal center-involved macular edema associated with BRVO on clinical examination; CRT $\geq$ 250  $\mu$ m
- BCVA (ETDRS letter score)  $\leq$ 70
- Age between 18 to 80y; no gender limitation
- Good behavior and understanding capability to comply with examination and treatment
- No refractive media opacity affects the fundus examination; the diameter of the pupil can be dilated to at least 6 mm
- Blood pressure can be controlled under 150/90 mm Hg; fasting blood glucose can be controlled under 10 mmol/L
- Normal systemic examinations, including blood routine examination, coagulation function, and blood platelet count

Exclusion criteria

- Macular edema due to a cause other than BRVO
- FFA shows non-perfusion area more than five optic disks' area or neovascularization on the retina
- Any other retinopathy, such as age-related macular degeneration, DR, and eye trauma
- Glaucoma, IOP $>$ 25 mm Hg; optic atrophy; uveitis
- Pseudophakic eye or aphakic eye
- Active inflammation in the eyeball or ocular adnexal region
- Prior treatment with any anti-VEGF treatment or local or systemic corticosteroid use within 6mo before randomization
- History of intraocular surgery, history of grid macular photocoagulation, panretinal photocoagulation, or iridotomy before randomization, or anticipated requirement to undergo any of these treatments
- Pregnant and lactating women; individuals simultaneously participating in any other clinical trial

BRVO: Branch retinal vein occlusion; CRT: Central retinal thickness; BCVA: Best corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; DR: Diabetic retinopathy; IOP: Intraocular pressure; VEGF: Vascular endothelial growth factor.

can inhibit the expression of VEGF and other proinflammatory cytokines, including monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule-1 (ICAM-1), and interleukin-6 (IL-6)<sup>[6]</sup>. TA is effective for BRVO-ME, and functions through the inhibition of VEGF and proinflammatory cytokine expression<sup>[7]</sup>. It had been reported that TA can effectively improve best corrected visual acuity (BCVA) and reduce central retinal thickness (CRT) in patients with BRVO-ME<sup>[7-8]</sup>. However, a subset of patients develop complications associated with steroid use, including cataract and elevated intraocular pressure (IOP) following intravitreal triamcinolone acetonide injection (IVTA)<sup>[9]</sup>.

The treatment of BRVO-ME with anti-VEGF agents or corticosteroids has gained widespread acceptance in recent years<sup>[10-11]</sup>. Currently, China's medical insurance does not cover conbercept for the treatment of BRVO-ME. TA remains an optional medicine for patients who cannot afford anti-VEGF agents or Ozurdex. This was the first study to compare the safety and efficacy of the intravitreal injection of conbercept and TA for BRVO-ME to provide guidelines for future treatment regimens.

**SUBJECTS AND METHODS**

**Ethical Approval** An independent ethics committee reviewed and approved the study protocol prior to initiation (the Ethic Committee of the Second Hospital of Dalian Medical University, No.123 in 2017). All patients provided written informed consent to participate. Clinical trial registration number: ChiCTR1900028003.

**Study Design** This was a prospective, randomized clinical study including patients with non-ischemia BRVO according to criteria outlined in Table 1. To observe the influence of the drugs on cataract progression, we excluded pseudophakic and aphakic eyes. According to the study design, 60 patients with BRVO-ME at the Department of Ophthalmology, the Second Hospital of Dalian Medical University, were randomly assigned into groups using the random number method from June 12<sup>th</sup>, 2017 to January 15<sup>th</sup>, 2019.

The sample size was calculated by GPower 3.1. The serial number of each patient included the order number of patient enrollment. Using the random seed number 20161201, PASS 11 generated 60 random numbers with the function Rv. Uniform. Random numbers were assigned to each serial number of each patient in order. When considering the reported side effects of TA, patients were randomized at a ratio of 2:1 for IVC and IVTA group. Twenty patients with smaller random numbers were assigned to the IVTA group. The remaining 40 patients were assigned to the IVC group.

All patients with BRVO-ME received complete ocular examination, including BCVA by ETDRS letter score measurements, IOP measurements by noncontact tonometer, slit lamp microscope examinations, fundus examinations, CRT measurements through optical coherence tomography (OCT; Zeiss Cirrus 4000, Germany), color fundus photography (Topcon TRC-50DX), and fluorescein fundus angiography (FFA; Topcon TRC-50DX, Japan).

