• Clinical Research •

Real-world outcomes of anti-vascular endothelial growth factor therapy for retinal vascular vein occlusion in Tibet, China

Xue-Mei Zhu[1,2], Ying-Ying Yu[1], Sina Zhuoga[2], Xiao Dawa[2], Yong-Kang Zhou[2], Ouzhu Wangmu[2], Deji Yangzong[2], Fang An[2], Heng Miao[1], Ming-Wei Zhao[1]

[1]Department of Ophthalmology & Clinical Centre of Optometry, Peking University People's Hospital, Eye Diseases and Optometry Institute, Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroid Diseases, College of Optometry, Peking University Health Science Center, Beijing 100044, China

[2]Department of Ophthalmology, Tibet Autonomous Region People's Hospital, Lhasa 850010, Tibet Autonomous Region, China

Co-first authors: Xue-Mei Zhu, Ying-Ying Yu, and Sina Zhuoga

Correspondence to: Heng Miao. Department of Ophthalmology & Clinical Centre of Optometry, Peking University People's Hospital, Eye diseases and Optometry Institute, Beijing Key Laboratory of Diagnosis and Therapy of Retinal and Choroid Diseases, College of Optometry, Peking University Health Science Center, Beijing 100044, China. sawyer_young@sina.com

Received: 2022-02-14 Accepted: 2022-05-18

Abstract

● **AIM:** To evaluate the outcomes of intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents for patients with retinal vein occlusion (RVO) related-macular edema (ME) in Tibetan.

● **METHODS:** A retrospective, observational, single-center study. The demographic and clinical data of 90 RVO Tibetan patients (93 eyes) treated with either ranibizumab or conbercept in Tibet Autonomous Region People's Hospital from Jan 2018 to December 2019 were collected.

● **RESULTS:** The mean patient age was 56.8±10.6y, 45 (50%) of them were female. The mean living altitude was 3867.8±567.9 m. At the last visit, the best-corrected visual acuity (BCVA) significantly increased (52.2±21.8 letters) in comparison with the baseline (38.2±24.1 letters, P<0.001); while the central retinal thickness (CRT) significantly reduced (245.5±147.6 μm) in comparison with the baseline (504.1±165.2 μm, P<0.001). The 43.0% of the eyes gained ≥15 letters, 60.2% of the eyes gained ≥10 letters, and 78.5% of the eyes gained ≥5 letters. No vision loss was noted in 92.5% of the eyes, 4 eyes lost more than 10 letters during follow-up period. The mean number of injections was 2.4±1.8. No severe ocular or systemic adverse events related to either the drug or injection were noted.

● **CONCLUSION:** Anti-VEGF therapy is effective and safe in Tibetan patients for the treatment of RVO related ME.

● **KEYWORDS:** anti-vascular endothelial growth factor therapy; macular edema; retinal venous occlusive disease; intravitreal; visual acuity; Tibet

DOI:10.18240/ijo.2022.11.12

Citation: Zhu XM, Yu YY, Zhuoga SN, Dawa X, Zhou YK, Wangmu OZ, Yangzong DJ, An F, Miao H, Zhao MW. Real-world outcomes of anti-vascular endothelial growth factor therapy for retinal vascular vein occlusion in Tibet, China. *Int J Ophthalmol* 2022;15(11):1814-1820

INTRODUCTION

Intravitreal anti-vascular endothelial growth factor (anti-VEGF) agents have been the first-line therapy for macular edema (ME) secondary to retinal vein occlusion (RVO) all over the world[1-2]. In many randomized clinical trials (RCTs), they have yielded meaningful improvement of vision in this disorder. However, whether the results from RCTs can be applied to the Tibet Autonomous Region (TAR), which is known as the roof of the world with low oxygen and pressure, is unknown.

