·Clinical Research·

Predictors of short-term outcomes related to central subfield foveal thickness after intravitreal bevacizumab for macular edema due to central retinal vein occlusion

Mei-Zi Wang[1], Kang Feng[2], Yao Lu[2], Fang Qian[2], Xin-Rong Lu[2], Si-Wen Zang[2], Lin Zhao[2]

[1]Department of Ophthalmology, Beijing Tiantan Hospital, Capital Medical University, Beijing 100050, China
[2]Peking University Eye Center, Peking University Third Hospital, Key Laboratory of Vision Loss and Restoration, Ministry of Education, Beijing 100191, China
Correspondence to: Lin Zhao. Peking University Eye Center, Peking University Third Hospital, Key Laboratory of Vision Loss and Restoration, Ministry of Education, Beijing 100191, China. zhaolinoph@126.com
Received: 2014-12-05 Accepted: 2015-02-25

Abstract

• AIM: To investigate the predictive factors for short-term effects of intravitreal bevacizumab injections on central subfield foveal thickness (CSFT) in patients with macular edema (ME) secondary to central retinal vein occlusion (CRVO).

• METHODS: This was a retrospective study in 60 eyes treated with intravitreal bevacizumab injections for ME due to CRVO. Follow-up was three months. The Early Treatment Diabetic Retinopathy Study (ETDRS) score and CSFT measured by spectral-domain optical coherence tomography (SD-OCT) were used to observe the changes in best-corrected visual acuity (BCVA). Baseline BCVA, CSFT, age, CRVO duration and the presence of cystoid macular edema (CME) or subretinal fluid (SRF) were analyzed as potential predictive factors of the effects of intravitreal bevacizumab injections.

• RESULTS: BCVA improved from 0.9 logMAR at baseline to 0.6 logMAR at 3mo, which was associated with a significant reduction in CSFT from 721 μm to 392 μm 3mo after injection. About 50% of CME cases and more than 90% of SRF cases responded to treatment with a complete resolution at 3mo. Age (P=0.036) and low baseline CSFT (P=0.037) were associated with a good 3-month prognosis. Patients >60 years old achieved better CME resolution (P=0.031) and lower CSFT at 3mo (305 μm *vs* 474 μm, P=0.003).

• CONCLUSION: Intravitreal bevacizumab significantly improved visual acuity and CSFT in patients with CRVO after 3mo. Older age and lower baseline CSFT were good predictors of short-term CSFT outcomes. The retinal thickness response to bevacizumab might depend on the resolution of CME rather than SRF.

• **KEYWORDS:** central retinal vein; bevacizumab; macular edema; intravitreal injection; central subfield foveal thickness
DOI:10.18240/ijo.2016.01.15

Wang MZ, Feng K, Lu Y, Qian F, Lu XR, Zang SW, Zhao L. Predictors of short-term outcomes related to central subfield foveal thickness after intravitreal bevacizumab for macular edema due to central retinal vein occlusion. *Int J Ophthalmol* 2016;9(1): 86-92

INTRODUCTION

Central retinal vein occlusion (CRVO) is a common vascular disease of the retina that often leads to severe vision loss due to macular edema (ME)[1]. Pathologically, CRVO often leads to increased retinal thickness, cystoid macular edema (CME) and subretinal fluid (SRF) because of the disruption of the blood-retinal barrier [2]. The age- and gender-standardized prevalence of CRVO is estimated to be 0.80 per 1000 individuals [1]. Risk factors include hypertension, age, diabetes, glaucoma, high intraocular pressure, high blood viscosity, cerebrovascular diseases and cardiovascular diseases [3]. Therapeutic options for ME include focal laser photocoagulation [4], intravitreal steroids[5] and surgery [6]. However, some of these options are still controversial.

Several studies have shown the efficacy of intravitreal injections of anti-vascular endothelial growth factor (VEGF) compounds such as bevacizumab, pegaptanib and ranibizumab [7-11]. VEGF levels are increased in the vitreous fluid of patients with CRVO and are positively correlated with retinal thickness, suggesting that VEGF plays an important part in the pathological process of CRVO [12-13]. Therefore, anti-VEGF agents were tried and were proven to be efficient in reducing ME and improving visual acuity (VA)[7,11,14-15].

However, not all patients benefit from anti-VEGF therapy. Some studies have indicated that the elimination of the thickening resulting from ME can improve the VA [16-17], but that the resolution of foveal thickness was incomplete or late in some patients. Several studies observed that age, duration of symptoms, baseline central subfield foveal thickness

(CSFT), and presence of CME or SRF could be potential predictors for VA, but their conclusions remain unclear[18-20]. Moreover, little is known about the predictors for the outcomes of retinal thickness after anti-VEGF treatments. A recent study have shown that after 3mo of ranibizumab, optical coherence tomography (OCT) images provided predictive information for patients with CRVO[18].

