

## Original Article

# Cytokine and chemokine profile changes in patients after intravitreal conbercept injection for center macular edema due to branch retinal vein occlusion

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**Abstract:** Purpose: This study aimed to ascertain cytokine concentrations in patients with center macular edema (CME) due to branch retinal vein occlusion (BRVO) before and during the period of treatment with intravitreal injection of conbercept (IVC) and to determine the relationship between these concentrations and disease activity. Materials and methods: The Bio-Plex<sup>®</sup> 200 System and the Bio-Plex<sup>™</sup> Human Cytokine Standard 27-Plex, Group I (Bio-Rad, Hercules, California, USA) were used to detect cytokine concentrations in aqueous humour. Experimental aqueous humour samples were collected from 22 patients with CME due to BRVO when IVC was administered at baseline and at 1 month, and control aqueous samples were collected by limbal paracentesis from 16 patients undergoing routine cataract surgery. Results: Significantly higher concentrations of vascular endothelial growth factor (VEGF), interleukin 6 (IL-6), IL-8, interferon gamma-induced protein 10 (IP-10), and monocyte chemoattractant protein-1 (MCP-1) were found in the BRVO group than in the control group. In the BRVO group, VEGF levels were significantly lower one month after IVC than at baseline. However, the other cytokines did not significantly change during IVC treatment. The decreases in VEGF levels were closely related to the decreases in central macular thickness (CMT) and the increases in best-corrected visual acuity (BCVA). Conclusions: Many factors, such as angiogenic, inflammatory and growth factors, contribute to the pathogenesis of CME due to BRVO. IVC had no significant effect on cytokines other than VEGF in patients with CME due to BRVO. The changes in BCVA and CMT were associated with VEGF levels after IVC treatment.

**Keywords:** Branch retinal vein occlusion, conbercept, intravitreal implant, intraocular cytokines

## Introduction

Branch retinal vein occlusion (BRVO) is a retinal disease that mainly affects elderly individuals. Center macular edema (CME) is the most critical factor for visual decline in BRVO patients [1]. Currently, there are many treatments available for CME due to BRVO. Anti-vascular endothelial growth factor (VEGF) therapy, such as intravitreal bevacizumab and ranibizumab injections, has become the first choice worldwide [2, 3]. Conbercept is a fusion protein of extracellular domain 2 of VEGF receptor (VEGFR)-1 and extracellular domains 3 and 4 of VEGFR-2 [4]. Specifically, conbercept has a good affinity

for VEGF binding and is superior to ranibizumab. Conbercept is effective at improving BCVA in patients with CME and has a low incidence of adverse effects [5]. However, some patients show recurrence or persistence of CME despite intravitreal anti-VEGF therapy [6, 7]. This phenomenon suggests that in addition to VEGF, other mechanisms may be involved in the occurrence and development of CME due to BRVO.

BRVO originates from intravascular or extravascular obstruction, leading to the development of retinal ischaemia, haemorrhage, and fluid exudation of varying severity. This vascular inju-

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ry is accompanied by a cascade of inflammatory reactions [8, 9]. These processes are controlled by chemokines, growth factors and inflammatory cytokines that regulate the behaviour of lymphocytes, macrophages and bone marrow-derived endothelial progenitor cells.

An imbalance in angiogenic and inflammatory cytokines occurs, possibly defining the anatomic and functional abnormalities in the eye [10-12]. Recent studies have shown that the levels of several inflammatory cytokines in the eye are closely correlated with the severity of CME in BRVO disease [11, 13], which suggests that inflammation plays a key role in the mechanism of CME. Some studies have also shown that the levels of interleukin (IL)-6, monocyte chemoattractant protein-1 (MCP-1), VEGF, and other cytokines in the vitreous fluid of BRVO patients are significantly related to the aqueous flare value (inflammation index) [12]. However, the actual changes in cytokines and chemokines (including VEGF) in BRVO patients after intravitreal anti-VEGF treatment remain unknown. Thus, we investigated the changes in cytokines and chemokines in patients with CME due to BRVO who received intravitreal injection of conbercept (IVC) therapy.