Situated in the Himalayan plateau in the Western part of China, TAR has an average altitude of roughly 4000 meters which resulted in a unique climate with thin air, low oxygen, and low pressure[3]. To adapt to the hypoxic environment, Tibetans, known as one of the largest and oldest high-altitude natives in the world, have a series of adaptive changes at the genomic and physiological levels[4]. The hemorheological adjustments include the increase of red blood cells (RBC) and hemoglobin

(Hb), the increase of blood viscosity and blood stasis, and so on[5-8]. These changes may account for the higher incidence of RVO in TAR[9]. On the other hand, there is growing evidence on association between systemic adverse events (SAEs) related to anti-VEGF therapy (cerebral infarction, myocardial infarction, *etc*.) and hemodynamic changes[10-11]. Despite several large sample studies concluded that intravitreal anti-VEGF therapy was well tolerated systemically within large real-world patient cohorts[12-13], concerns remain that anti-VEGF treatment in Tibet Plateau whether increase the risk of SAEs. For now, the efficacy and safety of different kinds of anti-VEGF drugs in the treatment of RVO related-ME in TAR have not been addressed yet.

Tibet Autonomous Region People's Hospital (TARPH), located in Lhasa, is one of the biggest class A tertiary general hospitals in TAR and committed to the medical services, medical education, research, and prevention of the whole area of Tibet. As intravitreal injection of anti-VEGF drugs has just been carried out in TARPH recent years, thus, this study was undertaken to estimate the outcomes of intravitreal anti-VEGF agents for patients with RVO related-ME in Tibetan.

SUBJECTS AND METHODS

Ethical Approval This investigation was a retrospective hospital-based, observational case series study approved by Ethical Committee and Institutional Review Board of the TARPH (Approval No. ME-TBHP-21-KJ-004). Informed consent was waived because of the retrospctive nature of the study.

Inclusion criteria were 18 years or older indigenous inhabitant diagnosed of RVO with ME, anti-VEGF as primary treatment (ranibizumab or conbercept), and follow-up of at least one month. Exclusion criteria included previous macular laser photocoagulation or local corticosteroid injection, history of ME due to conditions other than RVO, and history of vitreoretinal surgery. All the patients were treated using a *pro re nata* (PRN) regimen. Ranibizumab or conbercept (0.5 mg/0.05 mL) was intravitreally injected with a 30 G syringe needle approximately 3.5-4 mm posterior to the corneal limbus in an operating room under sterile conditions.

Clinical and demographic data collected included age, sex, type of RVO, comorbidities, RBC, Hb level, best-corrected visual acuity (BCVA), central retinal thickness (CRT). Treatment data included number of injections, type of anti-VEGF used, time to treatment, adjuvant laser or corticosteroid therapy.

Statistical Analysis Categorical data were presented as percentages, and continuous data were expressed as mean (±standard deviation). Snellen fractions were converted to Early Treatment Diabetic Retinopathy Study (EDTRS) letters by a standard conversion method[14]. Paired *t*-test was used to compare the baseline BCVA and optical coherence tomography (OCT) with the follow-up results. Wilcoxon rank sum tests were used to compare the two subgroups, including age, gender, and other parameters. Statistical analysis was performed using SPSS 19.0 and $P<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics Our retrospective study included 90 Tibetan patients (93 eyes) whose mean living altitude was 3867.8±567.9 m. Forty-five patients (50%) were female. Forty were right eyes and 53 were left eyes. The mean patient age was 56.8±10.6y. Fifty-five patients (61.1%) had hypertension, while 14 patients (15.6%) had type 2 diabetes but no diabetic retinopathy (DR). The mean Hb level was 160±25.8 g/L (range, 82-255 g/L), while the mean RBC count was $(5.4\pm0.8)\times10^9$/L (range, 3.9-9.1). The mean Hb level of the men was significantly higher than that of women.

Among these eyes, 24 of them were central retinal vein occlusion (CRVO), while the rest were branch retinal vein occlusion (BRVO). The 94.6% of the eyes baseline BCVA was worse than 20/40, while the mean baseline BCVA was 38.2±24.1 letters. The mean baseline CRT was 504.1±165.2 μm. The mean follow-up time was 6.1±7.3mo (range, 1 to 32mo). The 69.9% of the eyes followed more than 3mo, 36.6% of the eyes followed more than 6mo, while 19.3% followed more than 1y. Detailed data were presented in Table 1.

Treatment Profile At the last visit, the BCVA significantly increased (52.2±21.8 letters) in comparison with the baseline (38.2±24.1 letters, $P<0.001$); while the CRT significantly reduced (245.5±147.6 μm) in comparison with the baseline (504.1±165.2 μm, $P<0.001$). The 43.0% of the eyes gained ≥15 letters, 60.2% of the eyes gained ≥10 letters, and 78.5% of the eyes gained ≥5 letters. No vision loss was noted in 92.5% of the eyes, 4 eyes lost more than 10 letters during follow-up period. The mean number of injections was 2.4±1.8 (range, 1 to 11; median, 2). The 18.3% of the eyes received adjuvant laser therapy.