Therefore, the purpose of the present study was to investigate the efficacy and the potential predictors of short-term (3-month) outcomes related to CSFT measured by OCT after intravitreal injection of bevacizumab in patients with CRVO.

SUBJECTS AND METHODS

Subjects This was a retrospective study performed in 60 Chinese Han patients (60 eyes), who received at least one injection of 1.25 mg of bevacizumab intravitreally for ME due to CRVO at the Beijing University Eye Center, Beijing University Third Hospital, Beijing, China, between May 2012 and May 2014.

Inclusion criteria were: 1) ME due to CRVO involving the fovea; 2) minimal pretreatment CSFT of ≥320 μm; 3) fluorescein angiography-confirmed non-ischemic CRVO (<10 disc diameter of non-perfusion in CRVO [21]); 4) treatment-naïve; 5) follow-up of at least 3mo post- treatment. Exclusion criteria were: 1) previous treatments such as laser coagulation, intravitreal injection or retinal surgery; or 2) neovascularization or other retinal diseases at baseline.

The present study was approved by the Institutional Review Board of the Beijing University Third Hospital. This study adheres to the tenets of the Declaration of Helsinki. Informed consent was obtained after patients were informed about the nature and possible risks of the study and with special note of the off-label use of bevacizumab.

Examination Baseline examination included a best-corrected visual acuity (BCVA) testing using the Early Treatment Diabetic Retinopathy Study (ETDRS) chart, intraocular pressure measured by the Goldman method, slit-lamp biomicroscopy, color fundus photography, spectral-domain OCT (SD-OCT; Spectralis-OCT, Heidelberg Engineering, Heidelberg, Germany), and fluorescein angiography. CRVO was diagnosed by fundus photography and fluorescein angiography (ff450, Carl Zeiss GmbH, Oberkochen, Germany). BCVA results were converted to the logarithm of the minimum angle of resolution (logMAR) values. The average of all points within the inner circle of 1-mm radius was defined as the CSFT, which was calculated as the distance between the vitreoretinal interface and the retinal pigment epithelial-Bruch's membrane complex through the foveal area [22]. The presence of CME and SRF was also evaluated.

Study Treatment The eyes were anesthetized with 1% tetracaine eye drops. Intravitreal injections of bevacizumab (1.25 mg in 0.05 mL, Genentech, Inc., San Francisco, CA, USA) were administered under sterile conditions using a 30-gauge needle 3.5 mm posterior to the limbus, through the inferotemporal pars plana. Antibiotic drops (levofloxacin, Santen Pharmaceutical Co., Osaka, Japan) were given for 3d before and after the injection.

Study Follow-up and Observational Indexes After a single intravitreal injection of bevacizumab, the effects were evaluated monthly using BCVA and CSFT determined by SD-OCT for 3mo. Additional injections were given for recurrent or persistent ME. In our center, there is no algorithm for administration of bevacizumab; instead, bevacizumab injection is based on OCT results.

Data were interpreted at baseline, 1 and 3mo. Data collected included age, gender, CRVO duration, baseline BCVA, baseline CSFT, number of intravitreal injections, history of diabetes mellitus or arterial hypertension, and the presence of CME or SRF. The main outcomes of this study were changes in BCVA and CSFT measured by SD-OCT. A secondary outcome measure was the resolution of the CME and SRF. Complications and side effects were noted.

Patients with CRVO were divided into two subgroups according to treatment response at 3mo based on SD-OCT: responders (CSFT <320 μm, response group) and late or incomplete responders (CSFT ≥320 μm, incomplete response group). This threshold was based on a previous study suggesting a threshold of <315 μm for normal CSFT when using SD-OCT[23]. A threshold of <320 μm was used in the present study to be even more conservative.

Statistical Analysis Statistical analysis was performed using SPSS 17.0 (SPSS Inc, Chicago, IL, USA). Data are expressed as means±standard deviation (SD). Multivariate analysis was performed using a logistic regression model using the CSFT response as the outcome variable. Potential predictors tested in the multivariate model were BCVA, baseline CSFT, age, duration of the CRVO, and the presence of CME or SRF. Comparisons of baseline and final characteristics between the two groups were performed using the Chi-square test for categorical variables and the Student's t-test for continuous variables. Follow-up and baseline data were compared using the paired t-test. Correlations were tested using the Pearson correlation coefficient. P-values < 0.05 were considered statistically significant.

RESULTS

Demographics and Baseline Characteristics Baseline characteristics of the patients are shown in Table 1. Figures 1 and 2 present two typical cases.