### Materials and methods

#### Subjects

This study was approved by the Research Ethics Committee, Shanghai Tenth People's Hospital, Tongji University, Shanghai, China, and was performed at the Department of Ophthalmology, Shanghai Tenth People's Hospital, Tongji University, Shanghai, China. All participants provided written informed consent before inclusion in the study, and the study procedures abided by the tenets of the Declaration of Helsinki.

We included BRVO patients who were treated with IVC from October 2017 to March 2019. All BRVO patients were treated with an intravitreal injection of 0.05 mL (0.5 mg) conbercept (Chengdu Kanghong Biotechnologies Co., Ltd.; Chengdu, Sichuan, China). The control group was composed of patients who underwent cataract surgery. Criteria for IVC included macular oedema based on fundus fluorescein angiography (FFA), best-corrected visual acuity (BCVA)

less than 20/30, and macular foveal thickness greater than 300  $\mu$ m.

If CME was spontaneously absorbed and visual acuity improved within 4 weeks after the first ophthalmic assessment, the patient was not included in this study. BCVA is reported as the logarithm of the minimum angle of resolution (logMAR). The exclusion criteria for our study included retinal diseases other than BRVO, uveitis, glaucoma, ocular infections, rubeosis iridis, laser photocoagulation, diabetes mellitus, and intraocular surgery including cataract surgery within six months of the planned IVC treatment in our study eye.

#### Fundus findings

Patients underwent ophthalmic examinations before and after IVC. These examinations determined the BVCA and involved the slit-lamp and fundus camera (TRC-50EX; Tokyo Optical, Tokyo, Japan). The central macular thickness (CMT) was measured in a 1-mm central area using optical coherence tomography (OCT) (Zeiss-Humphrey, Dublin, California, USA). The CMT was calculated as the distance from the inner limited membrane of the retina to the basal membrane of the retinal pigment epithelium (RPE).

#### Sample collection

The aqueous humour samples were collected at the same time as IVC or cataract surgery. For IVC patients, aqueous humour samples were collected at baseline and at 1 month. For cataract surgery patients, approximately 100  $\mu$ l of aqueous humour was obtained by anterior chamber paracentesis during the operation. The aqueous humour samples were transferred to sterile plastic tubes immediately after collection and stored at -80°C until analysis.

#### Measurement of cytokine levels

Aqueous humour samples were analysed using a Bio-Plex® 200 System and Bio-Plex™ Human Cytokine Standard 27-Plex, Group I (Bio-Rad, Hercules, California, USA), and the experimental steps were in accordance with the instructions. The cytokines analysed in this study were selected according to previous studies [14-17]: platelet-derived growth factor BB (PDGF-BB), IL-1 $\beta$ , IL-1 receptor antagonist (IL-1ra), IL-2,

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**Table 1.** Demographic characteristics of the patients in the BRVO and control groups

	BRVO (n=22)	Control (n=16)	p value
Age, years	65.05±8.77	63.94±3.85	0.64
Gender (female), %	54.5	43.81	0.92
With hypertension, %	59.1	25	0.33
Duration of symptoms, months	9.18±5.18	NA	NA

The data are presented as the mean ± SD, number (%) or median (range). BRVO, branch retinal vein occlusion; NA, not applicable.

**Table 2.** Clinical characteristics of the patients in the BRVO group

	BRVO before IVC	BRVO after IVC	p value
BCVA (logMAR)	0.84±0.48	0.47±0.32	0.004*
CMT (µm)	495.18±142.30	353.91±122.66	0.001*
Vitreoretinal condition, no.			
Vitreous haemorrhage	0	0	-
Rubeosis iridis	0	0	-
Fibronovascular membranes	0	0	-
TRD	0	0	-

The data are presented as the mean ± SD or number. \*P<0.05. BCVA, best-corrected visual acuity; CMT, central macular thickness; BRVO, branch retinal vein occlusion; IVC, intravitreal injection of conbercept; logMAR, logarithm of the minimum angle of resolution; TRD, tractional retinal detachment.