Subgroup analysis of those patients who followed more than 6mo, the results are presented in Table 2. There were 34 eyes in this subgroup, the mean number of injections was 3.8±2.1 (median, 3), the mean follow-up time was 13.1±8.2mo (range, 6-33mo). The mean baseline BCVA was 40.1±22.9 letters, while the last visit BCVA was 55.5±21.6 letters ($P<0.001$). At the last visit, 70.6% of the eyes gained ≥10 letters, 3 eyes (8.8%) lost ≥10 letters. The mean BCVA improved greatly for the group with poor baseline BCVA.

Safety Profile In this study, a total of 220 injections were performed with same concentrations (0.5 mg/0.05 mL). The 60.9% (134/220) of the injections used ranibizumab, and the rest used conbercept. The most common recorded adverse event was subconjunctival hemorrhage, which resolved spontaneously without any treatment. Besides, mild uveal

Table 1 Summary data on baseline demographics and ocular variables of study population mean±SD

Characteristics	CRVO	BRVO	Total	*P* (CRVO *vs* BRVO)
Eyes, *n* (%)	24 (25.8)	69 (74.2)	93 (100)	/
Age, y, mean (range)	54.2±12.4 (32–78)	57.6±9.8 (31–78)	56.8±10.6 (31–78)	0.18
Female/male	8/16	38/29	45/45	0.05
Eyes (R/L)	11/13	29/40	40/53	0.75
BCVA	31.5±21.6	40.5±24.5	38.2±24.1	0.12
< 20/400	8 (33.3%)	19 (27.5%)	27 (29.0%)	/
20/400–20/40	15 (62.5%)	46 (66.7%)	61 (65.6%)	/
> 20/40	1 (4.2%)	4 (5.8%)	5 (5.4%)	/
CRT, μm	607.0±273.4	476.5±256.0	504.1±165.2	0.15
Living altitude, m	3748.5±314.1	3909.3±376.1	3867.8±567.9	0.07
RBC counting, $\times 10^9$/L	5.6±1.0	5.3±0.7	5.4±0.8 (3.9–9.1)	0.18
Male	5.9±1.1	5.6±0.7	5.7±0.9 (3.9–9.1)	0.36
Female	5.1±0.6	5.1±0.6	5.1±0.6 (4.0–6.7)	0.80
Hb level, g/L	170.9±25.6	156.2±24.8	160±25.8 (82–255)	0.02[a]
Male	179.0±26.5	171.0±19.8	173.8±22.7 (141–255)	0.27
Female	154.6±13.2	145.5±22.4	147.0±21.4 (82–198.1)	0.28
Hypertension, *n* (%)	15 (62.5)	40 (60.6)	55 (61.1)	0.81
Type 2 DM, *n* (%)	4 (16.7)	10 (14.5)	14 (15)	0.84

[a]*P*<0.05. RBC: Red blood cells; CRT: Central retinal thickness; DM: Diabetes mellitus; CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion.

Table 2 BCVA changes stratified by baseline BCVA and diagnosis among patients followed-up more than 6mo mean±SD

Parameters	Baseline BCVA	Last visit BCVA	Gained ≥10 letters, *n* (%)	*P* (baseline *vs* last visit BCVA)
Total	40.1±22.9	55.5±21.6	24/34 (70.6)	< 0.001
Baseline BCVA				
< 20/400	6.1±3.0	47.4±22.0	7/8 (87.5)	/
20/400–20/40	48.5±13.4	56.6±21.0	17/24 (70.8)	/
> 20/40	75±0	75±5	0/2 (0)	/
Subtypes				
CRVO	31.5±18.1	44.9±23.4	9/12 (75)	0.01
BRVO	44.8±23.8	61.3±18.0	15/22 (68.2)	0.007

CRVO: Central retinal vein occlusion; BRVO: Branch retinal vein occlusion; BCVA: Best-corrected visual acuity.

inflammation was recorded in four patients on the first day after the injection, which resolved after nonsteroid eye drops for several days. No severe injection-related or drug-related ophthalmologic adverse events, such as intraocular inflammation, rhegmatogenous retinal detachment, retinal artery occlusion, and so on, were recorded. Moreover, no drug-related SAEs, such as death, myocardial infarction, and stroke, were noted.

