• Clinical Research •

Efficacy and safety of intravitreal anti-VEGF for myopic choroidal neovascularization

Jing-Yao Liu, Ju-Ping Liu, Xiao-Rong Li

Tianjin Key Laboratory of Retinal Functions and Diseases, Tianjin Branch of National Clinical Research Center for Ocular Disease, Eye Institute and School of Optometry, Tianjin Medical University Eye Hospital, Tianjin 300384, China

Correspondence to: Xiao-Rong Li. Tianjin Key Laboratory of Retinal Functions and Diseases, Tianjin Branch of National Clinical Research Center for Ocular Disease, Eye Institute and School of Optometry, Tianjin Medical University Eye Hospital, Tianjin 300384, China. xiaorli@163.com

Received: 2024-02-09 Accepted: 2025-02-12

Abstract

• **AIM:** To report the 24mo outcomes of vascular endothelial growth factor (VEGF) inhibitors for myopic choroidal neovascularization (mCNV) in routine clinical practice and simultaneously evaluated the real-world safety.

• **METHODS:** The patients who received intravitreal injections of VEGF inhibitors of either ranibizumab (0.5 mg) or conbercept (0.5 mg) for mCNV were analyzed from 1 January 2017 to 1 January 2022. The primary outcome variables were mean change in best-corrected visual acuity (BCVA) and central macular thickness (CMT) changes. The secondary outcome variables included IOP changes, the period of mCNV re-treatment, and ocular adverse events.

• **RESULTS:** Totally 83 patients aged 56.40±15.36y with axial length 29.67±2.09 mm were included. In visual acuity, the mean logMAR BCVA at baseline was 0.81±0.43. After the initial improvement at 1, 3, and 6mo (P<0.05), from month 12 onwards, no statistical difference compared to baseline was found. The mean CMT from 1mo onwards had a statistically significant decrease compared with baseline CMT (P<0.05). The regression model showed better baseline BCVA and thicker baseline CMT, significantly associated with the final outcomes. In univariate analysis, choosing 3+*pro re nata* (PRN) as the initial injection treatment regimen was associated with better BCVA at 24mo [hazard ratio (HR)=-0.65, 95%CI: -1.23, -0.07, P=0.048]. However, the difference was not significant in multivariate analysis (HR=-0.59, 95%CI: -1.21, 0.03, P=0.089). Regarding mCNV recurrence, the mean period (P=0.725) and the proportion of mCNV reactivation (P=1.00) were similar between ranibizumab and conbercept. Kaplan-Meier plot also analyzed that the median time of re-injection was not significantly different among gender, drug, and initial injection treatment regimen. No systemic adverse events related to the therapy were observed.

• **CONCLUSION:** BCVA gains achieved by the end of our study maintain generally sustained at the 24-mo follow-up. The findings also indicate that ranibizumab and conbercept demonstrate comparable efficacy and safety profiles. Additionally, intravitreal anti-VEGF therapy using 1+PRN regimen, offers certain advantages in both efficacy and cost-effectiveness.

• **KEYWORDS:** vascular endothelial growth factor; choroidal neovascularization; conbercept; ranibizumab; myopia

DOI:10.18240/ijo.2025.09.09

Citation: Liu JY, Liu JP, Li XR. Efficacy and safety of intravitreal anti-VEGF for myopic choroidal neovascularization. *Int J Ophthalmol* 2025;18(9):1681-1688

INTRODUCTION

Myopic choroidal neovascularization (mCNV) is the leading cause of low vision or vision loss in patients[1-2]. Patients usually exhibit symptoms such as deformation of vision, central or paracentral scotoma, and decreased central vision[3-4]. In fundus examination, a flat, small, light gray subretinal lesion below or immediately adjacent to the fovea is often observed, which may be accompanied by macular hemorrhage. If mCNV is not treated with appropriate intervention, the patient's prognosis is usually poor. A 10-year follow-up study evaluated the visual outcomes of patients with untreated mCNV and found that visual acuity significantly decreased from baseline at 10y, with the proportion of patients with visual acuity of 20/200 or below increasing from 29.6% at baseline to 88.9% and 96.3% at 5 and 10y, respectively[5].