IL-4, IL-5, IL-6, IL-7, initiator, IL-9, IL-10, IL-12 p70, IL-13, IL-15, IL-17, eotaxin, basic fibroblast growth factor (bFGF), granulocyte colony stimulating factor (G-CSF), granulocyte/macrophage colony stimulating factor (GM-CSF), interferon gamma (IFN-γ), IFN-γ-induced protein 10 (IP-10), MCP-1, macrophage inflammatory protein 1α (MIP-1α), MIP-1β, regulated upon activation normal T cell expressed and secreted (RANTES), tumour necrosis factor α (TNF-α) and VEGF.

### Statistical analysis

SPSS V.19.0 for Windows (SPSS, Chicago, Illinois, USA) was used for statistical analyses. The one-sample Kolmogorov-Smirnov test was used to detect whether the samples were normally distributed. Student's t-test was used to compare normally distributed unpaired continuous variables in two groups. The  $\chi^2$  test or Fisher's exact test was performed to compare discrete variables. Variables with a skewed distribution were evaluated by the Mann-Whitney U test. We used Spearman's rank-order correlation coefficients or Pearson's correlation coefficients to examine the relationships among variables. P values less than 0.05 indicated statistical significance.

## Results

### Baseline characteristics and patient demographics

There were 38 patients included in this study, including 22 patients with CME due to BRVO in the experimental group and 16 cataract patients in the control group. There were no significant differences in age, gender or the proportion of hypertension between the experimental group and the control group (P>0.05). The mean duration of symptoms in the experimental group was 9.18 months (Table 1).

### Influence of IVC treatment on clinical parameters

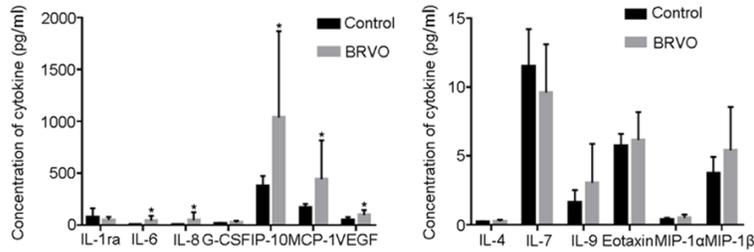
BCVA was significantly improved in the BRVO group after IVC treatment compared with baseline (P=0.004). The mean CMT at baseline was 495.18 µm, which decreased to 353.91 µm in the BRVO group after 1 month of IVC therapy (P=0.001). No patients in the experimental or control group experienced vitreous haemorrhage, fibronovascular membranes, rubeosis iridis, or tractional retinal detachment (TRD) (Table 2).

### Cytokine concentrations at baseline

The levels of VEGF, MCP-1, IL-4, IL-6, IL-8, and IP-10 were higher in the experimental group than in the control group. There were no significant differences in the levels of IL-1ra, IL-7, IL-7, IL-9, eotaxin, G-CSF, MIP-1α, or MIP-1β between the BRVO group and the control group. Other cytokines were below the minimum detectable concentration (Figure 1).

We also analysed relationships between cytokine levels in eyes before IVC in the BRVO group. There were significant correlations between the level of IL-4 and the levels of IL-6, IL-8, IP-10, and MCP-1. There were also significant correlations between the level of IL-6 and

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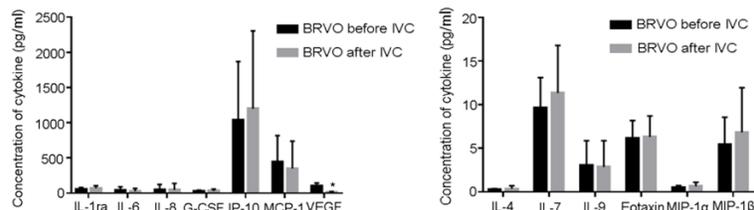


**Figure 1.** Clinical characteristics of the patients in the branch retinal vein occlusion (BRVO) group. \* $P < 0.05$ , BRVO vs Control.