Sixty eyes (60 patients; 28 males and 32 females) with ME due to CRVO were included in the analysis. Mean age was 58.14±16.58y (range: 13 to 86). CRVO was of the non-ischemic type in all patients. Duration of symptoms was 15.40±23.47wk (range: 1 to 144). The average number of

Table 1 Baseline characteristics of all patients with ME secondary to CRVO $\bar{x} \pm s$

Parameters	Responders (n=30)	Incomplete responders (n=30)	All patients (n=60)	P
Age (a)	62.33±16.77	48.64±15.73	58.14±16.58 (13-86)	0.040
Gender (M/F)	15/15	13/17	28/32	0.796
Eye (right/left)	9/21	12/18	21/39	0.135
DM/HTN	8/12	4/8	12/20	0.607
Duration of symptoms (wk)	18.53±30.24	12.04±12.60	15.40±23.47 (1-144)	0.336
Number of injections	1.880±0.600	1.688±0.622	1.80±0.60 (1-3)	0.323
BCVA (logMAR)	0.887±0.371	0.906±0.426	0.897±0.395 (0.1-1.6)	0.928
CSFT (μm)	687.2±164.9	757.6±192.7	721.2±180.8 (328-1157)	0.240
Presence of CME alone (%)	19/30	17/30	36/60 (60)	0.350
Presence of CME with SRF (%)	11/30	13/30	24/60 (40)	0.450

DM: Diabetes mellitus; HTN: Hypertension; BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; CSFT: Central subfield foveal thickness; CME: Cystoid macular edema; SRF: Subretinal fluid.

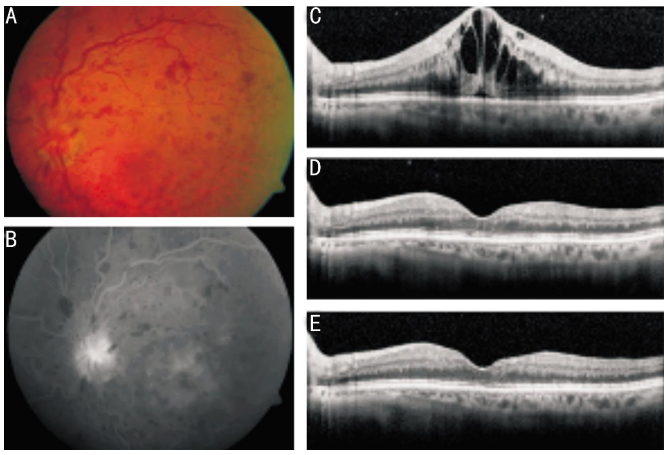

Figure 1 Left eye of an 84-year-old male with a 6-week history of CRVO A: Color fundus photography of the left eye at presentation showing retinal hemorrhages at the posterior pole, venous dilation and tortuosity; B: Fluorescein angiography showing the diffuse leakage at the posterior pole caused by CRVO; C: SD-OCT showing CME with SRF, the baseline CSFT was 592 μm; D: The CSFT at 1mo was 256 μm and ME was resolved; E: The CSFT at 3mo was 249 μm.

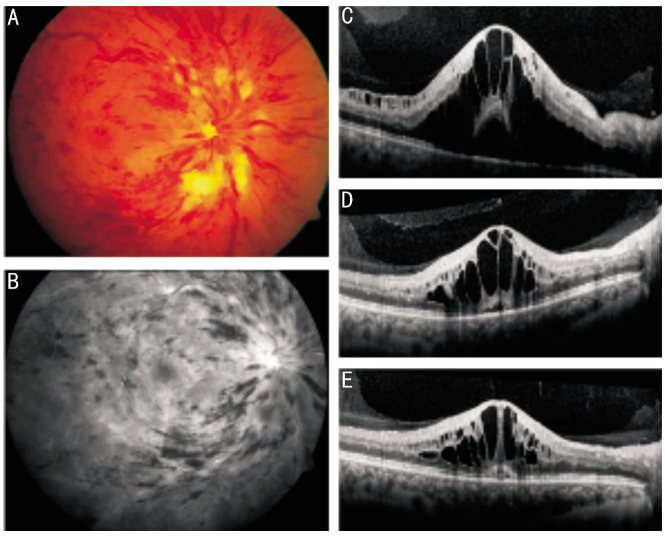

Figure 2 Right eye of an 55-year-old male with a 4-week history of CRVO A: Color fundus photography of the right eye at presentation showing retinal hemorrhages at the posterior pole, venous dilation and tortuosity; B: Fluorescein angiography showing the diffuse leakage at the posterior pole; C: SD-OCT showing CME with SRF, the baseline CSFT was 1157 μm; D: The CSFT at 1mo was 730 μm, but ME was not resolved; E: The CSFT at 3mo was 668 μm.

injections was 1.80 ±0.60. Arterial hypertension was found in 20 patients and diabetes in 12. Ten patients had arterial hypertension and diabetes. At baseline, the mean VA was 0.897 ±0.395 logMAR and the mean CSFT was 721.2±180.8 μm. All patients had CME at baseline. Among them, 36 patients (60%) had CME alone and 24 patients (40%) had SRF.

