

Long-term outcomes of anti-VEGF treatment with 5+PRN regimen for macular edema due to central retinal vein occlusion

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Abstract

• **AIM:** To assess the long-term outcomes of treating macular edema (ME) associated with central retinal vein occlusion (CRVO) with a regimen of “5+pro re nata (PRN)”.

• **METHODS:** This retrospective study included 27 eyes of 27 patients with ME associated with non-ischemic CRVO (non-iCRVO group, $n=15$) and ischemic CRVO (iCRVO group, $n=12$). The eyes were treated with five consecutive intravitreal injections of conbercept or ranibizumab, followed by reinjections as needed or PRN. Retinal laser photocoagulation or intravitreal dexamethasone implants (DEX) were implemented in both groups when necessary. The best-corrected visual acuity (BCVA, logMAR) and central retinal thickness (CRT) were recorded at baseline, at 1, 2, 3, 4, 5, 6, and 12mo, and at the final visit. The efficacy rates of BCVA and CRT before and after treatment were calculated. The number of injections at each visit and the incidence of adverse events were also recorded.

• **RESULTS:** The patients, aged 59.4 ± 15.1 y, were followed up for 24.7 ± 8.8 mo (range: 15-42mo). After treatment, BCVA improved significantly from 1.04 ± 0.56 logMAR at baseline to 0.59 ± 0.36 logMAR ($P=0.038$) at the final visit in all patients. Both the non-iCRVO and the iCRVO groups achieved improved BCVA compared to the baseline at all visit points, but there was no statistical significance ($P=0.197$ and 0.33 , respectively). The mean CRT was statistically

reduced compared to baseline at all visit points in all the eyes and in both groups (all $P<0.001$). The apparent effective rate was 22.22% for BCVA and 37.04% for CRT after the first injection, 48.15% for BCVA and 62.96% for CRT after 5 consecutive injections, and 74.08% for BCVA and 100% for CRT at the end of follow up. The average number of injections in all patients was 9.0 ± 2.4 at 12mo and 14.9 ± 8.1 finally with no statistical significance between both groups ($P>0.05$). Laser treatment was applied to all eyes in the iCRVO group, while only 5 patients in the non-iCRVO group. Six patients in the non-iCRVO group and 3 patients in the iCRVO group had a drug switch. DEX was applied to 4 eyes in the non-iCRVO group and 5 eyes in the iCRVO group.

• **CONCLUSION:** The 5+PRN anti-vascular endothelial growth factor (VEGF) regimen is found to be safe and effective for both iCRVO and non-iCRVO, especially in the iCRVO group. The best regimen for such patients needs to be further investigated. Adjuvant laser therapy and DEX are necessary in some cases.

• **KEYWORDS:** central retinal vein occlusion; macular edema; anti-vascular endothelial growth factor; regimen; laser; dexamethasone implant

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INTRODUCTION

Central retinal vein occlusion (CRVO) is the second most common vision-impairing retinal vascular disease in the world. Macular edema (ME) occurs as a major complication of CRVO and results in significant visual loss^[1]. The standard and first-line therapy for CRVO-ME is intravitreal injection of anti-vascular endothelial growth factor (VEGF) drugs^[2]. Several randomized clinical trials (RCTs) have confirmed the safety and efficacy of intravitreal injections of aflibercept monthly

for 6mo for CRVO-ME^[3-4], including the COPERNICUS^[5] and GALILEO^[6] studies. The SCORE2^[7] study included 362 patients who were randomized 1:1 and received 6 monthly injections of either bevacizumab or aflibercept. The LEAVO^[8] study included 436 patients allocated 1:1:1 to the ranibizumab, bevacizumab, and aflibercept groups. All patients received a 4+*pro re nata* (PRN) regimen and were followed up for 2y. The mean number of injections in the first year ranged from 8.2 to 11.8, and the mean best-corrected visual acuity (BCVA) improved from 12.7 to 18.9 letters at the endpoint.

However, the results of RCTs may not reflect real-world effectiveness, since the actual practices in clinics may differ from the conditions strictly controlled by RCTs. Inadequate or non-standard treatment in clinical practice often leads to unsatisfactory treatment outcomes, requiring additional injections or switching to a different anti-VEGF drug^[9-10] or dexamethasone implants (DEX)^[11-12] in follow-up visits. Several retrospective real-world studies^[13-15] that used 1+PRN or 3+PRN treatment regimens reported mean numbers of injections in the first year of 3.7 to 7.6, and a mean improvement in visual acuity (VA) of 8.0 to 14.8 letters at month 12, indicating that fewer injections in real clinical practices may result in unsatisfied BCVA improvement.

According to our observations in clinical practice, BCVA or macular structure in some CRVO patients is still unsatisfactory after two or three injections due to the recurrence of ME or persistent fluid cysts, and additional injections are required. Therefore, the aim of the study was to evaluate the clinical outcomes and patterns of the 5+PRN regimen in patients with ME secondary to ischemic CRVO (iCRVO) and non-ischemic CRVO (iCRVO), with a follow-up time exceeding 15mo.

SUBJECTS AND METHODS

Ethical Approval The current study adhered to the tenets of the Declaration of Helsinki and approved by the Medical Research Ethics Committee and Institutional Review Board of the Hospital, and the registration number of this study in the Chinese Clinical Trial Registry is ChiCTR2000040087. The risks/benefits of intravitreal injection and laser therapy were explained to all patients, and they all provided related written informed consent.

Enrollment of Subjects This retrospective study included 27 eyes of 27 patients diagnosed with CRVO-ME by the same ophthalmologist between November 2014 and September 2020. Records were collected for at least five consecutive loading doses of anti-VEGF injections within the study period, and a follow-up exceeded 15mo. Inclusion criteria were as follows: 1) fundus manifestation and fundus fluorescein angiography (FFA) conformed to diagnosis of CRVO; 2) macular thickness >250 μm by spectral-domain optical coherence tomography (OCT) scans at the initial visits;

3) ME treated with intravitreal injections of conbercept or ranibizumab. Exclusion criteria included eyes with branch retinal vein occlusion, vitreomacular traction, age-related macular degeneration, glaucoma, associated diabetes, hypertensive or renal retinopathy and that have not previously received surgical treatment or anti-VEGF therapy.