Vascular endothelial growth factor (VEGF) is a pro-angiogenic cytokine that causes the formation of choroidal neovascularization (CNV). Related studies have also found elevated levels of VEGF in the eyes of patients with

mCNV[3,6-8]. Numerous retrospective and prospective studies have confirmed that intravitreal injection of VEGF inhibitors is an effective and safe treatment option for mCNV[9-13] and has become the front-line treatment regimen in clinical practice. Based on RADIANCE and BRILLIANCE[14-16], the recommended treatment strategy is the 1+*pro re nata* (PRN) regimen, but there is still controversy over the treatment options. Some evidence suggests no significant difference in short-term prognosis between the two regimens[17-19], and some studies have shown that different options of drugs also have similar prognoses[20-21].

In the real world, we found that different doctors had different choices for the treatment plan for patients in clinical practice. The treatment plan was not limited to 1+PRN or 3+PRN but also included the option of 2+PRN. This study was based on the real world to evaluate the 24-mo treatment efficacy and safety of VEGF inhibitors for mCNV patients. It provided an opportunity to understand how physicians managed patients with mCNV in routine clinical practice. We also explored the real-world factors that influence the treatment outcomes.

PARTICIPANTS AND METHODS

Ethical Approval Each patient was informed carefully about the purpose of the research and provided signed consent. The research adhered to the tenets of the Declaration of Helsinki and this study was approved by the Ethical Committee of Tianjin Medical University Eye Hospital (2022ky-15).

Study Design and Selection This study was a retrospective data analysis of treatment-naive eyes that had received intravitreal injections of VEGF inhibitors for mCNV in Tianjin Medical University Eye Hospital. The consultation period was set from 1 January 2017 to 1 January 2022. All these patients were treated with intravitreal injections of ranibizumab 0.5 mg (Lucentis; Novartis Pharma Stein AG, Switzerland) or conbercept 0.5 mg (Lumitin; Chengdu Kanghong Biotechnologies Co.Ltd, China) at first. Patients were treated per clinical practice during the follow-up observation, without restricting the drugs or treatment regimens used to treat mCNV.

The inclusion criteria were diagnosis of highly myopic, defined as axial length >26 mm or refractive error at least of -6.0 diopters, or fundus examinations showing myopic retinal changes, such as chorioretinal atrophy, posterior staphyloma, or atrophic patches, complicated by a treatment-naive myopic CNV at the time of presentation (baseline). Excluded were patients with a previous history of photodynamic therapy (PDT) or intravitreal anti-VEGF injections, vitreoretinal surgery, or CNV secondary to neovascular age-related macular degeneration or other causes. Patients with unavailable or missing data were also excluded.

Data Collection and Measurement Data was collected from each clinical practice, including the medical charts and imaging studies of mCNV patients. Patient demographic data, such as age, gender, affected side, refractive error, and systemic disease, were also recorded. Time points were assessed at 1, 3, 6, 12, and 24mo from baseline.

The best corrected visual acuity (BCVA) was measured at 5 m and converted into the logarithm of the minimal angle of resolution (logMAR) for statistical analysis. Intraocular pressure (IOP) was measured by a non-contact tonometer three times for each eye, and an average value was recorded. Central macular thickness (CMT) was tracked by spectral domain optical coherence tomography (SD-OCT) centering on the macula. Vertical and horizontal scans were used for measurement. CMT was automatically calculated by the scanning machine's software and manually modified for segmentation errors by the same reader (Liu JY) when required.

Statistical Analysis Descriptive statistics for variables were summarized using the mean standard deviation (SD), median interquartile range (IQR), and percentages where appropriate. To explore the association, regression analysis was employed to calculate the hazard ratio (HR) along with their corresponding 95% confidence intervals (CI). The primary outcome variables were mean change in BCVA and CMT changes. The secondary outcome variables included IOP changes, the period of mCNV re-treatment, and ocular adverse events.