**Table 3.** Correlations between aqueous humour factors before IVC in BRVO patients

Variable	IL-6	IL-8	IP-10	MCP-1	VEGF
	<i>r</i>	<i>r</i>	<i>r</i>	<i>r</i>	<i>r</i>
	<i>p</i> value				
IL-6		0.701	0.706	0.789	0.071
		0.002*	<0.001*	<0.001*	0.867
IL-8			0.006	0.924	0.458
			0.004*	<0.001*	0.260
IP-10				0.730	0.167
				0.001*	0.693
MCP-1					0.452
					0.260

\* $P < 0.05$ . IL, interleukin; IP-10, interferon gamma-induced protein 10; MCP-1, monocyte chemoattractant protein-1; VEGF, vascular endothelial growth factor.



**Figure 2.** Baseline concentrations of the cytokines and chemokines. \* $P < 0.05$ , branch retinal vein occlusion (BRVO) after intravitreal injection of conbercept (IVC) vs BRVO before IVC.

the levels of IL-8, IP-10, and MCP-1. Moreover, the levels of IP-10 and MCP-1 were significantly correlated. However, there were no significant correlations between the levels of VEGF and those of IL-4, IL-6, IL-8, IP-10, or MCP-1 (Table 3).

### Changes in cytokine levels during treatment

The concentration of VEGF in the BRVO group declined significantly 1 month after the first IVC therapy compared with baseline ( $P < 0.0001$ ).

Except for the cytokines below the minimum detectable concentration, which could not be analysed, the other cytokines were not significantly affected by IVC treatment (Figure 2).

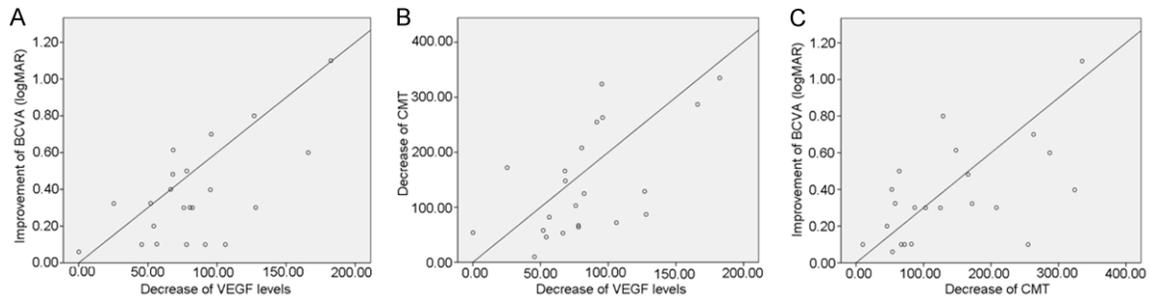
The decrease in VEGF levels was closely related to the decrease in CMT and the increase in VA at 1 month after the first IVC treatment. VEGF levels were significantly correlated with BCVA ( $r = 0.438$ ,  $P = 0.041$ ) and CMT ( $r = 0.624$ ,  $P = 0.002$ ) (Figure 3A, 3B). There was also a positive correlation between the changes in CMT and BCVA ( $r = 0.523$ ,  $P = 0.013$ ) (Figure 3C). The response of a typical BRVO patient to IVC treatment is shown in Figure 4, including fundus photography, OCT, BCVA, and VEGF concentration.