Ophthalmic Examinations At the initial visit, the patient's medical history, including systemic diseases, was collected through medical interviews. At 1, 2, 3, 4, 5, 6, and 12mo and the final visit, all patients underwent a comprehensive ophthalmic examination, including BCVA with the Snellen chart, which was converted to logarithm of the minimum angle of resolution (logMAR), intraocular pressure (IOP), indirect ophthalmoscopy, slit-lamp biomicroscope anterior segment, fundus examination, and OCT examination. FFA examination was performed on each patient at baseline and at each follow-up visit, based on the judgment of the ophthalmologists. A non-perfusion area larger than 10 disc areas on the FFA examination was defined as iCRVO. The CRVO subtypes (ischemic and non-ischemic) were determined by two masked retinal specialists. The deadline observation was March 2022.

Anti-Vascular Endothelial Growth Factor Treatment

Patients received either ranibizumab (0.5 mg/0.05 mL) or conbercept (0.5 mg/0.05 mL) monotherapy or underwent a switch between the two drugs. All 27 eyes received intravitreal injections every four weeks for five consecutive times. After the loading treatment, patients received an additional injection if they met any of the following criteria: 1) BCVA decrease of ≥ 0.1 logMAR; 2) central retinal thickness (CRT) increase of ≥ 50 μm ; or 3) BCVA decrease due to ME recurrence or persistent fluid sac cavity in the neuroepithelium. Drug switching between anti-VEGF may apply when ME persists or reappears after more than 2 consecutive injections of conbercept or ranibizumab.

Intravitreal Dexamethasone Implants DEX (Ozurdex Allergan Inc., Irvine, CA, USA) is the only glucocorticoid drug approved by the US Food and Drug Administration and the European Union for treating ME associated with retinal vein occlusion (RVO-ME). Multicenter clinical trials have shown that intravitreal injection of Ozurdex alone is safe and effective for RVO-ME^[16-17] and it can also be used for RVO-ME patients with poor anti-VEGF treatment efficacy^[18-19]. Thus, Ozurdex was applied to CRVO-ME patients who showed persistent or recurrent ME, despite repeated anti-VEGF therapy in this study.

Laser Treatment The Novus Varia multi-wavelength laser (Lumenis, USA) was used for panretinal photocoagulation (PRP) or treatment on partial non-perfusion areas in CRVO-ME patients. Laser irradiation was performed 500 μm away from the fovea. PRP was performed outside the superior and

Characteristics	All eyes (n=27)	Non-iCRVO (n=15)	iCRVO (n=12)	n (%)
Age (y), mean±SD	59.4±15.1	59.1±16.8	59.8±13.4	
Male	13 (48.1)	7 (46.7)	6 (50)	
Right eye	15 (55.6)	8 (53.3)	7 (58.3)	
IOP (mm Hg), mean±SD	16.2±2.6	16.3±2.3	16.1±3.1	
Hypertension	18 (66.7)	10 (66.7)	8 (66.7)	
Hyperlipidemia	12 (44.4)	6 (40)	6 (50)	
Diabetes	6 (22.2)	3 (20)	3 (25)	
Follow-up time (mo), mean±SD	24.7±8.8	25.7±8.6	23.5±9.4	
Baseline BCVA (logMAR), mean±SD	1.04±0.56	0.84±0.39	1.28±0.66	
Baseline BCVA (ETDRS), mean±SD	36.9±19.2	43.5±19.3	28.7±16.3	
Baseline CRT (μm), mean±SD	693.2±271.3	638.9±247.3	761.2±295.2	

logMAR: Logarithm of the minimum angle of resolution; BCVA: Best-corrected visual acuity; IOP: Intraocular pressure; CRT: Central retinal thickness; ETDRS: Early treatment diabetic retinopathy study.

inferior vascular arch, 2500 μm from the fovea on the temporal side and 500 μm from the optic disc edge on the nasal side. Laser parameters were as follows: the spot diameter was 200-300 μm, the power output was 200-500 mW, the exposure time was 200ms, and the reaction was grade II-III heavy white. The range was from the outer spot of the superior and inferior temporal vascular arch to the serrated margin, and the upper, lower, and nasal edges of the disc. The spot spacing was one spot diameter.

Efficacy Criteria In reference to the European Society of Retinal Diseases RVO Clinical Guidelines^[2], the efficacy criteria were defined in our study as follows: 1) Cured: CRT is in the normal range. Visual acuity was normal or restored to pre-onset VA; 2) Apparent effective: CRT decreased by more than 50% compared with the baseline; BCVA increased by 20 letters or more; 3) Effective: CRT decreased by <50% and ≥10% compared with baseline; BCVA increased by 10 letters or more; and 4) Ineffective: CRT remained unchanged or continued to worsen; BCVA did not change or decreased; complications such as neovascular glaucoma occurred.

Statistical Analysis All statistical analyses were carried out using SPSS statistical software version 25.0 (IBM, New York, USA). Data are presented as mean±standard deviation (SD). The logMAR and CRT parameters before and after treatment were compared using paired sample *t*-tests. Differences between treatment groups were compared using independent sample *t*-tests. A Chi-square test was used to compare the rates of VA improvement among the different groups at different periods. A *P*-value of <0.05 was considered statistically significant.

RESULTS

Demographic and Clinical Characteristics This study enrolled 27 eyes diagnosed with CRVO-ME. Table 1 shows the baseline characteristics of the included patients with different types of CRVO before anti-VEGF treatment. The patient

sample comprised 13 males and 14 females, with a mean age of 59.4±15.1y. The affected eyes included 12 left eyes and 15 right eyes. The mean follow-up period was 24.7±8.8mo (range: 15-42mo). The patients included 15 patients with non-iCRVO and 12 with iCRVO. The mean baseline BCVA was 0.84±0.39 logMAR for the non-iCRVO group and 1.28±0.66 logMAR for the iCRVO group. The mean baseline CRT was 638.9±247.3 μm for the non-iCRVO group and 761.2±295.2 μm for the iCRVO group.

