

# Characteristics of retinal vein occlusion with final vision better than 78 letters after sequential therapy with ranibizumab and triamcinolone acetate

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Received: 2015-12-01 Accepted: 2016-07-23

## Abstract

• **AIM:** To analyze the reasons that may lead to the different vision result by combining the ranibizumab and triamcinolone acetate (TA) in sequence to treat macular edema in retinal vein occlusion (RVO).

• **METHODS:** Ranibizumab and TA were combined in sequence to treat 43 patients with macular edema secondary to RVO. Six months after the treatment, patients with central fovea thickness (CFT) less than 300  $\mu\text{m}$  in optical coherence tomography (OCT) were collected into Groups I and II, based on vision acuity (VA) better than 78 letters or less than 60 letters. The age, baseline VA, duration from onset to treatment, CFT at the baseline, sub-retinal fluid (SRF), sub-foveal exudates and injection times of TA and ranibizumab were taken into comparison.

• **RESULTS:** The mean age of the subjects was 46.4y in Group I but 57.5y in Group II. The difference of age was significant between groups ( $P < 0.01$ ). The mean baseline VA was 51.4 letters in Group I and 43.9 letters in Group II ( $P < 0.05$ ). The baseline CFT were 670.9  $\mu\text{m}$  in Group I with SRF in 54.3% patients and 678.1  $\mu\text{m}$  in Group II with SRF in 52.9% ( $P > 0.05$ ). The mean number of injections of TA was 0.9 and the mean number of injections of ranibizumab was 2.3 in Group I but 1.7 and 2.9 respectively in Group II. The treatment times of ranibizumab had no difference between the 2 groups ( $P > 0.05$ ) but the difference of TA injection times was significant ( $P < 0.05$ ). Subfoveal exudates at final stage happened in no subjects in Group I but in 45.83% subjects in Group II.

• **CONCLUSION:** This combined treatment is safer than TA injection and cheaper than ranibizumab injection alone.

**Younger patients and earlier treatment will help to get better vision outcome. Subfoveal exudates at the final stage have significant relationship with vision outcome. No relationship existed between the baseline CFT, SRF and the vision outcome.**

• **KEYWORDS:** retinal vein occlusion; macular edema; ranibizumab; triamcinolone acetate; sequential therapy

**DOI:10.18240/ijo.2017.02.15**

Qin YW, Yu J, Zhang Q. Characteristics of retinal vein occlusion with final vision better than 78 letters after sequential therapy with ranibizumab and triamcinolone acetate. *Int J Ophthalmol* 2017;10(2):271-276

## INTRODUCTION

Retinal vein occlusion (RVO) is the second most common retinal vascular disease<sup>[1]</sup>. Macular edema is the main cause of vision loss in RVO sufferers. Laser photocoagulation is useful in the treatment of macular edema from branch retinal vein occlusion (BRVO), but not to the macular edema secondary to central retinal vein occlusion (CRVO)<sup>[2-3]</sup>. Over the past decade, advances in drug development have radically changed the standard of care. Two classes of drugs have emerged as alternative treatments for macular edema in RVO: corticosteroids [triamcinolone acetate (TA); Ozurdex, slow-release, intravitreal, biodegradable dexamethasone implant] and anti-vascular endothelial growth factor (VEGF) agents<sup>[4-8]</sup>. Intravitreal injection of TA was the first treatment shown to improve the visual prognosis in macular edema secondary to CRVO, and have shown a benefit in patients with CRVO as well as BRVO<sup>[5-6]</sup>. Steroid formulations however have side effects such as elevated intraocular pressure and cataract formation. Ozurdex has shown fewer side effects than TA<sup>[4]</sup>, but it is still unavailable in many country and is much more expensive than TA. VEGF inhibitors have a more favorable safety profile, but the cost of the anti-VEGF drug may be limiting factors for many patients<sup>[7-8]</sup>.

A few studies have reported the use of combination therapy with ranibizumab and Ozurdex in RVO patients<sup>[9-11]</sup>. But in this study, the ranibizumab and TA injection in sequence to treat RVO, a treatment safer than TA injection and cheaper

than anti-VEGF drug injection alone was discussed. In clinic, many patients get vision better than 78 letters while others get vision outcome less than 60 letters. The aim of this study is to analyze the reasons that may lead to the difference.