**Table 2 The visit schedule**

Items	Baseline	3d after initial injection	1mo after initial injection	3mo after initial injection	6mo after initial injection	9mo after initial injection	12mo after initial injection
BCVA	√	√	√	√	√	√	√
IOP	√	√	√	√	√	√	√
Slip lamp microscope examination	√	√	√	√	√	√	√
Fundus examination	√	√	√	√	√	√	√
OCT for CRT	√		√	√	√	√	√
Color fundus photography and FFA	√			√	√	√	√
Inclusion and exclusion criteria	√	√	√	√	√	√	√
Adverse events/complications		√	√	√	√	√	√
Additional injection criteria			√	√	√	√	√
Discontinued operation criteria		√	√	√	√	√	√

BCVA: Best corrected visual acuity; IOP: Intraocular pressure; OCT: Optical coherence tomography; CRT: Central retinal thickness; FFA: Fluorescein fundus angiography.

The IVC group was administered 0.5 mg conbercept through intravitreal injection. The IVTA group was administered 1 mg TA through intravitreal injection. All patients in two groups received one injection followed by *pro re nata* (PRN) regimen. Additional injections were administered if ME reoccurred, defined as an increase of CRT ( $\geq 100 \mu\text{m}$ ) or a decline of BCVA ( $\geq 10$  letters) compared to previous visits. Patients were administered the necessary retinal laser photocoagulation or control IOP medication if any discontinued operation criteria were met: 1) the non-perfused area (NPA) was  $\geq 5$  disc diameters on FFA; 2) neovascularization was evident on the retina; 3) IOP  $\geq 30$  mm Hg. Patients were followed up at day 3 and at months 1, 3, 6, 9, 12 after initial injection. The visit schedule is shown in Table 2. The purpose of the follow-up at day 3 after injection was to observe any adverse events and the data (BCVA, CRT, and IOP) at day 3 were not included in our statistical analysis.

The intravitreal injection procedures were as follows: antibiotic eye drops (0.5% levofloxacin eye drops, Santen, Japan) were applied two days prior to injection. Intravitreal injections were performed in a sterile operating room, with both topical anesthetic (oxybuprocaine hydrochloride eye drops, Santen, Japan) and mydriatic eye drops (tropicamide phenylephrine, Santen) applied prior to injection. Following the application of 5% povidone iodine to the periocular area, eyelids, eyelashes, and conjunctiva sacs, a 30 gauge needle was used to inject 0.5 mg (0.05 mL) conbercept (Chengdu Kanghong Biotechnology, Inc., Chengdu, China) or 1 mg (0.1 mL) TA (Tianjin Kingyork Group Co, LTD, China, dosage form: 50 mg/5 mL) through the pars plana 4 mm posterior to the limbus, with central retinal artery perfusion confirmed through indirect ophthalmoscopy. Patients were required to take antibiotic eye drops four times per day during for three days after injection.

**Outcome Assessments** Safety outcome measures included the BCVA and CRT in each group, and differences in BCVA

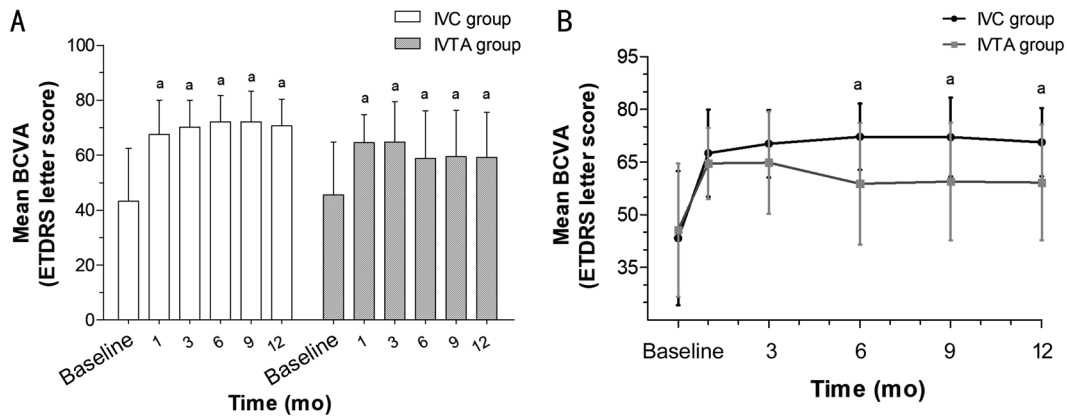
and CRT between the two groups. Adverse effects were evaluated through IOP elevation (IOP  $> 21$  mm Hg), cataract progression (according to LOCS II, grade progression  $\geq 1$  grade on any part of the lens), and other complications such as hemorrhage, vitreous floaters, retinal tears, retinal detachment, endophthalmitis, traumatic cataract and iris neovascularization. The average injection number (total injection number of all patients/total patients number), the ratio of re-injection, and the mean retreatment intervals were compared between the two groups.