Visual and Anatomical Outcomes After anti-VEGF treatment, the mean baseline BCVA (1.04±0.56 logMAR) of all included patients steadily improved and peaked to 0.59±0.36 logMAR at the final visit (*P*=0.038; Figure 1). BCVA improved throughout the observation time in both the non-iCRVO and iCRVO groups, but there was no statistical significance in both groups (*P*=0.197 and 0.33, respectively; Figure 1). The mean CRT at different time points for 27 patients is shown in Figure 2. CRT significantly decreased throughout the observation time in all included patients and both non-iCRVO and iCRVO groups (*P*<0.001), and reach to the lowest value at the last visit. Statistical differences at each visit time compared to the baseline for BCVA and CRT are shown in Figure 2.

Efficiency of BCVA and CRT Improvement After the first injection, the apparent effective rate for all included patients was 22.22% for BCVA and 37.04% for CRT. After five consecutive injections, the apparent efficiency and total effective rate for BCVA were 48.15% and 62.96%, respectively (Table 2). Moreover, the total effective rates for BCVA and CRT increased with the number of injections, reaching to 74.08% and 100% respectively at the last visit.

Therapeutic Intervention Twelve iCRVO eyes finished PRP treatment before and after the first injection (Figure 3). Five non-iCRVO eyes received local laser therapy targeting non-perfusion areas at 3, 6, and 12mo (Table 2). Four and five eyes received intravitreal injections of Ozurdex in the non-iCRVO

Table 2 Efficacy rate (%) and therapeutic intervention

Intervention	Apparent effective		Effective		Total effective		Ineffective		Laser intervention		Dexamethasone intravitreal injection		Drug switch between conbercept & ranibizumab	
	BCVA	CRT	BCVA	CRT	BCVA	CRT	BCVA	CRT	Non-iCRVO	iCRVO	Non-iCRVO	iCRVO	Non-iCRVO	iCRVO
1mo	22.22	37.04	37.04	44.44	59.26	81.48	40.74	18.52	/	12/12 (100)	/	/	/	/
2mo	29.63	48.15	29.63	44.44	59.26	92.59	40.74	7.41	/	/	/	/	/	/
3mo	44.44	59.26	11.11	33.33	55.55	92.59	44.44	7.41	1/15 (6.67)	/	1/15 (6.67)	/	1/15 (6.67)	3/12 (25)
4mo	37.04	59.26	25.93	33.33	62.97	92.59	37.04	7.41	/	/	1/15 (6.67)	/	/	/
5mo	48.15	62.96	18.52	22.22	66.67	85.18	33.33	14.82	/	/	/	/	1/15 (6.67)	/
6mo	44.44	66.67	22.22	22.22	66.66	88.89	33.33	11.11	3/15 (20)	/	1/15 (6.67)	2/12 (16.7)	2/15 (6.67)	/
12mo	44.44	70.37	14.81	25.93	59.25	96.3	40.74	3.7	1/15 (6.67)	/	1/15 (6.67)	3/12 (25)	2/15 (6.67)	/
Final visit	48.15	88.89	25.93	11.11	74.08	100	25.93	0	/	/	/	/	/	/

BCVA: Best-corrected visual acuity; CRT: Central retinal thickness; iCRVO: Ischemic central retinal vein occlusion.

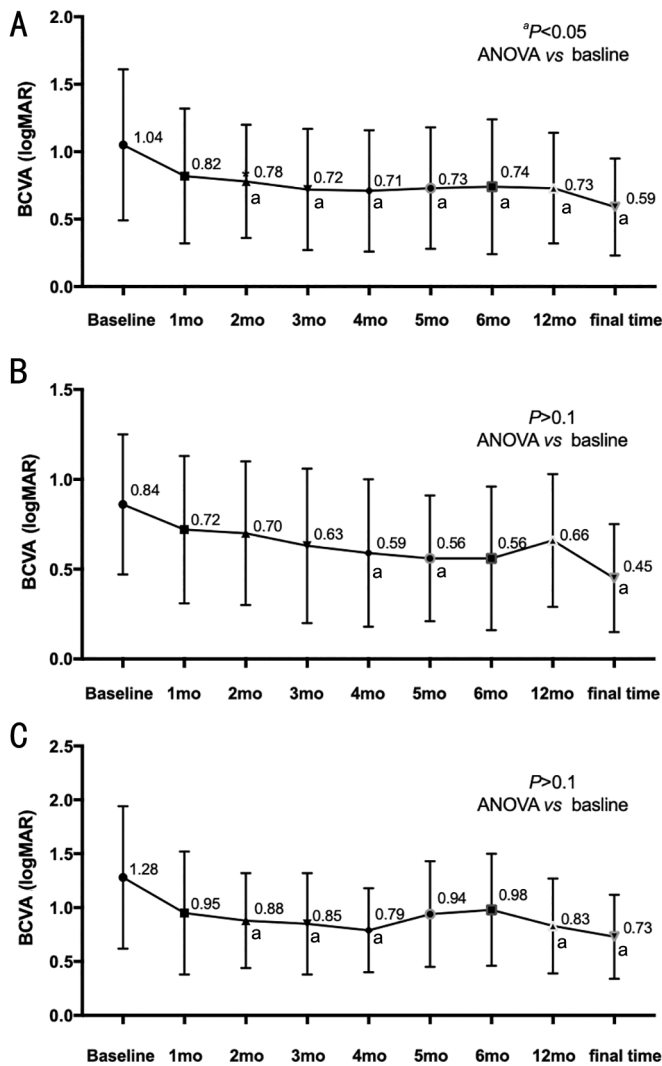


Figure 1 BCVA at each observation point during the follow up time
 A: BCVA in total; B: BCVA in non-iCRVO group; C: BCVA in iCRVO group. BCVA: Best-corrected visual acuity; CRVO: Central retinal vein occlusion; iCRVO: Ischemic central retinal vein occlusion. ^a*P*<0.05.