The mean BCVA change was reported and converted into the mean logMAR change from the baseline visit to each follow-up. Serial BCVA, IOP, and CMT comparisons on SD-OCT from baseline to the last follow-up were assessed using the Wilcoxon paired and Mann-Whitney *U* tests. A linear regression model, including univariate and multivariate analysis, was used to report the factors and predict 12mo and 24mo outcomes. The variables were analyzed by stepwise regression, and the univariate significant variables were analyzed by multivariate regression. The mean period of mCNV reactivation was reported by the type of drug administered and the initial injection treatment regimen. Recurrences were classified as any sign of reactivation of a previously regressed CNV or newly formed CNV. Kaplan-Meier survival analysis was used to plot survival curves. The proportion of patients and serious adverse events would be recorded if the patients had ocular adverse events.

Data processing analysis were performed using R version 4.3.0. and SPSS version 26.0 (USA). The difference was considered statistically significant only if the $P<0.05$.

RESULTS

Study Participants After a preliminary screening identified 133 patients, patients with unknown treatment, missing

Table 1 Baseline characteristics of study eyes

Parameters	Overall	Ranibizumab	Conbercept	*P*
Numbers	83	59	24	
Left eye	38 (45.8)	29 (49.2)	9 (37.5)	0.47
Female	62 (74.7)	44 (74.6)	18 (75.0)	1
Age (y)	56.40 (15.36)	56.02 (16.10)	57.33 (13.65)	0.726
Hypertension	20 (24.1)	14 (23.7)	6 (25.0)	1
Duration of hypertension (y)	2.13 (6.72)	1.76 (5.93)	3.04 (8.43)	0.436
Systolic blood pressure (mm Hg)	131.54 (14.85)	132.97 (14.76)	128.04 (14.80)	0.172
Diastolic blood pressure (mm Hg)	81.96 (7.80)	82.19 (7.61)	81.42 (8.39)	0.686
Diabetes	6 (7.2)	3 (5.1)	3 (12.5)	0.474
Duration of diabetes (y)	0.78 (3.33)	0.81 (3.68)	0.71 (2.33)	0.897
HbAC1 (%)	6.02 (1.19)	5.90 (1.22)	6.27 (1.10)	0.222
Creatinine (mmol/L)	65.85 (16.11)	66.82 (15.95)	63.80 (16.61)	0.462
Refractive error (D)	10.45 (5.10)	10.48 (5.50)	10.39 (4.18)	0.965
AL (mm)	29.67 (2.09)	29.95 (2.26)	28.64 (0.82)	0.357
IOL	20 (24.1)	16 (27.1)	4 (16.7)	0.468
IVT number	3.00 (3)	3.00 (4)	2.50 (3)	0.191
Injection treatment regimen				0.647
1+PRN	28 (33.7)	19 (32.2)	9 (37.5)	
2+PRN	28 (33.7)	19 (32.2)	9 (37.5)	
3+PRN	27 (32.5)	21 (35.6)	6 (25.0)	

Continuous variables were characterized by mean (SD) or median (IQR) whereas categorical variables were expressed as number (percent). Based on the initial injection, patients were divided into three treatment groups: 1+PRN: Patients received intravitreal injection of VEGF inhibitors once with further treatment determined by disease activity; 2+PRN: Patients received intravitreal injections of VEGF inhibitors once a month for two consecutive months, with further treatment determined by disease activity; 3+PRN: Patients received intravitreal injections of VEGF inhibitors once a month for three consecutive months, with further treatment determined by disease activity. AL: Axial length; IOL: Intraocular lenses; SD: Standard deviation; IQR: Interquartile range; IVT: Intravitreal injection; PRN: *Pro re nata*.

follow-up visits, *etc*. (*n*=50) were excluded. Totally 83 mCNV patients who started to receive intravitreal injections of VEGF inhibitors (59-ranibizumab, 24-conbercept) from 1 January 2017 to 1 January 2022 were included. All patients were of Asian ethnicity. Table 1 shows that the baseline characteristics of the eyes receiving ranibizumab and conbercept were generally similar.