**Statistical Analyses** SPSS 13.0 was used for all data analysis. Values are the mean  $\pm$  SD. Mann-Whitney *U* tests were used to compare BCVA, CRT and some of the data of demographics and baseline characteristics. Chi-Square statistic test and Fisher's exact tests were used for data comparison of the actual number of occurrences.  $P < 0.05$  was deemed significant (2-sided).

## RESULTS

**Patient Demographics and Baseline Characteristics** Sixty patients were randomly assigned to either IVC or IVTA groups. Seven patients were eliminated due to violation of the protocols, including failure to meet the selection criteria, meeting the exclusion criteria, or violating the provisions of the medicinal combinations. Finally, 53 patients (53 eyes), including 36 in the IVC group and 17 in the IVTA group (36 and 17 eyes, respectively), completed the study protocol.

Table 3 shows the patient demographics and characteristics at baseline. No differences in gender ( $P = 0.8227$ ), age ( $61.86 \pm 10.63$  y in IVC group vs  $63.41 \pm 7.37$  y in IVTA group;  $P = 0.7949$ ), symptom duration ( $30.75 \pm 18.90$  d in IVC group vs  $28.06 \pm 17.32$  d in IVTA group;  $P = 0.7490$ ), BCVA ( $43.36 \pm 19.09$  letters in IVC group vs  $45.65 \pm 19.01$  letters in IVTA group;  $P = 0.5485$ ), CRT ( $539.86 \pm 174.80 \mu\text{m}$  vs  $512.47 \pm 123.87 \mu\text{m}$ ;  $P = 0.6672$ ) and IOP ( $16.72 \pm 2.11$  mm Hg in IVC group vs  $16.24 \pm 2.36$  mm Hg in IVTA group;  $P = 0.3628$ ) were observed.



**Figure 1 BCVA outcomes** A: Mean BCVA from months 1 to 12 post-injection in the two groups and the comparison of BCVA at each follow-up time point from baseline in each group (IVC group,  $P<0.00001$ ; IVTA group; month 1:  $P=0.0006$ ; month 3:  $P=0.0014$ ; month 6:  $P=0.0139$ ; month 9:  $P=0.0099$ ; month 12:  $P=0.0069$ ); B: Comparison of the mean BCVA between IVC and IVTA groups from months 1 to 12 post-injection (Month 1,  $P=0.2713$ ; month 3,  $P=0.2937$ ; month 6,  $P=0.0015$ ; month 9,  $P=0.0004$ ; month 12,  $P=0.0004$ ). <sup>a</sup> $P<0.05$ .

**Table 3 Participants demographics and baseline characteristics**

Items	IVC group (n=36)	IVTA group (n=17)	mean±SD	P
Age, y	61.86±10.63	63.41±7.37		0.7949 <sup>a</sup>
Gender, n (%)				0.8227 <sup>b</sup>
Male	20 (55.56)	10 (58.82)		
Female	16 (44.44)	7 (41.18)		
Symptom duration, d	30.75±18.90	28.06±17.32		0.7490 <sup>a</sup>
BRVO combined with diabetes mellitus, n (%)	6 (16.67)	3 (17.65)		0.7618 <sup>b</sup>
BRVO combined with high blood pressure, n (%)	22 (61.11)	8 (47.06)		0.3353 <sup>b</sup>
Baseline BCVA (ETDRS letters score)	43.36±19.09	45.65±19.01		0.5485 <sup>a</sup>
Baseline CRT, μm	539.86±174.80	512.47±123.87		0.6672 <sup>a</sup>
Baseline IOP, mm Hg	16.72±2.11	16.24±2.36		0.3628 <sup>a</sup>

SD: Standard deviation; BRVO: Branch retinal vein occlusion; BCVA: Best corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; CRT: Central retinal thickness; IOP: Intraocular pressure. <sup>a</sup>Mann-Whitney *U* test; <sup>b</sup>Chi-square statistic test.