group and the iCRVO group, respectively. Table 3 illustrates the number of injections in each group at the 12-month and final visits. The median number of injections in the total CRVO population was 9.0±2.4 and 14.9±8.1 at the 12-month and final visits, respectively. The eyes received an average of

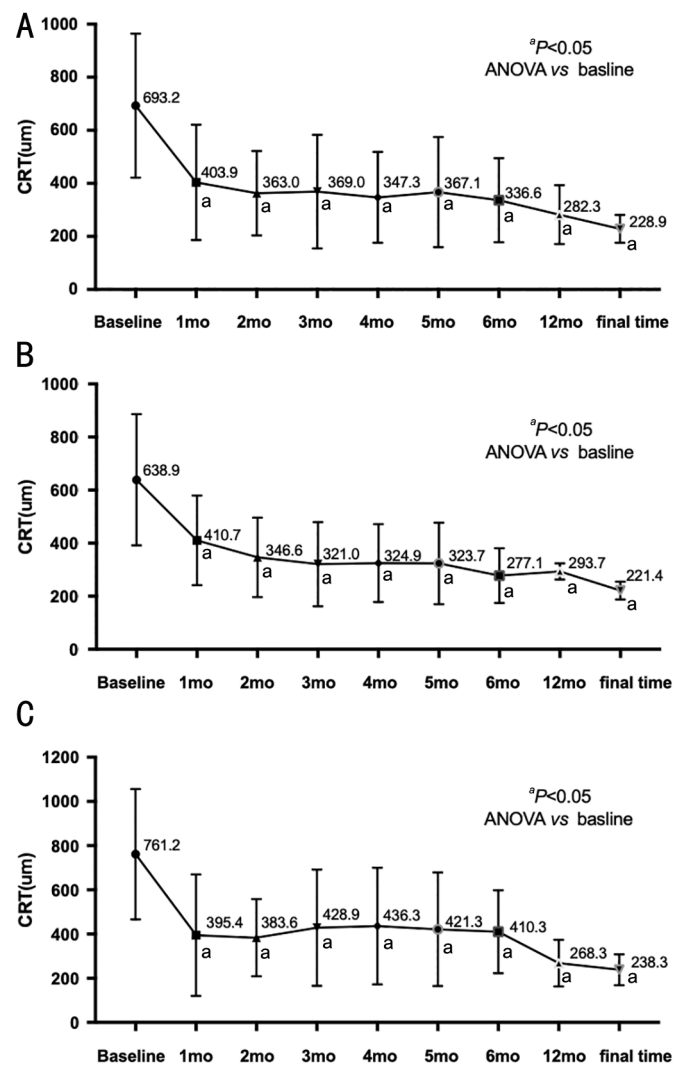


Figure 2 CRT at each observation point during follow up time
 A: CRT in total; B: CRT in non-iCRVO group; C: CRT in iCRVO group. CRT: Central retinal thickness; iCRVO: Ischemic central retinal vein occlusion. ^a*P*<0.05.

14.4±8.8 injections in the non-iCRVO group and 15.5±7.5 injections the iCRVO group at the final visit. After five consecutive injections, the injection intervals were 1.32±1.03 and 1.41±0.36mo in the non-iCRVO group and the iCRVO group, respectively (*P*>0.10). In the iCRVO group, the number