Except for age (responders: 62.33 ±16.77 *vs* incomplete responders: 48.64±15.73y, P=0.04), there were no differences between the two groups for any baseline characteristic (all P >0.05).

Response to Treatment Table 2 presents the changes in eye parameters after bevacizumab treatment in all patients. Mean CSFT decreased from 721.2 ±180.8 μm to 392.3 ± 180.9 μm (P<0.001) 1mo after treatment, and remained stable at 3mo (392.1 ±185.4 μm, P <0.001 *vs* baseline). Meanwhile, BCVA improved from 0.897±0.395 logMAR to 0.616 ±0.350 logMAR (P<0.001) at 1mo, and remained stable at 3mo(0.616±0.360 logMAR, P<0.001 *vs* baseline). The number of patients with complete resolution of ME was 53.3% at 1mo and 56.7% at 3mo (P=0.412). The frequency of CME alone decreased from 60% at baseline to 41.7% at 1

Table 2 Changes in eye parameters after intravitreal bevacizumab injections in patients with ME secondary to CRVO n (%)

Characteristics	Baseline	1mo	3mo
BCVA (logMAR)	0.897±0.395	0.616±0.350[b]	0.616±0.360[b]
CSFT (μm)	721.2±180.8	392.3±180.9[b]	392.1±185.4[b]
Complete resolution of ME	0	32/60 (53.3)	34/60 (56.7)
Presence of CME alone	36/60 (60.0)	25/60 (41.7)[a]	25/60 (41.7)[a]
Presence of CME+SRF	24/60 (40.0)	3/60 (5.0)[a]	1/60 (1.7)[b]

[a]P<0.05 *vs* baseline; [b]P<0.001 *vs* baseline; BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; CSFT: Central subfield foveal thickness; ME: Macular edema; CME: Cystoid macular edema; SRF: Subretinal fluid.

Table 3 Comparison of eye parameters 3mo after bevacizumab treatment between responders and non-responders *n* (%)

Characteristics	Responders (*n*=30)	Incomplete responders (*n*=30)	[a]*P*
BCVA improvement (logMAR)	-0.327±0.330	-0.175±0.238	0.051
[b]*P*	<0.001	0.001	0.051
CSFT improvement (μm)	-402.6±185.1	-254.9±228.9	<0.001
P	<0.001	0.009	<0.001
Complete resolution of ME	28/30 (93.3)	6/30 (20.0)	<0.001
Presence of CME alone	2/30(6.7)	23/30 (76.7)	<0.001
Presence of CME+SRF	0	1/30 (3.3)	0.390

[a]Intergroup *P*-value; [b]Intragroup *P*-value; DM: Diabetes mellitus; HTN: hypertension; BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; CSFT: Central subfield foveal thickness; CME: Cystoid macular edema; SRF: Subretinal fluid.

and 3mo (P=0.011). The frequency of CME and SRF decreased from 40% at baseline to 5% at 1mo (P=0.005) and to 1.7% at 3mo(P<0.001 *vs* baseline, P=0.308 *vs* 1mo). Baseline BCVA correlated with baseline CSFT (r= 0.573, P<0.001), and the improvement of VA was correlated with the decrease in CSFT (r=0.405, P=0.002).

No cases of endophthalmitis, retinal detachment or any other severe procedure-related complications were observed. No patient developed neovascular complications or systemic adverse events during follow-up.

Comparison Between Responders and Non-responders Table 3 presents the comparison of the outcomes between the two groups. BCVA was improved in both groups (responders: -0.327±0.330 logMAR, P<0.001; incomplete responders: -0.175±0.238 logMAR, P=0.001), but without difference between the two groups (P=0.051). CSFT was improved in both groups (responders: -402.6±185.1 μm, P< 0.001; incomplete responders: -254.9±228.9 μm, P=0.009), and the best improvement was observed among responders (P<0.001). However, more patients achieved a complete resolution of ME among responders compared with incomplete responders (93.3% *vs* 20.0%, P<0.001). The frequency of CME alone was lower among responders after treatment (6.7% *vs* 76.7%, P<0.001). There was no difference in the frequency of CME and SRF (P=0.390).

Multivariate Analysis Age, duration of the disease, baseline BCVA, baseline CSFT and the presence of baseline CME alone or CME and SRF were included in a multivariate analysis using the achievement of a CSFT <320 μm as the dependent variabler. Analysis revealed that young age (P=0.036) and high CSFT at baseline (P=0.037) were associated with a bad 3-month prognosis (Table 4).