**Efficacy Outcome Measures**

**Best corrected visual acuity** The mean BCVA at month 12 was 70.67±9.67 for the IVC group and 59.18±16.46 for the IVTA group. The mean BCVA in the IVC group significantly improved from months 1 to 12 following initial injection compared to baseline ( $P<0.00001$ ). The same results were observed in the IVTA group ( $P<0.05$ ) compared to baseline values (Figure 1A).

The mean improvement in BCVA at month 12 from baseline was 27.31±18.36 in the IVC group and 13.53±11.37 in the IVTA group. The mean BCVA did not significantly differ between the IVC and IVTA groups at month 1 ( $P=0.2713$ ) or month 3 ( $P=0.2937$ ), suggesting similar efficacies at the early stages of the follow-up period. However, the mean IVC group BCVA significantly improved relative to the IVTA group from months 6 to 12 (month 6,  $P=0.0015$ ; month 9,  $P=0.0004$ ; month 12,  $P=0.0004$ ; Figure 1B; Table 4).

**Central retinal thickness** In the IVC group, the mean CRT significantly decreased from 539.86±174.80 μm at baseline to 286.53±67.70 μm at month 12. The mean IVTA group CRT

significantly decreased from 512.47±123.87 μm at baseline to 362.24±97.26 μm at month 12. The mean decrease in CRT from month 12 to baseline was 253.33±163.69 μm in the IVC group and 150.24±134.32 μm in the IVTA group. The mean CRT significantly changed in both groups from months 1 to 12 compared to the baseline (IVC group:  $P<0.00001$ . IVTA group: month 1,  $P<0.00001$ ; month 3,  $P=0.0002$ ; month 6,  $P=0.0007$ ; month 9,  $P=0.0006$ ; month 12,  $P=0.0007$ ; Figure 2A). The mean CRT did not significant differ during the first 6mo between the two groups (month 1,  $P=0.2543$ ; month 3,  $P=0.2846$ ; month 6,  $P=0.0930$ ). Thereafter, these values remained lower in the IVC group from months 9 to 12 relative to the IVTA group (month 9,  $P=0.0047$ ; month 12,  $P=0.0034$ ; Figure 2B; Table 4).

**Re-injection** IVC patients underwent an average of 1.56±0.69 injections (range, 1-3) and 44.44% (16/36) of patients required additional injections over 12mo. Patients in the IVTA group underwent 1.82±0.81 injections (range, 1-3), and 58.82% (10/17) patients required additional injections over 12mo. The mean injection number ( $P=0.2891$ ) and the ratio of re-

**Table 4 The mean BCVA, CRT and IOP results**

Items	IVC group (n=36)	IVTA group (n=17)	<sup>a</sup> P
Mean BCVA (ETDRS letters score)			
Baseline	43.36±19.09	45.65±19.01	0.5485
Month 1	67.56±12.38	64.59±10.15	0.2713
Month 3	70.22±9.63	64.82±14.57	0.2937
Month 6	72.22±9.41	58.82±17.31	0.0015
Month 9	72.11±11.20	59.47±16.77	0.0004
Month 12	70.67±9.67	59.18±16.46	0.0004
Mean CRT (μm)			
Baseline	539.86±174.80	512.47±123.87	0.6672
Month 1	286.19±68.19	296.94±50.58	0.2543
Month 3	284.50±65.63	319.59±105.23	0.2846
Month 6	303.03±86.65	348.94±102.38	0.0930
Month 9	296.86±89.17	361.12±82.83	0.0047
Month 12	286.53±67.70	362.24±97.26	0.0034
Mean IOP (mm Hg)			
Baseline	16.72±2.11	16.24±2.36	0.3628
Month 1	15.81±2.29	16.94±1.75	0.0949
Month 3	16.14±1.69	18.76±2.68	0.0004
Month 6	16.39±1.92	19.59±3.71	0.0018
Month 9	16.19±1.55	20.53±4.95	0.0004
Month 12	16.61±1.99	21.88±6.08	0.0005

BCVA: Best corrected visual acuity; CRT: Central retinal thickness; IOP: Intraocular pressure; IVC: Intravitreal injection of conbercept; IVTA: Intravitreal injection of triamcinolone acetonide. <sup>a</sup>Mann-Whitney *U* test.

injections ( $P=0.3284$ ) between two groups did not significantly differ. The mean retreatment interval in patients with re-injection was  $97.40\pm36.27$ d in the IVC group and  $68.71\pm36.38$ d in the IVTA group. The mean retreatment interval significantly differed between the two groups ( $P=0.0030$ ).