### Discussion

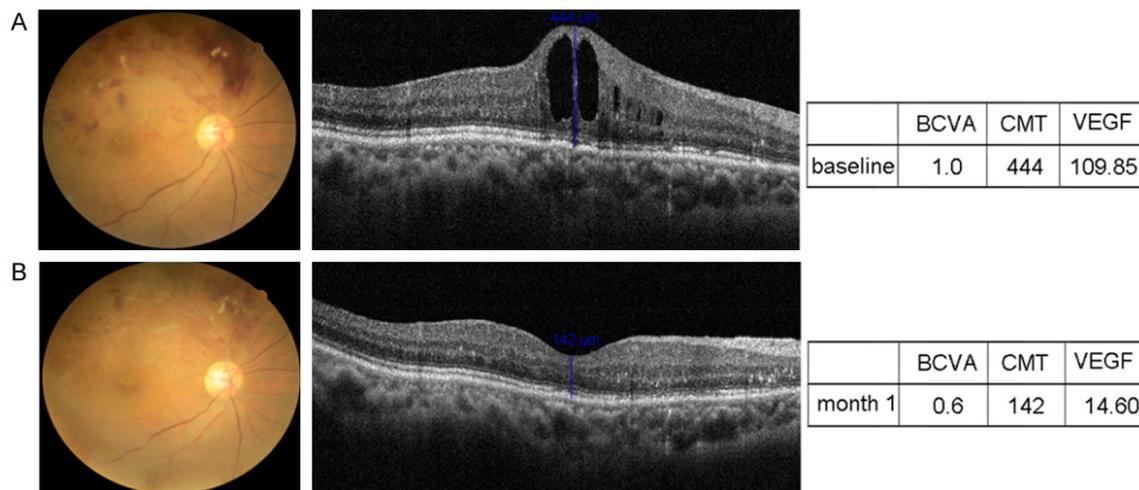
It is necessary to understand the concentrations of cytokines and chemokines and their response to treatment to better elucidate disease pathogenesis and develop improved treatment strategies. Therefore, this study focused on investigating changes in cytokine concentrations in the aqueous humour of patients with CME secondary to BRVO. VEGF levels have a key role in CME due to BRVO [6]; increased VEGF levels can lead to vascular leakage and macular oedema [18].

Intraocular injection of drugs that inhibit VEGF can quickly improve visual function in patients with CME due to BRVO [19]. Our results showed that intraocular VEGF levels were significantly higher in the BRVO group than in the control group, suggesting that VEGF plays an important role in CME secondary to BRVO; these results are in accordance with those of previous studies [15].

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**Figure 3.** Correlations among the changes in vascular endothelial growth factor (VEGF) levels, best-corrected visual acuity (BCVA) and central macular thickness (CMT) at 1 month after intravitreal injection of conbercept (IVC). A. Significant positive correlation between the decrease in VEGF level and the improvement in BCVA at 1 month after IVC ( $r=0.438$ ,  $P=0.041$ ). B. Significant positive correlation between the decrease in VEGF level and the decrease in CMT at 1 month after IVC ( $r=0.624$ ,  $P=0.002$ ). C. Significant positive correlation between the improvement in BCVA and the decrease in CMT at 1 month after IVC ( $r=0.523$ ,  $P=0.013$ ). The decrease in VEGF level was calculated as the VEGF level 1 month after IVC treatment minus the basal level before IVC treatment. The decrease in CMT was calculated as the CMT 1 month after IVC treatment minus the CMT at baseline before IVC treatment.



**Figure 4.** Patient presenting with macular oedema (ME) due to branch retinal vein occlusion (BRVO). Intravitreal injection at baseline (A) and 1 month (B). BCVA, best-corrected visual acuity (logMAR); CMT, central macular thickness (micrometres). Vascular endothelial growth factor (VEGF) levels are presented as picograms/millilitre.