Subgroup Analysis Based on Age The subgroup of patients who were older than 60y (34 eyes, 56.7%) revealed a considerable decrease of 408.1 μm in the mean CSFT (from 731.8 μm to 305.1 μm, P<0.001). In contrast, patients aged 60y or less (26 eyes, 43.3%) only showed a decrease of 236.7 μm (from 708.2 μm to 474.5 μm, P<0.01), and the difference was significant between the two age subgroups

Table 4 Multivariate analysis of final CSFT

Parameters	OR	95%CI	*P*
Age	0.960	0.924-0.997	0.036
Duration	0.986	0.960-1.012	0.282
Baseline BCVA	1.186	0.027-1.290	0.089
Baseline CSFT	1.005	1.001-1.011	0.037
Baseline CME or CME+SRF	0.764	0.205-1.849	0.688

OR: Odds ratios; CI: Confidence interval; BCVA: Best- corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; CSFT: Central subfield foveal thickness; CME: Cystoid macular edema; SRF: Subretinal fluid. Final CSFT was used as the depdendent variable (<320 μm *vs* ≥320 μm).

(P=0.003). Although the initial CSFT was not different between the two groups (P=0.646), the final CSFT in the younger group was significantly worse than in the older group (P=0.003). No significant differences regarding duration, baseline VA, presence of CME or SRF were observed. However, CME resolution was better in the older group compared with the younger one (67.6% *vs* 38.4%, P=0.031) (Table 5).

DISCUSSION

The aim of the present study was to investigate the predictive factors for short-term outcomes related to CSFT after intravitreal bevacizumab injection in patients with ME secondary to CRVO. Results showed that BCVA was improved at 3mo, and was associated with a significant reduction in CSFT after 3mo. About 50% of CME cases and more than 90% of SRF cases responded to treatment with a complete resolution at 3mo. Age and a low baseline CSFT were associated with a good 3-month prognosis. Patients >60 years old achieved better CME resolution and lower CSFT at 3mo compared with patients aged ≤60y.

Although some studies showed the efficacy of intravitreal injection of anti-VEGF drugs [9-11], the causes for the lack of response in some patients with ME due to CRVO remain unknown [18]. The present study showed that most non-ischemic CRVO patients had an immediate response to bevacizumab injections. Moreover, the early responders (CSFT <320 μm at 3mo) achieved better visual improvements

Table 5 Comparisons of baseline and final characteristics between the two age groups $\bar{x} \pm s$

Characteristics	Age≤60a	Age>60a	*P*
n	26	34	
Duration (wk)	11.88±13.07	18.25±29.27	0.309
Baseline BCVA (logMAR)	0.839±0.440	0.891±0.360	0.622
Baseline CSFT (μm)	708.2±235.8	731.8±122.4	0.646
Presence of CME/CME+SRF	16/10	20/14	0.522
3-month BCVA (logMAR)	0.623±0.433	0.609±0.294	0.891
3-month CSFT (μm)	474.6±218.4	305.1±119.9	0.003
Baseline *vs* 3-month BCVA (logMAR)	0.216±0.191	0.284±0.361	0.356
Baseline *vs* 3-month CSFT (μm)	236.7±233.6	408.1±174.1	0.003
Resolution of CME	10/26	23/34	0.031

BCVA: Best-corrected visual acuity; logMAR: Logarithm of the minimum angle of resolution; CSFT: Central subfield foveal thickness; ME: Macular edema; CME: Cystoid macular edema; SRF: Subretinal fluid.

than the late or incomplete responders (CSFT ≥320 μm at 3mo). Multivariate analysis revealed that patients with favorable response to treatment were older and had lower CSFT at baseline. Thus, the foveal thickness response to bevacizumab may depend on the resolution of CME, rather than the presence of SRF. Patients who were older than 60y achieved better resolution of CME and lower CSFT at 3mo. This is supported by Bhisitkul *et al* [18], who observed that early responders to ranibizumab achieved better visual outcomes than late responders, and that early responders had a CSFT of 250 μm or less at baseline; however, they did not observe any effect from age.

In the present study, intravitreal bevacizumab therapy resulted in a significant short-term improvement of the mean VA and a decrease in the mean CSFT at 3mo, which is supported by recent studies[24-25]. The correlation between the improvement of VA and the decrease in CSFT was also observed by Bhisitkul *et al* [18]. Furthermore, CME was resolved in 53% of patients after the first injection without recurrence at 3mo, which is supported by studies by DeCroos *et al* [26] and Hoeh *et al* [27]. In these two previous studies, the response to the first injection was the most important and seemed to be predictive of short-term treatment results[26-27].