**Safety Outcomes** No severe systemic or ocular adverse effects occurred. In both groups, no cases of retinal tears, retinal detachment, endophthalmitis, vitreous hemorrhage, traumatic cataracts, or iris neovascularization were reported. No patients received further treatment of retinal photocoagulation. The most common complications were conjunctival hemorrhage (25 eyes in the IVC group, 11 eyes in the IVTA group,  $P=0.7301$ ) and vitreous floaters (12 eyes in the IVC group, 15 eyes in the IVTA group,  $P=0.0006$ ) after injection, all of which required no further treatment.

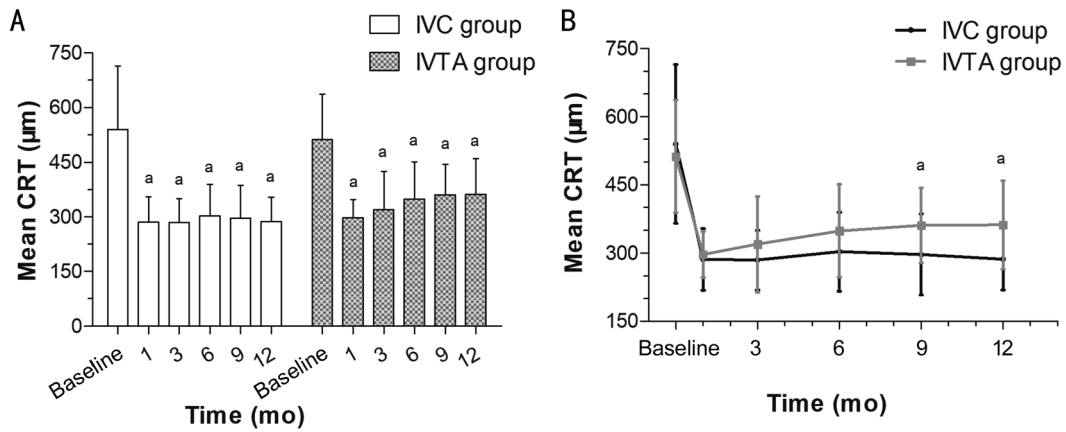
**Intraocular pressure** During the 12-month observational period, one eye (2.78%) in the IVC patient group and seven eyes (41.18%) in the IVTA patient group developed IOP elevation (IOP>21 mm Hg), suggesting a greater possibility of IOP elevation in IVTA vs IVC patients ( $P=0.0012$ ). Over the 12mo, topical IOP-lowering medication (IOP≥30 mm Hg) was administered to a greater number of eyes in the IVTA group (4 eyes, 23.53%) compared to the IVC group (0 eyes, 0;  $P=0.0081$ , Fisher exact test). No patients in either group

received trabeculectomy or other surgery to control the IOP.

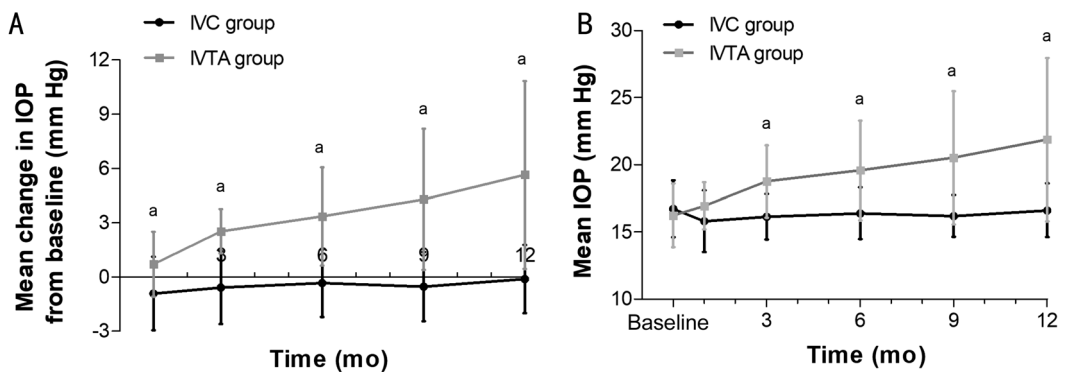
The mean IOP changes at month 12 to baseline were  $-0.11\pm1.89$  mm Hg in the IVC group and  $5.65\pm5.20$  mm Hg in the IVTA group. The mean IOP changes at each observational time point relative to baseline were notably elevated in the IVTA group compared to the IVC group ( $P<0.01$ , Figure 3A), suggesting that IOP fluctuation after injection in the IVTA patients was more evident, reminding us that changes in IOP should be closely monitored.