Two Cases Report Case 1, a 59-year-old woman was diagnosed of CRVO with ME in the left eye, with a visual acuity of count finger and CRT of 870 μm. The patient received 3 times of intravitreal ranibizumab injection, and then ME subsided. Thirteen months after initial treatment, fluorescence angiography revealed peripheral retinal non-perfusion, so the patient received adjuvant laser therapy. The patient has been followed up for 18mo. The latest visual acuity was 0.1 and the latest CRT was 124 μm, fundus photograph revealed neovascularization of disc and linear hemorrhage, the patient refused further treatment and then lost follow-up (Figure 1). No adverse event occurred during the whole period.

Case 2, a 65-year-old woman was diagnosed of BRVO with ME in the right eye, with a visual acuity of 0.4 and a CRT of 267 μm. The patient received 3+PRN regimen. The patient has been followed up for 28mo and totally received 6 times of intravitreal injection. The latest visual acuity was 0.8 and the latest CRT was 157 μm (Figure 2). No adverse event noted during the whole period.

DISCUSSION

This study is the first report of outcomes of intravitreal anti-VEGF agents for Tibetan RVO patients. Our results showed that anti-VEGF treatment was effective and safe for Tibetan RVO patients, no severe ocular or SAEs related to either the drug or injection were noted in Tibetan Plateau. This study provides insights into the real-world outcome of anti-VEGF treatment for RVO related ME.

Anti-VEGF treatment has been the first-line therapy for RVO related ME all over the world, however, little is known about its efficiency and, especially, safety in Tibetan. TARPH is a class A tertiary comprehensive hospital and one of the two