Multivariate analysis revealed that patients with favorable retinal thickness response to the treatment were older and had lower CSFT at baseline, whereas baseline VA, duration, and presence of CME or SRF had no predictive value. Only a few studies have examined baseline CSFT as a prognostic factor for OCT treatment outcomes[18-19], but a study reported no significant correlation between baseline CSFT and foveal thickness at the last follow-up [20]. In the present study, lower baseline CSFT was associated with a better response to bevacizumab.

The present study suggested that the early responders (CSFT <320 μm at 3mo) had a tendency to achieve better visual improvements compared with late or incomplete responders (CSFT ≥320 μm at 3mo), with better resolution of CME (P<0.001). Some studies have reported that the presence of SRF at baseline did not influence the response to bevacizumab [20,28]. In addition, results of the present study showed that SRF was present at baseline in 40% of patients and disappeared in more than 90% of patients at 3mo in both groups. Noma *et al* [29] have suggested that the vitreous levels of VEGF were higher in patients with CRVO and SRF than in those with CME alone, suggesting a greater effect of bevacizumab in these patients. Compared with the negative impact of SRF, the resolution of CME might determine the retinal thickness and VA outcomes. As reported by Bhisitkul *et al* [18], patients who had residual CME at 3mo had a worse visual outcome at 6mo. The presence of cystic spaces might be more disruptive to the retinal architecture, predicting that CME would have a negative impact on vision.

Interestingly, in the present study, older patients achieved better resolution of CME and lower CSFT at 3mo. Age has been proven to be a risk factor for retinal vein occlusion[21], and younger age was always predictive of better response for VA outcomes[19,27,30-32]. In addition, some studies have reported that age had no predictive value for VA outcomes [33-34]. Few studies reported the impact of age on foveal thickness outcomes. Ach *et al* [19] suggested that the patients who showed better OCT responses were younger, which may be due to generally healthier ocular tissues in younger patients. However, in the present study, younger age might be predictive of late or incomplete response for foveal thickness outcomes. However, these results should be interpreted with caution because of the small subgroup size. As we know, younger patients with CRVO may have greater association with inflammatory conditions compared with older ones [35] because inflammatory cytokines may play an important role[33,36]. Moreover, inflammatory cytokines were more often correlated with morphologic changes assessed by SD-OCT rather than VEGF-A [37]. A more marked decrease in ME in younger patients after intravitreal anti- angiogenic therapy

was also reported by several studies [21,28,38]. Therefore, VEGF inhibition alone may not be sufficient to decrease the inflammatory response, especially in younger patients with CRVO[37]. Accordingly, addition of an anti- angiogenic agent may be more effective in younger patients.

The present study is not without limitations. First, the sample size was small. Although we could not exclude the effects of the small sample size, the impact of age on the response to retinal thickness outcomes after bevacizumab should be underlined. Second, in spite of the absence of a control group, the retrospective nature of the study was a limitation in itself. In addition, despite the fact that the intervention in our center is based on the Branch Retinal Vein Occlusion: Evaluation of Efficacy and Safety (BRAVO) trial [39], the treatment regimen do not follow a strict treatment algorithm, but is based primarily on OCT-guided therapy, which was reported by previous studies [33,40]. Finally, the follow-up period was not very long (1 and 3mo) because these are the standard post-injection follow-up visits after intravitreal injection of bevacizumab in our center. Therefore, prospective studies with larger sample sizes are necessary to determine factors responsible for the response to bevacizumab in these patients.

In conclusion, the present study suggests that intravitreal bevacizumab injections given by OCT-guided dosing regimen improved VA and CSFT in non-ischemic CRVO patients after 3mo. Lower baseline CSFT and older age were good predictors of short-term CSFT outcomes. Further studies with a larger sample size are necessary to validate these conclusions.

ACKNOWLEDGEMENTS

Conflicts of Interest: Wang MZ, None; **Feng K,** None; **Lu Y,** None; **Qian F,** None; **Lu XR,** None; **Zang SW,** None; **Zhao L,** None.

REFERENCES

1 Rogers S, McIntosh RL, Cheung N, Lim L, Wang JJ, Mitchell P, Kowalski JW, Nguyen H, Wong TY, International Eye Disease Consortium. The prevalence of retinal vein occlusion: pooled data from population studies from the United States, Europe, Asia, and Australia. *Ophthalmology* 2010; 117(2):313-319 e311.

2 Klein R, Klein BE, Moss SE, Meuer SM. The epidemiology of retinal vein occlusion: the Beaver Dam Eye Study. *Trans Am Ophthalmol Soc* 2000;98: 133-141; discussion 141-143.

3 Bertelsen M, Linneberg A, Christoffersen N, Vorum H, Gade E, Larsen M. Mortality in patients with central retinal vein occlusion. *Ophthalmology* 2014;121(3):637-642.

4 Glacet-Bernard A, Mahdavi KN, Coscas G, Zourdani A, Fardeau C. Macular grid photocoagulation in persistent macular edema due to central retinal vein occlusion. *Eur J Ophthalmol* 1994;4(3):166-174.