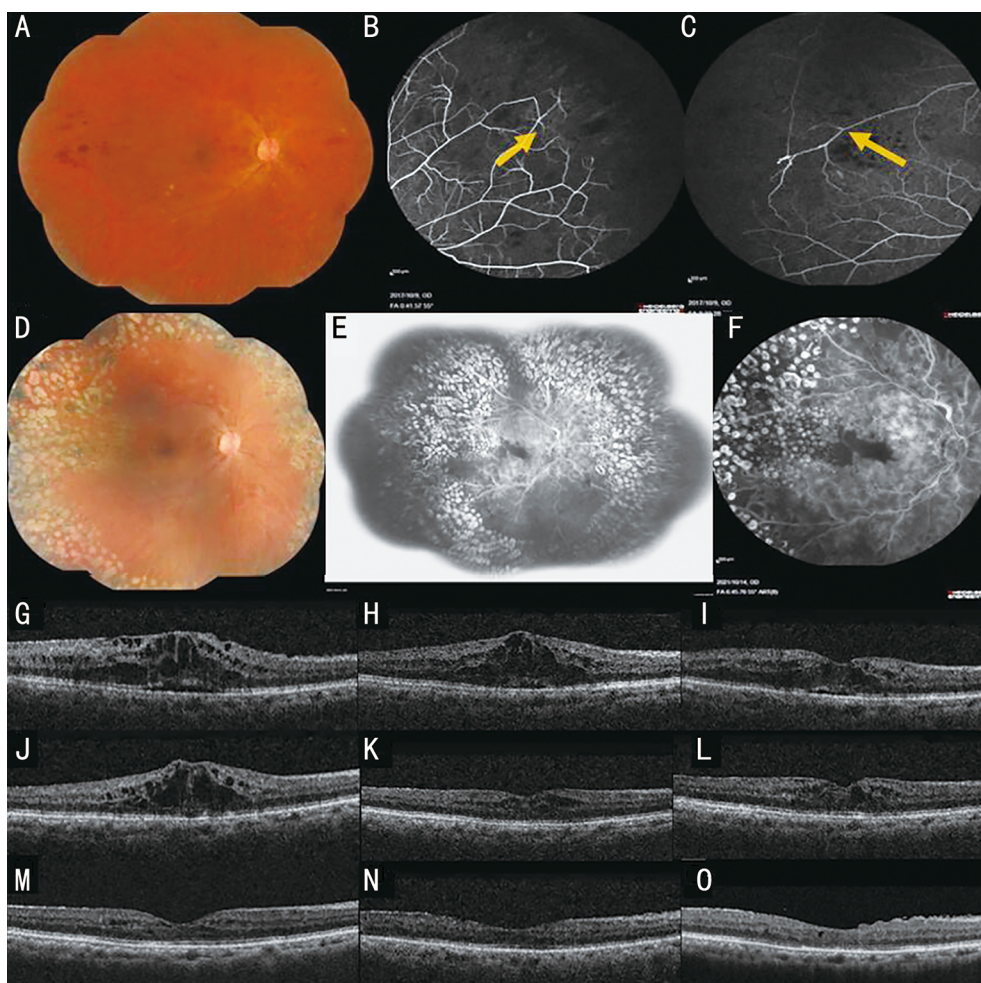


Figure 3 Changes in ME after treatment of a patient with iCRVO A 30-year-old male patient diagnosed with iCRVO-ME in the right eye, with baseline BCVA of 1.0 logMAR and CRT 533 μm , received 26 injections of conbercept during a 34mo follow-up period, and received PRP within 1mo. The patient had a delayed response to anti-VEGF treatment. After 5 consecutive injections, the macular edema appeared. BCVA was 1.0 logMAR, and the CRT was 235 μm at the final visit; no adverse event occurred during the follow-up period. A: Tortuous and dilated retinal veins with extensive flaky retinal hemorrhage; B-C: Large areas of nonperfusion before treatment (yellow arrows); D: Fundus color photograph of this patient who underwent panretinal photocoagulation; E-F: A laser photocoagulation spot and posterior polar retinal capillary fluorescence leakage. After treatment, the ME was gradually absorbed and the CRT decreased to normal (G: 533 μm , baseline; H: 510 μm , 1mo; I: 395 μm , 2mo; J: 497 μm , 3mo; K: 312 μm , 4mo; L: 327 μm , 5mo; M: 227 μm ; 6mo; N: 211 μm , 12mo; O: 235 μm ; 34mo). ME: Macular edema; iCRVO: Ischemic central retinal vein occlusion; CRT: Central retinal thickness; BCVA: Best-corrected visual acuity; PRP: Panretinal photocoagulation; VEGF: Vascular endothelial growth factor.

Table 3 Anti-VEGF therapy status for different types of CRVO during the observation period

Items	Non-iCRVO	iCRVO	<i>P</i>
Injection interval after initial 5 loadings (mo)	1.32 \pm 1.03	1.41 \pm 0.36	>0.1
Mean No. of injections at 12mo	9.1 \pm 2.6	8.8 \pm 2.3	>0.1
Mean No. of total injections	14.4 \pm 8.8	15.5 \pm 7.5	>0.1
6-10 injections	33.3%	41.7%	
11-20 injections	53.3%	33.3%	
\geq 21 injections	13.4%	25%	

VEGF: Vascular endothelial growth factor; CRVO: Central retinal vein occlusion; iCRVO: Ischemic central retinal vein occlusion.

of the eyes received 6-10 injections and \geq 21 injections was larger than that in the non-CRVO group. Table 4 shows the overview of 27 patients treatment, 6 and 3 eyes treated with anti-VEGF drugs switched therapy in the non-iCRVO group

(Figure 4) and the iCRVO group, respectively, of which 1 eye had no change in CRT after switching from conbercept to ranibizumab, and 1 eye had no change in CRT after switching from ranibizumab to conbercept, but the CRT all improved after

Table 4 Overview of 27 patients treatment

No.	Age (y)	Type of CRVO	Follow up (mo)	Pre. CRT (μm)	Pre. BCVA (logMAR)	Anti-VEGF drug and switch	Injection No.	DEX intravitreal injection	Laser treatment	Final CRT (μm)	Final BCVA (logMAR)
1	79	Non-iCRVO	24	402	0.82	Ranibizumab	19	No	No	199	1.3
2	55	Non-iCRVO	38	767	1.7	C→R ^a	26	Yes ^a	No	253	0.6
3	67	iCRVO	16	1256	2.48	R→C	9	Yes ^a	Yes	185	1.4
4	40	Non-iCRVO	42	580	0.6	R→C ^a	37	Yes ^a	Yes	235	0.6
5	18	Non-iCRVO	34	564	0.6	C→R	20	Yes ^a	No	234	0.52
6	74	iCRVO	15	753	0.92	R→C ^a	9	Yes ^a	No	214	0.52
7	52	Non-iCRVO	17	595	0.7	R→C ^a	9	Yes ^a	No	222	0.7
8	30	iCRVO	34	533	1	Conbercept	26	No	Yes	235	0.22
9	42	iCRVO	32	503	1	Conbercept	13	No	Yes	281	1
10	44	Non-iCRVO	33	1399	0.92	Conbercept	16	No	No	214	0.3
11	64	iCRVO	39	826	1	Conbercept	26	No	Yes	184	0.52
12	64	Non-iCRVO	19	470	0.4	Conbercept	15	No	Yes	147	0.4
13	66	Non-iCRVO	36	787	0.7	Conbercept	13	No	No	251	0.4
14	57	iCRVO 2	30	568	0.7	Ranibizumab	20	No	Yes	287	0.5
15	66	Non-iCRVO	24	435	0.3	Conbercept	12	No	No	174	0.3
16	77	Non-iCRVO	15	490	0.7	Conbercept	5	No	Yes	210	0.3
17	69	iCRVO	34	457	0.7	Conbercept	27	Yes ^a	Yes	186	0.82
18	58	iCRVO	17	687	1.22	Conbercept	9	No	Yes	227	0.82
19	49	iCRVO	19	859	1.3	Conbercept	8	No	Yes	220	0.3
20	57	Non-iCRVO	22	625	0.82	Conbercept	17	No	No	290	0.22
21	67	iCRVO	16	545	1.3	Conbercept	14	No	Yes	176	0.52
22	71	iCRVO	15	754	1	R→C ^a	10	Yes ^a	Yes	430	0.92
23	77	Non-iCRVO	18	455	1	R→C ^a	5	No	No	222	0.4
24	77	Non-iCRVO	18	589	1.4	R→C ^a	5	No	No	228	0.4
25	70	iCRVO	15	1393	2.79	Conbercept	13	Yes ^a	Yes	235	1.4
26	64	Non-iCRVO	16	841	1.4	Ranibizumab	11	No	No	231	0.7
27	50	Non-iCRVO	20	584	0.6	Conbercept	6	No	No	211	0

Pre. BCVA: Pretreatment best-corrected visual acuity; Pre. CRT: Pretreatment central retinal thickness; DEX: Dexamethasone; R→C: Ranibizumab switch to conbercept; C→R: Conbercept switch to ranibizumab; CRVO: Central retinal vein occlusion; iCRVO: Ischemic central retinal vein occlusion. ^aCRT improved.