In addition to VEGF, other anti-inflammatory cytokines and growth factors were also examined in this study. IL-6 is an important cytokine that shows functional redundancy and evokes robust responses. IL-6 plays a valuable role in regulating the immune response and inducing the acute inflammatory response [20, 21]. IL-6 levels are related to the severity of CME in BRVO [22]. IL-8 is mainly related to regulation of the acute inflammatory response [23]. IP-10 inhibits VEGF-induced endothelial cell movement and plays an antiangiogenic role by inhibiting endothelial cell proliferation and inducing endothelial cell apoptosis [24, 25]. However, IP-10 overexpression is related to the

proinflammatory functions of VEGF [26]. MCP-1 is a powerful chemoattractant that regulates monocyte infiltration and migration and plays an important role in vascular injury [27]. Endothelial cell injury leads to increased vascular permeability and CME development [28]. After RVO, the levels of eosinophil chemokines (such as MCP-1) increase, providing further evidence that eosinophils play an important role in tissue and vascular reconstruction. In our study, the concentrations of IL-6, IL-8, IP-10 and MCP-1 were significantly higher in the BRVO group than in the control group. We also found significant correlations among IL-6, IL-8, IP-10 and MCP-1. Other cytokines, such as IL-4, IL-7, IL-8,

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IL-9, IL-1ra, eotaxin, G-CSF and MIP-1, showed no significant changes in BRVO patients. These results indicate that some inflammatory factors have key roles in the pathogenesis of CME due to BRVO. Therefore, inflammatory, angiogenic and growth factors participate in the development of CME secondary to BRVO. There is value in determining whether inflammatory factors or proangiogenic proteins play a dominant role in intraocular fluids, and these findings may lead to more individualised treatment.

Conbercept is a fusion protein of extracellular domain 2 of VEGFR-1 and extracellular domains 3 and 4 of VEGFR-2 that has a very good affinity for VEGF [29]. Many studies have shown that conbercept has a good effect on CME and a low incidence of adverse effects in patients with CME due to RVO [5, 30]. In this study, we found a significant improvement in BCVA and a significant reduction in CMT in the first month after IVC treatment compared to baseline in the BRVO group. The BCVA and CMT results are in accordance with previous studies, which have proven the clinical efficacy of conbercept for BRVO [31].

In addition, we observed a significant decrease in VEGF levels at 1 month after IVC treatment in the BRVO group. Furthermore, there were no significant differences in the levels of IL-6, IL-8, IP-10 or MCP-1 in BRVO patients. These results indicated that although IVC therapy for CME caused by BRVO has considerable benefit, the effects of conbercept on inflammatory mediators seem to be limited. Fauser's study indicated that anti-VEGF monotherapy has a limited effect on inflammatory components [32]. In addition, Singer's study showed that the combination of bevacizumab and dexamethasone has a synergistic effect, thereby decreasing the need for retreatment [33]. Thus, comprehensive treatment seems to be a reasonable way to improve efficacy.

VEGF is an effective osmotic factor and a very important regulatory factor in the development of CME induced by BRVO [34]. Our study revealed that the decrease in VEGF level was closely related to the decline in CMT and the increase in VA at 1 month after the first IVC therapy. These findings indicate that VEGF levels are a potential indicator of the disease condition. The changes in intraocular CMT and VEGF levels upon IVC therapy also indicate that

OCT parameters play an important role in guiding VEGF inhibition therapy and retreatment.

This study has some limitations. First, this was a retrospective comparative study. Furthermore, significant differences in cytokine levels may be masked due to the small sample size. Finally, the significant trends and correlations need to be validated in prospective randomised studies. However, the purpose of this study was to provide preliminary evidence for which immune cytokines and growth factors are present and potential top priorities for further research.

### Conclusions

In conclusion, we confirmed that the distribution of cytokines and growth factors in BRVO patients was different from that in control individuals. Our results reveal the cytokines and growth factors that may be particularly important in the context of BRVO and should be further studied. In addition, our study is the first to show no significant differences in factors other than VEGF after IVC treatment in patients with CME due to BRVO. Changes in intraocular VEGF levels were associated with disease activity. These findings may provide evidence for the safety of IVC therapy in patients with CME due to BRVO and help us better understand the mechanism of CME in BRVO patients and develop novel treatment strategies.

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### Disclosure of conflict of interest

None.

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