5 Jonas JB, Akkoyun I, Kamppeter B, Kreissig I, Degenring RF. Intravitreal triamcinolone acetonide for treatment of central retinal vein occlusion. *Eur J Ophthalmol* 2005;15(6):751-758.

6 Berker N, Batman C. Surgical treatment of central retinal vein occlusion. *Acta Ophthalmol* 2008;86(3):245-252.

7 Costa RA, Jorge R, Calucci D, Melo LA, Cardillo JA, Scott IU. Intravitreal bevacizumab (avastin) for central and hemicentral retinal vein occlusions: IBeVO study. *Retina* 2007;27(2):141-149.

8 Ferrara DC, Koizumi H, Spaide RF. Early bevacizumab treatment of central retinal vein occlusion. *Am J Ophthalmol* 2007;144(6):864-871.

9 Priglinger SG, Wolf AH, Kreutzer TC, Kook D, Hofer A, Strauss RW, Alge CS, Kunze C, Haritoglou C, Kampik A. Intravitreal bevacizumab injections for treatment of central retinal vein occlusion: six-month results of a prospective trial. *Retina* 2007;27(8):1004-1012.

10 Jaissle GB, Ziemssen F, Petermeier K, Szurman P, Ladewig M, Gelisken F, Volker M, Holz FG, Bartz-Schmidt KU. Bevacizumab for treatment of macular edema secondary to retinal vein occlusion. *Ophthalmologe* 2006; 103(6):471-475.

11 Braithwaite T, Nanji AA, Lindsley K, Greenberg PB. Anti-vascular endothelial growth factor for macular oedema secondary to central retinal vein occlusion. *Cochrane Database Syst Rev* 2014;5:CD007325.

12 Noma H, Funatsu H, Mimura T, Eguchi S, Shimada K, Hori S. Vitreous levels of pigment epithelium-derived factor and vascular endothelial growth factor in macular edema with central retinal vein occlusion. *Curr Eye Res* 2011;36(3):256-263.

13 Noma H, Funatsu H, Mimura T, Harino S, Hori S. Vitreous levels of interleukin-6 and vascular endothelial growth factor in macular edema with central retinal vein occlusion. *Ophthalmology* 2009;116(1):87-93.

14 Funk M, Kriechbaum K, Prager F, Benesch T, Georgopoulos M, Zlabinger GJ, Schmidt-Erfurth U. Intraocular concentrations of growth factors and cytokines in retinal vein occlusion and the effect of therapy with bevacizumab. *Invest Ophthalmol Vis Sci* 2009;50(3):1025-1032.

15 Pai SA, Shetty R, Vijayan PB, Venkatasubramaniam G, Yadav NK, Shetty BK, Babu RB, Narayana KM. Clinical, anatomic, and electrophysiologic evaluation following intravitreal bevacizumab for macular edema in retinal vein occlusion. *Am J Ophthalmol* 2007;143(4): 601-606.

16 Brown DM, Campochiaro PA, Singh RP, Li Z, Gray S, Saroj N, Rundle AC, Rubio RG, Murahashi WY; CRUISE Investigators. Ranibizumab for macular edema following central retinal vein occlusion: six-month primary end point results of a phase III study. *Ophthalmology* 2010;117 (6): 1124-1133.e1

17 Matsumoto Y, Freund KB, Peiretti E, Cooney MJ, Ferrara DC, Yannuzzi LA. Rebound macular edema following bevacizumab (Avastin) therapy for retinal venous occlusive disease. *Retina* 2007;27(4):426-431.

18 Bhisitkul RB, Campochiaro PA, Shapiro H, Rubio RG. Predictive value in retinal vein occlusions of early versus late or incomplete ranibizumab response defined by optical coherence tomography. *Ophthalmology* 2013; 120(5):1057-1063.

19 Ach T, Hoeh AE, Schaal KB, Scheuerle AF, Dithmar S. Predictive factors for changes in macular edema in intravitreal bevacizumab therapy of retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol* 2010;248 (2): 155-159.

20 Hoeh AE, Ruppenstein M, Ach T, Dithmar S. OCT patterns of macular edema and response to bevacizumab therapy in retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol* 2010;248(11):1567-1572.

21 Natural history and clinical management of central retinal vein occlusion. The Central Vein Occlusion Study Group. *Arch Ophthalmol* 1997;115(4):486-491.

22 Grover S, Murthy RK, Brar VS, Chalam KV. Comparison of retinal thickness in normal eyes using Stratus and Spectralis optical coherence tomography. *Invest Ophthalmol Vis Sci* 2010;51(5):2644-2647.