DEX injection, and the CRT height in 1 eye did not return to normal at the observation deadline.

Safety Profile Two eyes (7.4%) developed severe lens opacities that affected the BCVA, and one eye (3.7%) developed macular epiretinal membrane. Mild adverse events included mild subconjunctival hemorrhage, vitreous opacity, and temporarily elevated IOP. The above adverse events returned to normal after observation or drug treatment.

DISCUSSION

Unlike the traditional 3+PRN regimen for CRVO-ME, we screened 27 patients who received the 5+PRN regimen and summarized their baseline characteristics, clinical treatment strategies, and efficacy. These eyes had worse mean baseline BCVA (1.04 ± 0.56 logMAR) and higher mean CRT (693.2 ± 271.3 μm). The present study showed that treatment of ME secondary to non-iCRVO and iCRVO with a 5+PRN anti-VEGF regimen combined with Ozurdex and laser treatment achieved significant improvement in BCVA and CRT at the

final visit. During the five consecutive anti-VEGF treatments, the total effective rate for BCVA and CRT declined mildly at 3 and 5mo, respectively. However, the total effective rate for BCVA and CRT increased at 6mo with continuous treatment, suggesting the inevitability and effectiveness of 5+PRN treatment in clinical practice. The mean BCVA improved significantly from 1.04 at baseline to 0.74 ($P > 0.1$) at the 6-month visit and 0.59 ($P < 0.01$) at the final visit for the entire CRVO population, corresponding to an increase of 13 ETDRS letters at the 6-month visit and 21 ETDRS letters at the final visit. Compared to other anti-VEGF drugs, patients injected with aflibercept gained a mean of 18.0 letters and 17.3 letters at 6mo in the COPERNICUS^[5] study and the GALILEO^[6] study, respectively, but our study showed a lower level of visual improvement. The reason may be the smaller number of patients in our study and the lower baseline BCVA compared to these two studies. Moreover, 9 out of 12 eyes in the iCRVO group had baseline BCVA lower than 1.0 logMAR.

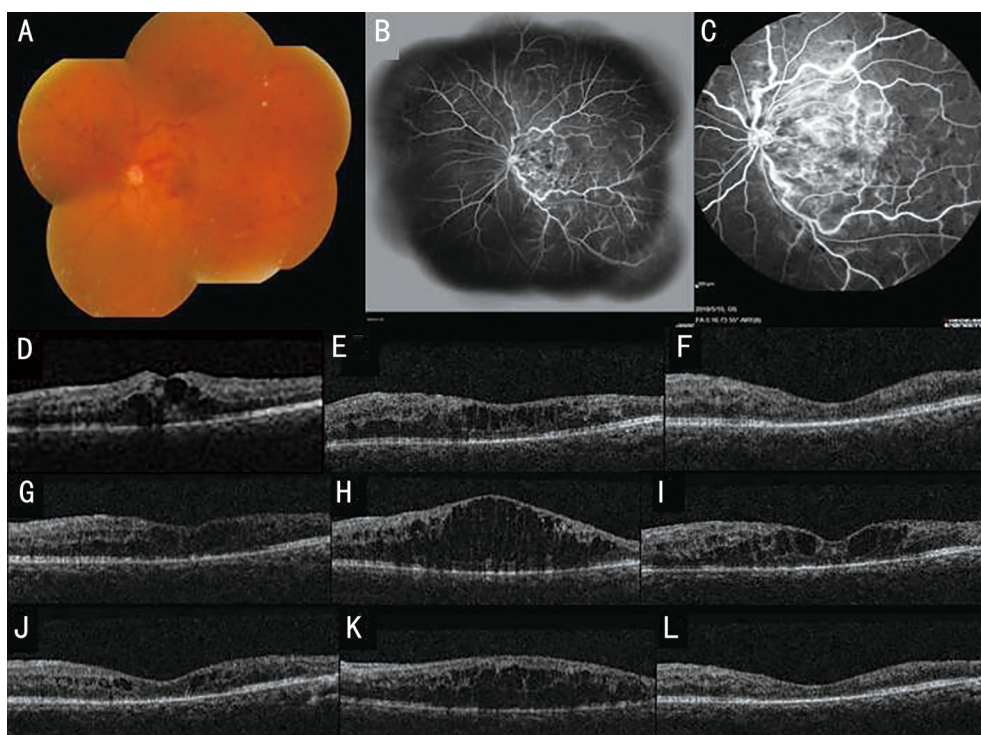


Figure 4 Changes in ME after treatment in a patient with non-iCRVO A 64-year-old female patient, with a baseline BCVA of 0.4 logMAR and CRT 470 μm , diagnosed with non-iCRVO-ME in the left eye, received 15 anti-VEGF injections during a 19mo follow-up period. CRT decreased gradually after 4 consecutive injections, but increased at 5mo, BCVA was 0.4 logMAR and CRT was 147 μm at the final visit; no adverse event occurred during the follow-up period. A: Tortuous and dilated retinal veins with extensive flaky retinal hemorrhage; B-C: Retinal vein wall fluorescence staining, retinal telangiectasia at the posterior pole, fluorescence leakage, and spreading to the macular area. After treatment, the ME was gradually absorbed and the CRT decreased to normal (D: 470 μm , baseline; E: 310 μm , 1mo; F: 146 μm , 2mo; G: 267 μm , 3mo; H: 685 μm , 4mo; I: 233 μm , 5mo; J: 167 μm , 6mo; K: 275 μm , 12mo; L: 147 μm , 19mo). ME: Macular edema; iCRVO: Ischemic central retinal vein occlusion; CRT: Central retinal thickness; BCVA: Best-corrected visual acuity; VEGF: Vascular endothelial growth factor.