### **SUBJECTS AND METHODS**

The study was retrospective in design, and entailed a review of the medical records of eligible subjects. Individuals with macular edema secondary to RVO (including CRVO and BRVO) who were treated at the Eye Clinic of the EENT hospital, Fudan University from July 2012 to August 2014 were eligible. The approval of the Institutional Review Board at the University of the EENT hospital, Fudan University was obtained, and the study adhered to the Declaration of Helsinki. OCT (Heidelberg, Germany) were used to exam the thickness of macular. The selected participants 1) had a baseline central foveal thickness (CFT) of  $\geq 300$   $\mu\text{m}$ , 2) fluorescein fundus angiography exam results showed nonischemic RVO and 3) had followed up for at least 6mo without macular edema recurrence after last treatment. Subjects were excluded if they had received macular laser treatment or any intravitreal injection prior to the treatment programs. Those who experienced panretinal photocoagulation during the period of study were also excluded. Eyes with cataract which precludes the evaluation of macula, ocular hypertension or coexisting epiretinal membranes were also excluded. The type of treatment investigated were sequential therapy with ranibizumab (Novartis, Switzerland) injection followed by TA (Zhenshiming company, China) injection (2 mg/0.05 mL) 4wk later, then followed by ranibizumab injection if the CFT  $>300$   $\mu\text{m}$  meet the retreatment criteria on every 4wk visit. The second TA injection will be given 6mo after the first TA injection if the CFT  $>300$   $\mu\text{m}$ , and no intraocular pressure  $>25$  mm Hg were found before. OCT were performed on every visits. The selected subjects were divided into two groups (based on the vision outcome they had achieved) for the main analysis.

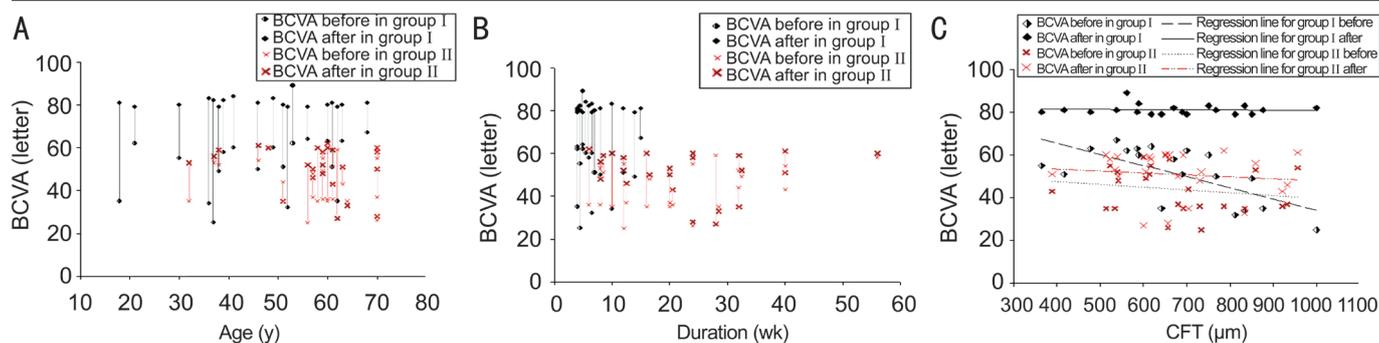
Data were collected on background demographics, changes in vision acuity (VA), changes in CFT, duration from onset to treatment, duration of the macular edema resolution and any complications encountered during the whole course of treatment. CFT was measured using spectral-domain optical-coherence tomography (Spectralis, Heidelberg Engineering). An ETDRS vision chart was used to measure best corrected vision acuity (BCVA). Subjects were collected into Group I if the vision outcome was better than 78 letters but collected into Group II if the vision outcome was less than 60 letters. The age, duration from onset to treatment, duration of the whole treatment, CFT, sub-retinal fluid (SRF) at the baseline, and sub-foveal exudates were taken into comparison.

**Statistical Analysis** Data were analyzed using Stata12.0 (Stata Corporation, College Station, TX, USA). Results for normally distributed continuous variables were expressed as mean $\pm$ SD and continuous variables with non-normal distribution were presented as median (interquartile range). Two groups were compared with an unpaired Student's *t*-test or Mann-Whitney *U* test when the variance was heterogeneous. Statistical analysis of categorical variable was performed using Pearson Chi-square test and Fisher's exact test as appropriate. Statistical significance level was set at 0.05.