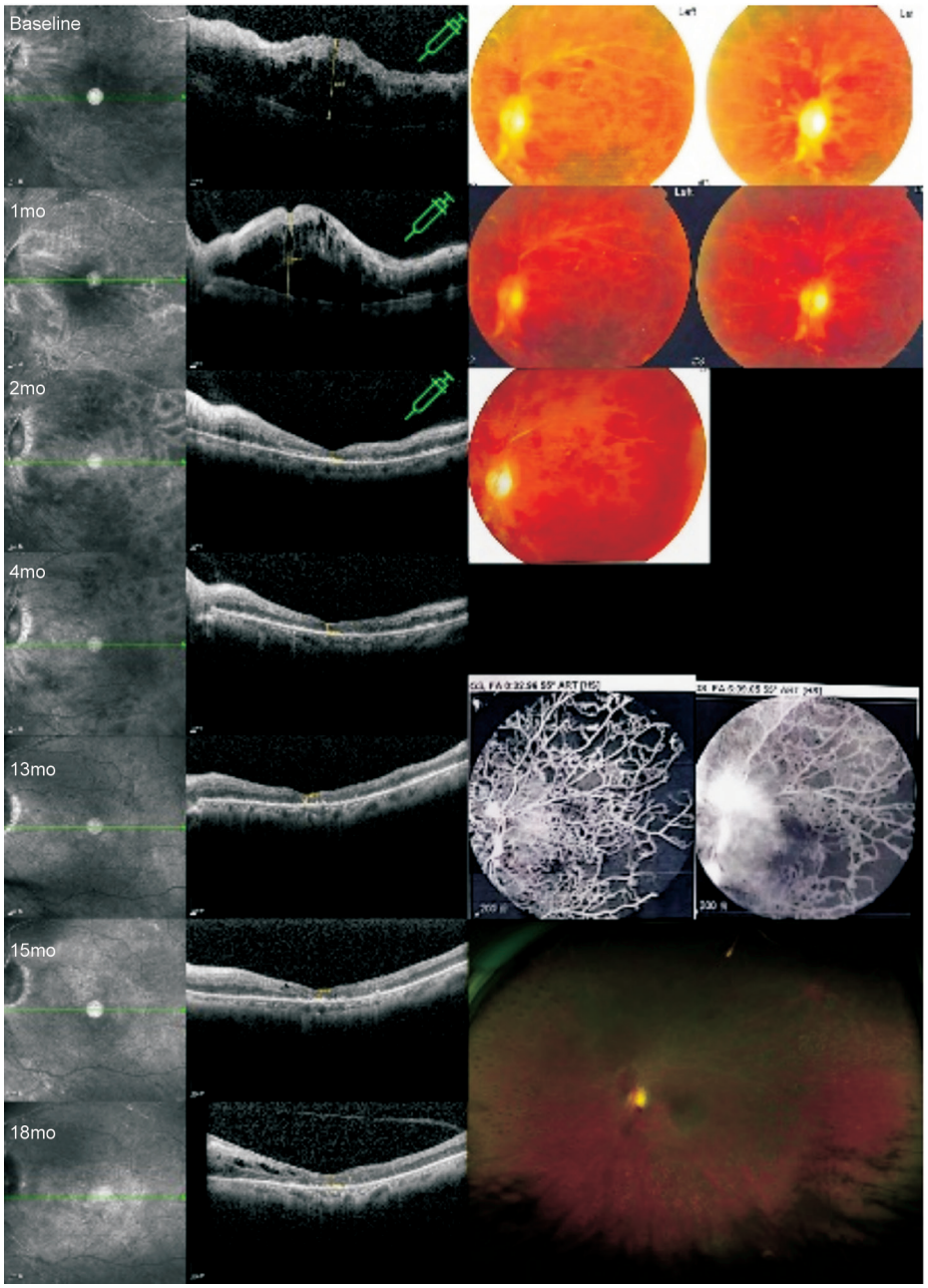

Figure 1 Fundus status of a CRVO patient with anti-VEGF treatment The OCT images of the patient during an 18-month follow-up and its corresponding fundus photographs. The patient received intravitreal injection at baseline, 1-, and 2-month. Macular edema subsided at month 2 and maintained during the follow-up. At month 13, fluorescence angiography revealed peripheral retinal non-perfusion, so the patient received adjuvant laser therapy. At the last follow-up, the CRT was 124 μm, fundus revealed neovascularization of disc and linear hemorrhage, the patient refused further treatment. VEGF: Vascular endothelial growth factor; CRVO: Central retinal vein occlusion; OCT: Optical coherence tomography.

eye centers in Lhasa; therefore, these data could represent the situation of RVO in TAR. In the clinical practice, we observed several characteristics of RVO in Tibetan Plateau.

RVO is the most common retinal vascular disease in TAR rather than DR. About 70% of ME in the hospital records is caused by RVO; while the rest common cause is diabetic ME, then age-related macular degeneration (AMD). Among the patients received laser therapy in TARPH, RVO is also much more common than DR. Several reasons can account for this phenomenon. First of all, the prevalence of hypertension which was revealed as the strongest risk factor for any RVO is much higher than other districts. Previous studies reported that the prevalence of hypertension in TAR was between 19.54% and 56%[15-16]. Low levels of awareness, treatment, and control of hypertension among Tibetan population has also been reported[16-17]. Consistently, 61.1% of the RVO patients in our study had hypertension, and 15% of them were newly detected at the ophthalmic clinic, then transferred to cardiology