23 Grover S, Murthy RK, Brar VS, Chalam KV. Normative data for macular thickness by high-definition spectral-domain optical coherence tomography (spectralis). *Am J Ophthalmol* 2009;148(2):266-271.

24 Mehany SA, Mourad KM, Shawkat AM, Sayed MF. Early Avastin management in acute retinal vein occlusion. *Saudi J Ophthalmol* 2010;24 (3):87-94.

25 Epstein DL, Algvere PV, von Wendt G, Seregard S, Kvanta A. Bevacizumab for macular edema in central retinal vein occlusion: a prospective, randomized, double-masked clinical study. *Ophthalmology* 2012;119(6):1184-1189.

26 DeCroos FC, Ehlers JP, Stinnett S, Fekrat S. Intravitreal bevacizumab for macular edema due to central retinal vein occlusion: perfused vs. ischemic and early vs. late treatment. *Curr Eye Res* 2011;36(12):1164-1170.

27 Hoeh AE, Ach T, Schaal KB, Scheuerle AF, Dithmar S. Long-term follow-up of OCT-guided bevacizumab treatment of macular edema due to retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol* 2009;247(12): 1635-1641.

28 Cinal A, Ziemssen F, Bartz-Schmidt KU, Gelisken F. Intravitreal bevacizumab for treatment of serous macular detachment in central retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol* 2011;249(4):513-520.

29 Noma H, Funatsu H, Mimura T. Vascular endothelial growth factor and interleukin-6 are correlated with serous retinal detachment in central retinal vein occlusion. *Curr Eye Res* 2012;37(1):62-67.

30 Wolf-Schnurrbusch UE, Ghanem R, Rothenbuehler SP, Enzmann V, Framme C, Wolf S. Predictors of short-term visual outcome after anti-VEGF therapy of macular edema due to central retinal vein occlusion. *Invest Ophthalmol Vis Sci* 2011;52(6):3334-3337.

31 Epstein DL, Algvere PV, von Wendt G, Seregard S, Kvanta A. Benefit from bevacizumab for macular edema in central retinal vein occlusion: twelve-month results of a prospective, randomized study. *Ophthalmology* 2012;119(12):2587-2591.

32 Daien V, Navarre S, Fesler P, Vergely L, Villain M, Schneider C. Visual acuity outcome and predictive factors after bevacizumab for central retinal vein occlusion. *Eur J Ophthalmol* 2012;22(6):1013-1018.

33 Kriechbaum K, Michels S, Prager F, Georgopoulos M, Funk M, Geitzenauer W, Schmidt-Erfurth U. Intravitreal Avastin for macular oedema secondary to retinal vein occlusion: a prospective study. *Br J Ophthalmol* 2008;92(4):518-522.

34 Kang HM, Chung EJ, Kim YM, Koh HJ. Spectral-domain optical coherence tomography (SD-OCT) patterns and response to intravitreal bevacizumab therapy in macular edema associated with branch retinal vein occlusion. *Graefes Arch Clin Exp Ophthalmol* 2013;251(2):501-508.

35 Fong AC, Schatz H. Central retinal vein occlusion in young adults. *Surv Ophthalmol* 1993;37(6):393-417.

36 Feng J, Zhao T, Zhang Y, Ma Y, Jiang Y. Differences in aqueous concentrations of cytokines in macular edema secondary to branch and central retinal vein occlusion. *PLoS One* 2013;8(7):e68149.

37 Koss M, Pfister M, Rothweiler F, Rejdak R, Ribeiro R, Cinatl J, Schubert R, Kohnen T, Koch F. Correlation from undiluted vitreous cytokines of untreated central retinal vein occlusion with spectral domain optical coherence tomography. *Open Ophthalmol J* 2013;7:11-17.

38 Scott IU, VanVeldhuisen PC, Oden NL, Ip MS, Blodi BA, Hartnett ME, Cohen G, Standard Care versus Corticosteroid for Retinal Vein Occlusion Study Investigator Group. Baseline predictors of visual acuity and retinal thickness outcomes in patients with retinal vein occlusion: Standard Care Versus Corticosteroid for Retinal Vein Occlusion Study report 10. *Ophthalmology* 2011;118(2):345-352.

39 Varma R, Bressler NM, Suner I, Lee P, Dolan CM, Ward J, Colman S, Rubio RG, BRAVO and CRUISE Study Groups. Improved vision-related function after ranibizumab for macular edema after retinal vein occlusion: results from the BRAVO and CRUISE trials. *Ophthalmology* 2012;119(10): 2108-2118.

40 Pieramici DJ, Rabena M, Castellarin AA, Nasir M, See R, Norton T, Sanchez A, Risard S, Avery RL. Ranibizumab for the treatment of macular edema associated with perfused central retinal vein occlusions. *Ophthalmology* 2008;115(10):e47-54.