Visual Acuity Outcomes The mean BCVA at baseline was 0.81±0.43 logMAR. The 24mo changes in mean BCVA from the first injection to the last follow-up visit are summarized in Table 2. The mean BCVA at 1mo after the first intravitreal injections was 0.73±0.36 logMAR (*P*=0.001), at 3mo it was 0.67±0.38 logMAR (*P*<0.001), at 6mo it was 0.59±0.30 logMAR (*P*=0.003), at 12mo it was 0.96±0.56 logMAR (*P*=0.532), and at 24mo it was 0.65±0.56 logMAR (*P*=0.147). After the initial improvement in visual acuity at 1, 3 and 6mo (*P*<0.05), from month 12 onwards, no statistical difference compared to baseline was found (Table 2).

The changes in mean logMAR BCVA were similar between ranibizumab and conbercept (Table 2). Both ranibizumab and conbercept subgroups had statistically significant logMAR BCVA improvement in the first month [intravitreal ranibizumab (IVR): *P*=0.012; intravitreal conbercept (IVC): *P*=0.018] and 3mo [IVR: *P*=0.001; IVC: *P*=0.027] of follow-up from baseline logMAR BCVA. However, in the ranibizumab subgroup, the mean logMAR BCVA improved at 6mo (*P*=0.006). There was also no statistical difference compared to baseline from 12 onwards, no matter ranibizumab or conbercept (12mo: IVR: *P*=0.272; IVC: *P*=0.670; 24mo: IVR: *P*=0.635; IVC: *P*=0.074).

Better baseline logMAR BCVA was significantly associated with a better 12-mo logMAR BCVA (HR=0.93, 95%CI: 0.50, 1.36, *P*<0.001; Table 3). In univariate analysis, choosing 3+PRN as the initial injection treatment regimen was associated with better logMAR BCVA at 24mo (HR=-0.65, 95%CI: -1.23, -0.07, *P*=0.048). However, the difference was not significant in multivariate analysis (HR=-0.59, 95%CI: -1.21, 0.03, *P*=0.089; Table 3).

IOP and CMT Outcomes IOP at baseline was 14.70±3.41 mm Hg. The follow-up changes in IOP are also summarized in Table 2. There was an improvement in IOP at 12mo (mean IOP=15.31±2.88 mm Hg; *P*=0.041). No statistical difference compared to the baseline was found in other months until the last follow-up visit (Table 2). However, there were no

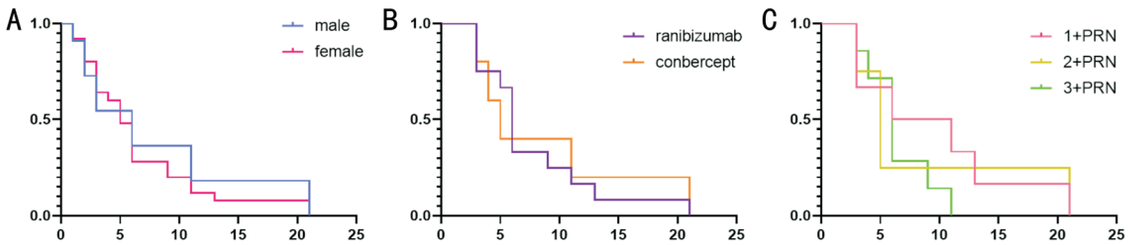

Figure 1 Kaplan-Meier plots for time from starting treatment to mCNV recurrences A: Differences between male and female; B: Differences between ranibizumab and conbercept; C: Initial injection treatment regimen divided into three types: 1+PRN, 2+PRN, and 3+PRN. 1+PRN: Patients received intravitreal injection of VEGF inhibitors once with further treatment determined by disease activity; 2+PRN: Patients received intravitreal injections of VEGF inhibitors once a month for two consecutive months, with further treatment determined by disease activity; 3+PRN: Patients received intravitreal injections of VEGF inhibitors once a month for three consecutive months, with further treatment determined by disease activity. mCNV: Myopic choroidal neovascularization; VEGF: Vascular endothelial growth factor.