The mean IOP was stable for patients in the IVC group from  $16.72\pm2.11$  mm Hg at baseline to  $16.61\pm1.99$  mm Hg at month 12. The mean IOP was evidently elevated for patients in the IVTA group from  $16.24\pm2.36$  mm Hg at baseline to  $21.88\pm6.08$  mm Hg at month 12. The mean IOP did not differ between the groups at baseline or after 1 month ( $P>0.05$ ). The mean IOP was significantly higher in the IVTA group compared to the IVC group from 3 to 12mo after injection ( $P<0.01$ ), suggesting a higher probability of IOP increases in the IVTA group (Figure 3B; Table 4).

**Cataract progression** The proportion of eyes with new-onset or progressive lens opacity over the 12mo period according to slit-lamp microscopy assessments after mydriasis was 19.44% (7/36) for the IVC group, and 64.71% (11/17) for the IVTA group. The proportion of eyes with cataract progression in the



**Figure 2 CRT outcomes** A: Mean CRT from months 1 to 12 after injection and the comparison of CRT at each follow-up time point compared to baseline in each group (IVC group:  $P < 0.00001$ ; IVTA group: month 1,  $P < 0.00001$ ; month 3,  $P = 0.0002$ ; month 6,  $P = 0.0007$ ; month 9,  $P = 0.0006$ ; month 12,  $P = 0.0007$ ); B: Comparison of the mean CRT between IVC and IVTA groups from months 1 to 12 after injection (month 1,  $P = 0.2543$ ; month 3,  $P = 0.2846$ ; month 6,  $P = 0.0930$ , month 9,  $P = 0.0047$ ; month 12,  $P = 0.0034$ ). <sup>a</sup> $P < 0.05$ .



**Figure 3 IOP outcomes** A: Comparison of the mean IOP changes from baseline between IVC and IVTA groups from month 1 to 12 post-injection (month 1,  $P = 0.0065$ ; month 3,  $P < 0.00001$ ; month 6,  $P < 0.00001$ ; month 9,  $P < 0.00001$ ; month 12,  $P < 0.00001$ ); B: Comparison of the mean IOP between IVC and IVTA groups from months 1 to 12 post-injection (month 1,  $P = 0.0949$ ; month 3,  $P = 0.0004$ ; month 6,  $P = 0.0018$ ; month 9,  $P = 0.0004$ , month 12,  $P = 0.0005$ ). <sup>a</sup> $P < 0.05$ .

IVTA group were markedly elevated relative to the IVC group ( $P = 0.0012$ ). No patients underwent cataract surgery during the 12-month observational period.

**DISCUSSION**

ME is the most common RVO complication to potentially impact vision. Increased levels of VEGF and inflammatory factors are thought to promote vascular hyperpermeability resulting in the movement of fluid and plasma constituents into the retinal layers of the macula, leading to ME<sup>[12]</sup>. Anti-VEGF agents and corticosteroids are beneficial to the treatment of ME caused by RVO.

Intravitreal medicines, including bevacizumab, ranibizumab, or TA are relatively safe and encouraging results have been reported in patients with ME due to RVO<sup>[8,13-16]</sup>. However, there are few reports about the use of another anti-VEGF medicine called conbercept for the treatment of RVO and no reports on the comparison between conbercept and TA for RVO treatment. This was the first study to compare conbercept and TA for the treatment of BRVO-ME. From our data, IVC and

IVTA both effectively improve BCVA and reduce CRT. IVC maintains longer efficiency and shorter retreatment intervals compared to IVTA.