Therefore, it is important to highlight the results of our iCRVO group, given that there have recently been a few studies about iCRVO-ME. Some studies have revealed that anti-VEGF drugs are effective for iCRVO eyes. Pielen *et al*^[20] found that BCVA gain over six months in ranibizumab-treated RVO patients is not affected by ischemia, and is associated with less development of new ischemia during the first 6mo, but long-term observations are still lacking. Spooner *et al*^[21] analyzed the 8-year outcomes of eyes with ischemic and non-ischemic RVO following treatment with a 3+PRN anti-VEGF regimen. BCVA (0.88 ± 0.7 logMAR) and CRT (714.6 ± 275.5 μm) improved significantly in eyes with iCRVO at 8y. Mean BCVA improved by 18 letters at 1y and 16 letters at 8y. In the present study, the BCVA of eyes in the iCRVO group gradually improved, with an improvement equivalent to 13 letters at 1y and 21 letters at the final time. CRT also gradually dropped from the baseline of 761.2 ± 295.2 to 238.3 ± 70.3 μm . We should mention that the baseline VA was lower and CRT was higher in the iCRVO group than in the above study, but a smaller sample size was involved; thus, reasonable comparisons could not be made.

Notably, laser treatment plays an important role in the

treatment of iCRVO-ME. Each iCRVO patient in this study underwent PRP treatment. Five eyes (33.3%) in the non-iCRVO group underwent local photocoagulation targeting the ischemic areas. Liu *et al*^[22] showed that conbercept with retinal photocoagulation could effectively improve VA and reduce CRT caused by iCRVO-ME. A systematic review^[23] of the efficacy of PRP in ischemic CRVO indicated that laser therapy achieved better outcomes in neovascularization of the retina, improvement in the visual field, ME, and macular thickness. Our results suggest that significant vision improvements could be achieved over longer periods of treatment, despite the more severe baseline conditions. This is an important finding, especially for iCRVO patients.

During the average follow-up of 24.7mo, the mean number of injections in the first year was 9.0, while a previous retrospective study^[13] administered 7.6 anti-VEGF injections in the first year using a 3+PRN regimen. However, the SCORE2 Report 10 study^[24] (a Phase III prospective, multicenter, randomized clinical trial) reported 9.7-10.8 injections in the first year, and a mean of 4.7 injections in the aflibercept group and 5.5 in the bevacizumab group during months 12 to 24. These previous findings are comparable to the average number

of 14.9 injections at the final visit in the present study. There was no significant difference in the number of injections between the two groups at 12mo (8.8 vs 9.1) and at the final visit time (15.5 vs 14.4). In total, 25% of eyes in the iCRVO group received ≥ 21 injections, nearly twice as many as in the non-iCRVO group, which may suggest that iCRVO patients need more injections.

In this study, 9 eyes underwent drug switching. When ME persisted or reappeared after more than 2 consecutive injections of conbercept or ranibizumab, the switching between the two drugs was performed, 7 eyes switched from initial ranibizumab injection to subsequent conbercept injection, 2 eyes switched from initial conbercept injection to subsequent ranibizumab injection. The conversion from ranibizumab to conbercept was more common, and the improvement rate of CRT (85.7%) is significantly improved. It has been reported that patients with refractory or continuous CRVO-ME who had received at least three consecutive intravitreal injections of bevacizumab or ranibizumab had improved macular thickness and prolonged injection interval after switching to conbercept injection^[10]. As a fusion protein, conbercept bonded to not only VEGF-A but also VEGF-B and placental growth factor, conbercept contains one additional binding domain of VEGF receptor 2 which enhances the affinity. It was believed that the molecular characteristics of the higher affinity of conbercept to VEGF-A might contribute to the superior treatment effect^[25].

Overall, our primary findings suggest that the 5+PRN anti-VEGF regimen was safe and effective for both iCRVO and non-ischemic CRVO in a real-world clinical situation, especially in the iCRVO group. CRVO eyes with lower baseline BCVA and higher baseline CRT may require more anti-VEGF injections and adjuvant therapy, suggesting that continuing long-term anti-VEGF therapy may be necessary to improve and maintain visual and anatomic outcomes.

This study had several limitations, including a related small study population and retrospective design, and the absence of a control group. Several confounding factors were involved, such as glucocorticoid intravitreal injections and laser treatment. The integrity of the outer foveal layers is not reported, and therefore the interpretation of the VA outcome is lacking these relevant data. Future studies with a larger population and a standard treatment protocol and control group will be required to strengthen the statistical validity of the findings of this study, the relationship between OCT characteristics as a predictor and BCVA and CRT in patients with non-iCRVO and iCRVO will be observed.