Table 2 The follow-up changes in BCVA, IOP, and CMT

Parameters	Baseline	1mo	3mo	6mo	12mo	24mo
BCVA	0.23±0.20	0.25±0.19	0.29±0.20	0.31±0.19	0.19±0.18	0.38±0.33
logMAR BCVA	0.81±0.43	0.73±0.36	0.67±0.38	0.59±0.30	0.96±0.56	0.65±0.56
P	-	0.001	<0.001	0.003	0.532	0.147
Ranibizumab	0.80±0.40	0.71±0.34	0.66±0.40	0.60±0.30	1.08±0.61	0.57±0.64
P		0.012	0.001	0.006	0.272	0.635
Conbercept	0.83±0.52	0.78±0.42	0.71±0.31	0.59±0.29	0.72±0.36	0.78±0.42
P		0.018	0.027	0.205	0.67	0.074
IOP	14.70±3.41	14.90±3.38	14.45±4.08	14.35±2.64	15.31±2.88	16.21±7.05
P	-	0.64	0.421	0.855	0.041	0.326
Ranibizumab	14.66±3.67	15.10±3.66	14.19±4.52	14.00±2.63	15.37±2.57	17.52±7.73
P		0.495	0.421	0.38	0.187	0.083
Conbercept	14.80±2.75	14.29±2.38	15.23±2.37	15.26±2.62	15.19±3.57	14.03±5.67
P		0.796	0.833	0.327	0.208	0.917
CMT	286.71±83.68	236.83±73.41	236.93±77.46	235.51±82.95	244.63±93.05	223.43±72.58
P	-	<0.001	<0.001	<0.001	0.001	0.011
Ranibizumab	282.27±81.20	226.23±50.37	222.58±53.01	226.09±61.40	220.91±58.39	212.00±58.66
P		<0.001	<0.001	<0.001	0.002	0.008
Conbercept	297.63±90.33	279.23±124.59	288.33±122.63	268.50±133.57	290.08±128.52	244.88±94.18
P		0.016	0.065	0.037	0.126	0.401

BCVA: Best corrected visual acuity; IOP: Intraocular pressure; CMT: Central macular thickness.

statistical changes in mean IOP between ranibizumab and conbercept.

The mean CMT at baseline was 286.71±83.68 mm. The mean CMT from 1mo onwards had a statistically significant decrease compared with baseline CMT (P<0.05). The 24mo changes in mean CMT from the first injection to the last follow-up visit are summarized in Table 2. In conbercept subgroup, no statistical differences compared to baseline at 12mo and 24mo were found (P=0.126; P=0.401). The regression model showed only thicker baseline CMT was significantly associated with the thicker CMT at 12 and 24mo (12mo: HR=0.59, 95%CI: 0.32, 0.85, P<0.001; 24mo: HR=0.56, 95%CI: 0.15, 0.98, P=0.015; Table 4).

Myopic Choroidal Neovascularization Recurrences During the 24mo follow-up, no patient switched the drug after the initial injection. The overall median number of intravitreal injections for each patient was 3.00 (IQR=3, range 1-17), with a non-significantly higher number of injections for eyes between ranibizumab (median=3.00, IQR=4, range 1-14) and conbercept (median=2.50, IQR=3, range 1-17; P=0.191).

The mean period of mCNV recurrence was 8.00±5.77mo, and the mean period of mCNV reactivation during the follow-up 24mo was similar between ranibizumab and conbercept (7.67±5.25 *vs* 8.80±7.50mo, P=0.725). After the initial injection treatment regimen, 20.34% in ranibizumab and 20.83% in the conbercept appeared to have mCNV recurrences (P=1.00). Kaplan-Meier plot analyzed that the median time of re-injection was not significantly different among gender, drug, and initial injection treatment regimen (Logrank P=0.394; Logrank P=0.873; Logrank P=0.669; Figure 1).