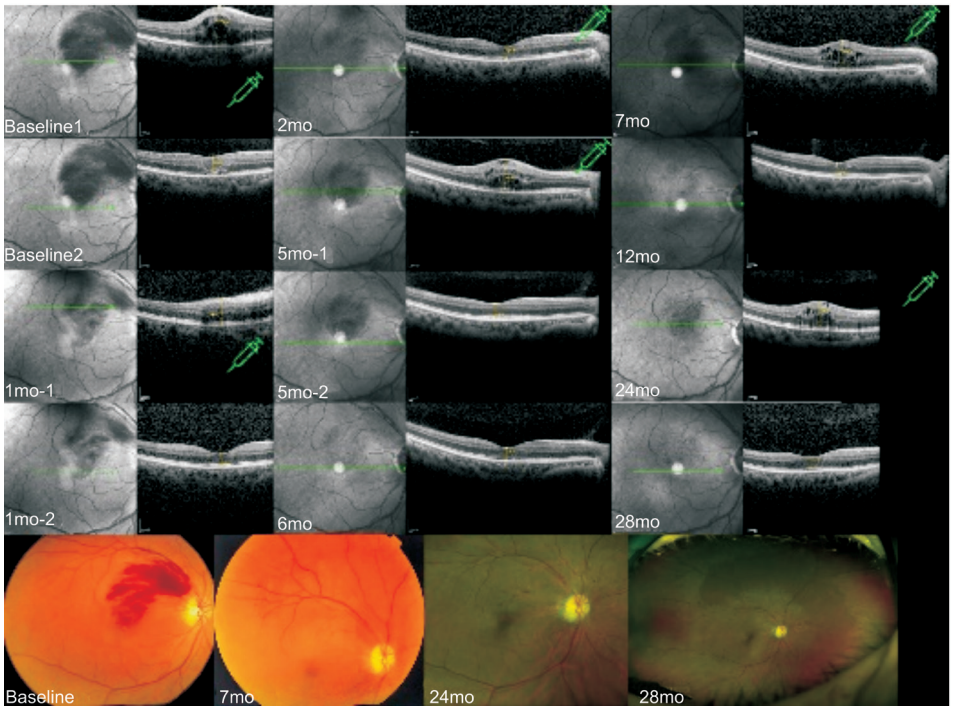

Figure 2 Fundus status of a BRVO patient with anti-VEGF treatment The OCT images and the fundus photographs during a 28-month follow-up. The patient received 3+PRN regimen. She totally received 6 injections without adjuvant laser therapy. The latest CRT was 157 μm. VEGF: Vascular endothelial growth factor; BRVO: Branch retinal vein occlusion; OCT: Optical coherence tomography; CRT: Central retinal thickness; PRN: *Pro re nata*.

clinic. Second, abnormal hemorheology is another vital risk factor for high altitude retinal vascular disease. As we know, people live in TAR demonstrate an increased number of RBCs, increased platelet aggregation, and elevated Hb to adapt to the hypoxic environment. These factors lead to increased blood viscosity and reduced blood flow, affecting the retinal microcirculation. Previous study demonstrated that patients were more likely to develop in-hospital cerebral infarction when the Hb concentration was higher than 152 g/L[18]. In our study, the mean Hb level was 160 g/L, the median Hb level of male was 169 g/L, while the median Hb level of female was 149 g/L. Compared to Tibetans with AMD or cataract, there's no difference between the RVO patients and other in-patient. Third, it was reported the prevalence of DM in Tibet was lower than that in other regions of China[19-20]. Compared to individuals living at <3500 m, the risk of DM decreased by 65% for those living at 3500–3999 m and by 89% for those living at ≥4000 m. All these alterations contribute to the higher prevalence of RVO than DR in TARPH clinic. Besides, it was reported that the global prevalence of BRVO and CRVO in people aged 30-89y was 0.64% and 0.13%[21], but our study found a slightly higher rate (25.8%) of CRVO which had a significantly higher mean Hb level than patient with BRVO (P=0.02). These findings require further investigation.

In addition, a younger mean baseline age and higher rate of patients lost to follow-up were observed in Tibetan. The mean baseline age of the RVO Tibetan patients was 56.8y, which was much younger than other Caucasian studies. Large sample studies in the United States and the United Kingdom demonstrated that the mean baseline age of RVO was over 70y[22-23]. However, in other Chinese studies, a similar baseline age was observed[24-25]. We speculate that this difference may be caused by sample size and selection bias. As we know, the prevalence of RVO increased steadily with advanced age. But the elder Tibetans were less likely to present at the clinic as their special beliefs about life. Besides, TAR has a large area with a sparse population, relatively backward economic and medical conditions, therefore, we observed that nearly 30% of patients lost to follow-up after the first month examination. Long-distance, cost, and transportation inconvenient were the common barriers for the regular visit, visual improvement also played a role.