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REFERENCES

- 1 Costa JV, Moura-Coelho N, Abreu AC, *et al.* Macular edema secondary to retinal vein occlusion in a real-life setting: a multicenter, nationwide, 3-year follow-up study. *Graefes Arch Clin Exp Ophthalmol* 2021; 259(2):343-350.
- 2 Schmidt-Erfurth U, Garcia-Arumi J, Gerendas BS, *et al.* Guidelines for the management of retinal vein occlusion by the European society of retina specialists (EURETINA). *Ophthalmologica* 2019; 242(3):123-162.
- 3 Callizo J, Ziemssen F, Bertelmann T, *et al.* Real-world data: ranibizumab treatment for retinal vein occlusion in the OCEAN study. *Clin Ophthalmol* 2019;13:2167-2179.
- 4 Daien V, Eldem B, Talks J, *et al.* Real-world data in retinal diseases treated with anti-vascular endothelial growth factor (anti-VEGF) therapy—a systematic approach to identify and characterize data sources. *BMC Ophthalmol* 2019;19(1):206.
- 5 Boyer D, Heier J, Brown DM, *et al.* Vascular endothelial growth factor trap-eye for macular edema secondary to central retinal vein occlusion. *Ophthalmology* 2012;119(5):1024-1032.
- 6 Holz FG, Roeder J, Ogura Y, *et al.* VEGF Trap-Eye for macular oedema secondary to central retinal vein occlusion: 6-month results of the phase III GALILEO study. *Br J Ophthalmol* 2013;97(3):278-284.
- 7 Scott IU, VanVeldhuisen PC, Ip MS, *et al.* Effect of bevacizumab vs aflibercept on visual acuity among patients with macular edema due to central retinal vein occlusion: the SCORE2 randomized clinical trial. *JAMA* 2017;317(20):2072-2087.
- 8 Hykin P, Prevost AT, Vasconcelos JC, *et al.* Clinical effectiveness of intravitreal therapy with ranibizumab vs aflibercept vs bevacizumab for macular edema secondary to central retinal vein occlusion: a randomized clinical trial. *JAMA Ophthalmol* 2019;137(11):1256-1264.
- 9 Spooner K, Fraser-Bell S, Hong T, Chang A. Prospective study of aflibercept for the treatment of persistent macular oedema secondary to retinal vein occlusions in eyes not responsive to long-term treatment with bevacizumab or ranibizumab. *Clin Exp Ophthalmol* 2020;48(1):53-60.
- 10 Zhao T, Zhang HS, Chen Y, Wang ZJ. Efficacy of conbercept after switching from bevacizumab/ranibizumab in eyes of macular edema secondary to central retinal vein occlusion. *Int J Ophthalmol* 2022;15(4):609-614.
- 11 Yap TE, Husein S, Miralles de Imperial-Ollero JA, Colizzi B, Cordeiro MF, Younis S. The efficacy of dexamethasone implants following anti-VEGF failure for macular oedema in retinal vein occlusion. *Eur J Ophthalmol* 2021;31(6):3214-3222.
- 12 Ip MS, Oden NL, Scott IU, *et al.* Month 12 outcomes after treatment change at month 6 among poor responders to aflibercept or bevacizumab in eyes with macular edema secondary to central or hemiretinal vein occlusion. *JAMA Ophthalmol* 2019;137(3):281.
- 13 Zeng HY, Liu QA, Li XX, *et al.* One-year efficacy of intravitreal conbercept injection for macular oedema secondary to central retinal vein occlusion in Chinese patients. *Eye (Lond)* 2020;34(8):1459-1464.

- 14 Ozkaya A, Tulu B, Garip R. Aflibercept in macular edema secondary to retinal vein occlusion: a real life study. *Saudi J Ophthalmol* 2017;31(4):211-215.
- 15 Chatziralli I, Theodosiadis G, Chatzirallis A, *et al.* Ranibizumab for retinal vein occlusion: Predictive factors and long-term outcomes in real-life data. *Retina* 2018;38(3):559-568.
- 16 Georgalas L, Tservakis I, Kiskira EE, *et al.* Efficacy and safety of dexamethasone intravitreal implant in patients with retinal vein occlusion resistant to anti-VEGF therapy: a 12-month prospective study. *Cutan Ocul Toxicol* 2019;38(4):330-337.
- 17 Ming S, Xie KP, Yang MZ, He HJ, Li Y, Lei B. Comparison of intravitreal dexamethasone implant and anti-VEGF drugs in the treatment of retinal vein occlusion-induced oedema: a meta-analysis and systematic review. *BMJ Open* 2020;10(6):e032128.
- 18 Houben I, De Zaeytjyd J, Deghislage C, Frost NA, Nijs I, Van Calster J. Efficacy of multiple dexamethasone intravitreal implants for refractory retinal vein occlusion-related macular edema and effect of prior vitrectomy. *J Ocul Pharmacol Ther* 2018;34(10):710-719.
- 19 Călugăru D, Călugăru M. Safety and efficacy of dexamethasone intravitreal implant for treatment of macular edema secondary to retinal vein occlusion in Chinese patients: randomized, sham-controlled, multicenter study. *Graefes Arch Clin Exp Ophthalmol* 2018;256(6):1209-1210.
- 20 Pielen A, Feltgen N, Hattenbach LO, *et al.* Ranibizumab pro Re nata versus dexamethasone in the management of ischemic retinal vein occlusion: *Post-hoc* analysis from the COMRADE trials. *Curr Eye (Lond) Res* 2020;45(5):604-614.
- 21 Spooner KL, Fraser-Bell S, Hong T, Wong JG, Chang AA. Long-term outcomes of anti-VEGF treatment of retinal vein occlusion. *Eye* 2022;36(6):1194-1201.
- 22 Liu ZF, Wang XR, Zhang XY, *et al.* Short-term effects of intravitreal Conbercept injection combined with laser photocoagulation on macular edema secondary to ischemic retinal vein occlusion. *Int J Ophthalmol* 2021(5):732-736.
- 23 Li CF, Wang RR, Liu GJ, *et al.* Efficacy of panretinal laser in ischemic central retinal vein occlusion: a systematic review. *Exp Ther Med* 2019;17(1):901-910.
- 24 Scott IU, Oden NL, VanVeldhuisen PC, Ip MS, Blodi BA, Chan CK, SCORE2 Investigator Group. Month 24 outcomes after treatment initiation with anti-vascular endothelial growth factor therapy for macular edema due to central retinal or hemiretinal vein occlusion. *JAMA Ophthalmol* 2019;137(12):1389.
- 25 Qian TW, Zhao MY, Wan YJ, Li MX, Xu X. Comparison of the efficacy and safety of drug therapies for macular edema secondary to central retinal vein occlusion. *BMJ Open* 2018; 8(12):e022700.