Table 3 Results from univariate and multivariate regression models for 12-mo and 24-mo visual acuity outcomes

Variables	12-month logMAR BCVA				24-month logMAR BCVA			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)	*P*
Age (y)	0.01 (-0.01 to 0.02)	0.381			0.01 (-0.00 to 0.03)	0.176		
Hypertension	-0.12 (-0.61 to 0.36)	0.625			-0.22 (-1.07 to 0.64)	0.626		
Duration of hypertension (y)	-0.00 (-0.03 to 0.03)	0.982			-0.02 (-0.08 to 0.04)	0.47		
Systolic blood pressure (mm Hg)	-0.00 (-0.02 to 0.01)	0.523			0.01 (-0.01 to 0.03)	0.334		
Diastolic blood pressure (mm Hg)	-0.01 (-0.05 to 0.03)	0.714			0.01 (-0.02 to 0.03)	0.538		
Diabetes years, mean (SD)	0.02 (-0.03 to 0.07)	0.377			-0.02 (-0.08 to 0.03)	0.446		
HbAc1 (%)	0.03 (-0.19 to 0.24)	0.798			0.02 (-0.59 to 0.64)	0.94		
IOL	-0.02 (-0.58 to 0.55)	0.951			-0.23 (-0.88 to 0.42)	0.502		
Baseline logMAR	0.93 (0.50 to 1.36)	<0.001	0.97 (0.50 to 1.43)	<0.001	0.37 (-0.13 to 0.87)	0.165		
Gender								
Male	0.00 (Reference)				0.00 (Reference)			
Female	0.12 (-0.38 to 0.62)	0.644			-0.24 (-0.85 to 0.36)	0.439		
Affected side								
Right eye	0.00 (Reference)				0.00 (Reference)			
Left eye	0.20 (-0.26 to 0.66)	0.401			0.14 (-0.43 to 0.71)	0.645		
Injection treatment regimen								
1+PRN	0.00 (Reference)				0.00 (Reference)		0.00 (Reference)	
2+PRN	-0.14 (-0.82 to 0.55)	0.696			-0.49 (-1.14 to 0.16)	0.161	-0.43 (-1.13 to 0.26)	0.241
3+PRN	-0.05 (-0.72 to 0.63)	0.897			-0.65 (-1.23 to -0.07)	0.048	-0.59 (-1.21 to 0.03)	0.089
Drug type								
Ranibizumab	0.00 (Reference)				0.00 (Reference)			
Conbercept	-0.36 (-0.82 to 0.11)	0.145			0.21 (-0.37 to 0.79)	0.486		

The variables were analyzed by stepwise regression, and those of the univariate significant variables were analyzed using multivariate regression. Continuous variables were characterized by their mean (SD) whereas categorical variables were expressed as number (percent). Based on the initial injection, patients were divided into three treatment groups: 1+PRN: Patients received intravitreal injection of VEGF inhibitors once with further treatment determined by disease activity. 2+PRN: Patients received intravitreal injections of VEGF inhibitors once a month for two consecutive months, with further treatment determined by disease activity. 3+PRN: Patients received intravitreal injections of VEGF inhibitors once a month for three consecutive months, with further treatment determined by disease activity. SD: Standard deviation; BCVA: Best corrected visual acuity; IOL: Intraocular lenses; CI: Confidence intervals.

Systemic Adverse Events During the follow-up period, no changes in blood pressure, creatinine, or other changes in blood pressure and systemic adverse events associated with anti-VEGF drug therapy, including myocardial infarction, stroke, congestive heart failure, venous thrombotic events, arterial thrombotic events, cerebral hemorrhage, pulmonary hemorrhage, or gastrointestinal hemorrhage, and death, were identified in this study.

DISCUSSION

We analyzed data from the mCNV patients who received intravitreal injections of VEGF inhibitors of either ranibizumab or conbercept from 1 January 2017 to 1 January 2022 in Tianjin Medical University Eye Hospital. In visual acuity, the mean logMAR BCVA at baseline was 0.81±0.43 logMAR. During follow-up observation, BCVA improved, but there was no significant difference from month 12 onwards. VEGF is a pro-angiogenic cytokine that causes the formation of CNV, and studies have proved that elevated levels of VEGF in the eyes of patients with mCNV[3,6-7]. mCNV without relevant interventions usually results in poorer patient prognostic outcomes[5]. Although there was no statistical difference between the baseline and the 24mo logMAR BCVA, our study still found that mCNV patients maintained the same visual acuity.