BCVA is the primary means of the assessment of treatment efficacy, making it a critical outcome measure in this study. We found that improvements in BCVA in eyes treated with conbercept or TA were significant at each follow-up time point after injection, which suggests that both conbercept and TA are effective in BCVA improvements in patients with BRVO-ME. This study also showed no significant differences in BCVA from baseline to month 3 when comparing IVC and IVTA groups, suggesting a similar efficacy during the early stages of the observational period. However, for 6-12mo post-injection, BCVA in the IVC group significantly improved compared to the IVTA group, suggesting a long-term stability of BCVA improvement with IVC. The differences in BCVA between the two groups may have resulted from differences in the half-life and the pharmacological kinetics of the vitreous body between conbercept and TA.

CRT is a strong prognostic indicator of ME. We observed decreased CRTs in both IVC and IVTA groups at each follow-up time point, suggesting that both treatment options could effectively reduce CRT. The mean CRT did not significantly differ between IVC and IVTA from baseline to 6mo after injection. However, the CRTs were significantly thinner in the IVC group compared to the IVTA group at months 9 and 12, indicating that IVC is better than IVTA in continuously reducing CRT.

Regarding the mean number of injections and retreatment ratios, we observed no differences between the two groups during the 12-month follow-up. However, longer retreatment intervals in patients with re-injection were observed in the IVC group vs the IVTA group, which showed more sustained improvements in the IVC group.

There are several reports on the comparison between TA and anti-VEGF agents in BRVO treatment, which were inconsistent with our study results. Byun *et al*<sup>[17]</sup> reported that IVTA and intravitreal bevacizumab injections (IVB) were comparably effective in improving visual acuity. However, compared with the IVB group, the IVTA group required fewer injections and had longer mean improvement duration with reduced disease recurrence. Higashiyama *et al*<sup>[18]</sup> reported no significant differences between IVTA and IVB groups in terms of the mean reduction in CRT from baseline to 12mo following initial injections. IVTA is reportedly more efficient than IVB in improving BCVA in non-ischemic BRVO at months 3 and 6<sup>[19]</sup>. These differences could be attributed to the different protocols, different anti-VEGF agents and different dosage of TA. The differences may also be because conbercept, a new-generation fully humanized anti-VEGF fusion protein with multiple targets and high affinity, has a longer lasting effect than bevacizumab, a small-molecule anti-VEGF antibody.

IVTA has several complications, including cataract progression, IOP elevation and vitreous floaters<sup>[20]</sup>. We observed a greater propensity of IOP elevation (>21 mm Hg) in the IVTA group than the IVC group, and more eyes in the IVTA group received topical IOP-lowering medication over the 12mo period. Our data also suggested that IOP fluctuation after injection in the IVTA group was more obvious than the IVC group. As such, changes in IOP should be closely monitored in IVTA patients. The occurrence of cataract progression was higher in the IVTA group than in the IVC group. For patients with high-risk factors for glaucoma and young patients lacking cataracts, IVTA should be performed with caution due to the cumulative of side-effects.

It should be noted that conbercept has not been included in China's medical insurance for the treatment of RVO. TA remains an optional medicine for patients who cannot afford anti-VEGF agents or Ozurdex. This highlights the necessity for

adequate informed consent and close follow-up observations in IVTA patients.

There were several limitations in this study. The sample size was relatively small, particularly in the IVTA group. Due to the concentration of TA in our hospital (50 mg/5 mL) and side-effect of 4 mg TA injection reported, we used 1 mg (0.1 mL) and not 4 mg (0.4 mL, oversized volume) of IVTA. Blind methods were not adopted in our protocols, and the observation duration was short. In future studies, multi-center controlled clinical trials aimed at discovering the advantages and disadvantages of conbercept vs other kinds of anti-VEGF medicines will be performed.

In conclusion, we found that: 1) IVC and IVTA are both effective treatments for BRVO-ME to improve BCVA and reduce CRT without serious complications; 2) IVC could maintain a longer efficiency than IVTA in improving BCVA and reducing CRT. Retreatment injection intervals of IVC are longer than IVTA. 3) Patients treated with IVTA have a higher incidence of IOP increase and cataract progression.

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