Besides, this study demonstrated that anti-VEGF therapy was effective for RVO-related ME in Tibetan Plateau. For all the patients, at the last visit, the BCVA significantly increased and the CRT significantly reduced in comparison with the baseline. The 60.2% of the eyes gained ≥10 letters, and no vision loss was noted in 92.5% of the eyes. These patients gained a mean BCVA improvement of 14 letters with a mean of 2.4 anti-VEGF injections. For those patients followed more than 6mo, BCVA improved by 15.4 letters after a mean of 3.8 anti-VEGF injections with a 13.1mo of mean follow-up time. And

70.6% of these eyes gained ≥10 letters, 8.8% of these eyes lost ≥10 letters at the last visit. In this subgroup, 12 CRVO eyes treated with a mean of 4.1 anti-VEGF injections gained 13.4 letters, while 22 BRVO eyes treated with a mean of 3.6 anti-VEGF injections gained 16.5 letters. The baseline BCVA for patients with CRVO was slightly worse than that for patients with BRVO as shown in Table 1. There were no differences in Visual acuity changes and number of injections between BRVO and CRVO eyes. Previous BRVO-related and CRVO-related ME RCTs[26-30] demonstrated an average 1-year BCVA improvement of 17.7 letters and 15.7 letters, respectively. It seemed that real-world patients in Tibet receive fewer anti-VEGF injections and experience appreciable visual acuity gains compared with RCTs. While the real-world RVO studies[22-23] demonstrated an average 1-year BCVA improvement of 8.8 letters and 7.1 letters after a mean of 6.2 and 7.6 anti-VEGF injections for BRVO-related ME and CRVO-related ME, respectively. Compared with those real-world RVO studies, it seems that Tibetan patients receive fewer anti-VEGF injections and experience better outcomes.

Furthermore, as presented in Table 2, when stratified by baseline BCVA, the mean BCVA improved greatly for the group with poor baseline BCVA, which is consistent with the aforementioned real-world outcomes studies[22-23]. When stratified by both anti-VEGF injection frequency and baseline visual acuity, subgroup size became limiting. The mean BCVA change generally improved in eyes with both increased anti-VEGF injection frequency and decreased baseline BCVA. Overall, the Tibetan patients were treated using a PRN regimen and experienced the constraints of the distance and economic burden. It is thus not surprising that they are undertreated. These results highlight the need for appropriate patient counselling and education in Tibet.

Moreover, from this study, we didn't observe a higher incidence of adverse events of anti-VEGF treatment in Tibet than that in other regions. Several large sample studies concluded that intravitreal anti-VEGF therapy is well tolerated systemically within large real-world patient cohorts[12-13]. This study supplied the data of intravitreal anti-VEGF therapy in highland. Additionally, this study demonstrates a similar systemic safety profile for ranibizumab and conbercept as intravitreal pharmacotherapies for RVO in routine clinical practice, which is consistent with another study that found no differences in the risk of systemic adverse reactions between different anti-VEGF agents[31]. Overall, these anti-VEGF agents were well tolerated and prescribed safely in Tibetan Plateau.

The present real-world study had several limitations, including its retrospective nature, the relatively small sample size, non-standardized visual acuity assessment, short and irregular follow-up period, and the high incidence of loss to follow-up. These limitations may partly account for different outcomes in real-world studies compared with RCTs, which include protocol BCVA testing as well as explicit inclusion and exclusion criteria. The long-term safety and efficacy of anti-VEGF agents in treating RVO related ME in Tibetan Plateau requires further large sample investigations.

In summary, this study revealed that anti-VEGF therapy is effective and safe in Tibetan patients for the treatment of ME secondary to RVO, although they experience worse visual acuity gains compared with patients in RCTs. These results indicate that the highly efficacious anti-VEGF reagents can be prescribed safely in Tibetan Plateau for ME secondary to other posterior segment pathologies.

ACKNOWLEDGEMENTS

Authors' contributions: Conception and design of the study: Miao H and Zhu XM. Data collection: Zhuoga SN, Dawa X, Wangmu OZ, Yangzong DJ and Zhou YK. Statistical analysis and interpretation of data: Zhu XM, An F, Yu YY, and Zhou YK. Drafting of the manuscript: Zhu XM, Zhuoga SN, and Yu YY. Critical revision of the manuscript: Miao H and Zhu XM. Study supervision: Miao H and Zhao MW.

Foundations: Supported by Beijing Bethune Charitable Foundation (No.BJ-LM2019003J; No.BJ2021IIT006); Tibet Natural Science Funding Committee Grant (No.2019ZR-ZY21).

Conflicts of Interest: Zhu XM, None; **Yu YY,** None; **Zhuoga SN,** None; **Dawa X,** None; **Zhou YK,** None; **Wangmu OZ,** None; **Yangzong DJ,** None; **An F,** None; **Miao H,** None; **Zhao MW,** None.

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