Both ranibizumab and conbercept subgroups had statistically significant logMAR BCVA improvement at 1mo and 3mo (P=0.018; P=0.027). However, we found no significant difference between ranibizumab and conbercept in final treatment outcomes. Our study found similar visual outcomes with a previous 2-year outcomes study of predominantly Asian mCNV patients treated with ranibizumab and conbercept[21]. But in ranibizumab subgroup, the mean logMAR BCVA still improved at 6mo (P=0.006), which did not occur in conbercept. Iacono *et al*[22] found that the efficacy in controlling

Table 4 Results from univariate and multivariate regression models for 12-mo and 24-mo outcomes of CMT

Variables	12-month CMT				24-month CMT			
	Univariate analysis		Multivariate analysis		Univariate analysis		Multivariate analysis	
	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)	*P*	Hazard ratio (95%CI)	*P*
Age (y)	-1.34 (-3.54 to 0.85)	0.24			-0.46 (-2.54 to 1.61)	0.666		
Hypertension	50.12 (-15.07 to 115.32)	0.141			-44.77 (-115.84 to 26.31)	0.231		
Duration of hypertension (y)	2.00 (-2.11 to 6.10)	0.347			-4.65 (-11.24 to 1.94)	0.181		
Systolic blood pressure (mm Hg)	-1.27 (-3.13 to 0.58)	0.187			-0.96 (-2.79 to 0.87)	0.316		
Diastolic blood pressure (mm Hg)	-4.17 (-8.71 to 0.36)	0.081			-2.41 (-5.47 to 0.65)	0.137		
Diabetes years, mean (SD)	1.73 (-4.61 to 8.08)	0.596			-2.59 (-9.15 to 3.96)	0.447		
HbAC1 (%)	-1.33 (-34.04 to 31.38)	0.937			-20.25 (-68.78 to 28.27)	0.424		
IOL	-9.82 (-81.34 to 61.70)	0.79			-53.46 (-123.42 to 16.51)	0.149		
Baseline CMT	0.57 (0.31 to 0.83)	<0.001	0.59 (0.32 to 0.85)	<0.001	0.52 (0.15 to 0.90)	0.012	0.56 (0.15 to 0.98)	0.015
Gender								
Male	0.00 (Reference)				0.00 (Reference)			
Female	-44.21 (-120.97 to 32.55)	0.267			-11.20 (-84.65 to 62.25)	0.768		
Affected side								
Right eye	0.00 (Reference)				0.00 (Reference)			
Left eye	-23.73 (-86.44 to 38.98)	0.463			0.02 (-62.20 to 62.23)	1		
Injection treatment regimen								
1+PRN	0.00 (Reference)				0.00 (Reference)			
2+PRN	-64.12 (-143.12 to 14.89)	0.122			-52.20 (-132.01 to 27.61)	0.215		
3+PRN	-41.30 (-116.17 to 33.57)	0.288			-28.67 (-96.12 to 38.79)	0.415		
Drug type								
Ranibizumab	0.00 (Reference)		0.00 (Reference)		0.00 (Reference)			
Conbercept	69.17 (7.62 to 130.72)	0.035	50.50 (-0.85 to 101.84)	0.063	32.88 (-29.30 to 95.05)	0.312		

The variables were analyzed by stepwise regression, and those of the univariate significant variables were analyzed using multivariate regression. Continuous variables were characterized by their mean (SD) whereas categorical variables were expressed as number (percent). Based on the initial injection, patients were divided into three treatment groups: 1+PRN: Patients received intravitreal injection of VEGF inhibitors once with further treatment determined by disease activity; 2+PRN: Patients received intravitreal injections of VEGF inhibitors once a month for two consecutive months, with further treatment determined by disease activity; 3+PRN: Patients received intravitreal injections of VEGF inhibitors once a month for three consecutive months, with further treatment determined by disease activity. SD: Standard deviation; CI: Confidence intervals; CMT: Central macular thickness; PRN: *Pro re nata*.

mCNV activity was associated with vitreoretinal interface alterations especially in BCVA. We also found no statistical differences compared to baseline at 12mo and 24mo in CMT changes of injecting conbercept (*P*=0.126; *P*=0.401). Because of the lack of observation of the vitreoretinal interface and the slight imbalance between these two drugs, there were some limitations in the results. The RADIANCE study showed that patients continued to show statistically significant gains in BCVA at up to 36mo of follow-up[23]. In contrast, patients in our study maintained BCVA at comparable levels to baseline at months 12 and 24, with no statistically significant differences observed. This difference, in addition to possibly being due to the characteristics of the patient population, may be related to the fact that our study focused on real-world office visit data. In a real-world setting, factors such as the timing of treatment and the specific implementation of the treatment regimen may influence the final outcome of patients to some extent.

We also found no adverse events related to the treatment during the follow-up period. Whether in a strict treatment regimen or the real world, the results presented here demonstrate the effectiveness and safety of VEGF inhibitors for treating mCNV. Also, we found no difference in the mean period or the proportion of mCNV reactivation. Patients with mCNV treated with ranibizumab or conbercept maintained good treatment outcomes within clinical practice settings for up to 24mo of follow-up.

Similar results have been reported regarding baseline BCVA as a functional predictive factor in visual outcomes[24-28]. In univariate analysis, we also found that choosing 3+PRN was associated with better BCVA at 24mo (*P*=0.048). However, the difference was not significant in multivariate analysis. The initial injection treatment regimen had a conflicting result. Many studies had also compared the differences in prognostic outcomes between 1+PRN and 3+PRN, finding that the two

regimens were similar in visual improvement at 12mo[17-18,29-32]. The multivariate regression model also showed no statistical differences between the 12-month and 24-month outcomes of CMT in the initial injection treatment regimen. Despite the extended observation period, the results of different regimens were similar.

There is a paucity of literature on incidence and re-treatment outcomes in mCNV recurrence[33-35]. Jain *et al*[36] found that eyes requiring a more significant number of injections for disease control in the first episode are at risk of early mCNV recurrence. So, our study observed whether gender, the initial injection treatment regimen, or drug type was related to the treatment outcome. The median number of intravitreal injections for each patient was 3.00 (IQR=3, range 1-17), with a non-significantly higher number of eye injections between ranibizumab and conbercept (P=0.191). Kaplan-Meier survival analysis also showed there were no significant differences among gender, drug, and initial injection treatment regimen (all P>0.05). Due to the possibility of recurrence in mCNV, 3.61% of patients in this study experienced recurrence within 6mo, while an additional 12.05% of patients relapsed between the 6th and 12th months. This recurrence may have impacted the BCVA outcomes at the 6 and 12mo, particularly as the BCVA at the 12mo showed a relative decline.

Our study has several limitations, mainly inherent in observational studies. First, treatment decisions in routine clinical practice are not guided by a management protocol or reading center, leading to variations among physicians and centers, unlike randomized controlled trials (RCTs). The reasons for selecting a specific VEGF inhibitor, regimen, and treatment switch decision cannot be determined from our data. Second, the data we used were based on patients' examinations. Most of them were SD-OCT, so we mainly observed CMT changes. Progressive visual loss is related to the expansion of chorioretinal atrophy[37]. The changes in blood flow[38] and the development of chorioretinal atrophy associated with mCNV were lacking. Thus, larger cohorts and forward-looking observations are needed, and a more complete fundus examination is needed to assess the functional and anatomical outcomes in these eyes better.

No systemic adverse events which were considered related to intravitreal injection of VEGF inhibitor therapy received, were observed during the follow-up observation period. Many studies have suggested that this therapy for mCNV is safe[39-41], but safety conclusions should be interpreted with caution due to the limited sample size.

In conclusion, the BCVA gained at the end of our study was generally sustained at 24-month follow-up in clinical practice settings. The results also suggest that ranibizumab and conbercept achieve similar efficacy and safety during 24mo. Intravitreal injection of VEGF inhibitors therapy and using the 1+PRN regimen has some advantages in terms of efficacy and economics. However, the mechanism of mCNV still needs to be further explored to target the relevant influencing factors for intervention better and enable patients to achieve better long-term visual outcomes.

ACKNOWLEDGEMENTS

Data Availability: Data is openly available in a public repository.

Foundation: Supported by Tianjin Key Medical Discipline (Specialty) Construction Project (No.TJYXZDXK-037A).

Conflicts of Interest: Liu JY, None; **Liu JP,** None; **Li XR,** None.

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