### **RESULTS**

**Baseline Characteristics** Macular edema was assessed in one eye of each of the 43 subjects, 19 in Group I and 24 in Group II. The mean age of the subjects was 46.4y (range 18-68y, 42% under 40y) in Group I, 68.4% were male while 31.6% were female and in group II, the mean age was 57.5y (range 32-70y, 12% under 40y), 58.3% were male while 41.7% were female. The difference of age was significant between groups,  $P<0.01$ . The 57.9% subjects in Group I and 54.2% subjects in Group II had CRVO when the left had BRVO. The mean baseline VA was 51.4 letters (range 25-64 letters) in Group I and 43.9 letters (range 25-60 letters) in Group II, which indicated that better baseline vision will predict better vision outcome,  $P<0.05$ . The baseline CFT were 670.9  $\mu\text{m}$  (range 365-1000  $\mu\text{m}$ ) in Group I with SRF in 84.3% patients and 678.1  $\mu\text{m}$  (range 389-956  $\mu\text{m}$ ) in Group II with SRF in 82.9%. No difference was found in baseline CFT and SRF between the 2 groups. On average, the subjects received first injection 6.7wk (range 4-15wk) after the onset in Group I and 22wk (range 6-56wk) after the onset in Group II, a significant difference happened between the 2 groups,  $P<0.001$ , which indicated that earlier treatment will help to get better vision outcome (Table 1; Figure 1).

**Treatment Differences** In Group I ( $n=19$ ), all patients received first ranibizumab injection and 16 patients received first TA injection. Two patients received the second TA injection 6mo after that. The mean number of injections of TA was 0.9 and the mean number of injections of ranibizumab was 2.3. In Group II ( $n=24$ ), all patients received first ranibizumab injection followed by first TA injection. Sixteen patients received the second TA injection 6mo after that. The mean number of injections of TA was 1.7 and the mean number of injections of ranibizumab was 2.9. The treatment times of ranibizumab had no difference between the 2 groups ( $P>0.05$ ) but the difference of TA injection times was significant,  $P<0.05$ . The working duration of TA was 2.6mo in average, ranging 2-4mo. Duration of the whole treatment (from the first injection to one month after the last injection) was 7.1mo in Group I, which was significantly shorter than that in Group II, 11.6mo,  $P<0.01$ . Less cataract and ocular hypertension happened in Group I than that in Group II,  $P<0.05$  (Table 2).



**Figure 1** Distribution of BCVA with age, duration from onset to treatment and CFT A: Distribution of BCVA (before or after treatment) and age in 2 groups; B: Distribution of BCVA (before or after treatment) and duration from onset to treatment in 2 groups; C: Distribution of BCVA (before or after treatment) and CFT before or after treatment in 2 groups.

**Table 1** Patient demographics and baseline characteristics n (%)

Parameters	Group I	Group II	P
Gender			
M	13 (68.4)	14 (58.3)	0.497
F	6 (31.6)	10 (41.7)	
Age (a)			
Mean	46.4	57.5	0.007
Range	18-68	32-70	
SD	11.7	7.6	
Baseline VA			
Mean	51.4	43.9	0.048
Range	25-64	25-60	
SD	10.6	9.3	
Baseline CFT (µm)			
Mean	670.9	678.1	0.880
Range	365-1000	389-956	
SD	130.9	114.1	
SRF (%)	84.3	82.9	
Mean duration from onset to treatment (wk)			
Mean	6.7	22.0	<0.001
Range	4-15	6-56	
SD	2.7	9.8	
Type of RVO			
CRVO	11 (57.9)	13 (54.2)	
BRVO	8 (42.1)	11 (45.8)	0.606

BRVO: Branch retinal vein occlusion; CRVO: Central retinal vein occlusion; RVO: Retinal vein occlusion; CFT: Central foveal thickness; VA: Visual acuity.

**Final Stage Characteristics** All patients got anatomic macular edema resolve for at least 6mo in the 2 groups (CFT <300 µm). The CFT was 268.13 µm (range 210-300 µm) in Group I and 237.89 µm (range 166-300 µm) in Group II. No difference was found in the mean CFT in the 2 groups but 6 subjects in Group II got final CFT less than 200 µm.

The presence of subfoveal hard exudates (HE) at baseline and final stage changed a lot in both groups. Five subjects had subfoveal exudates at baseline in Group I but all of them disappeared at the end of the treatment, which means that no subjects with vision better than 78 letters had exudates under

**Table 2** Treatment types and treatment duration n (%)

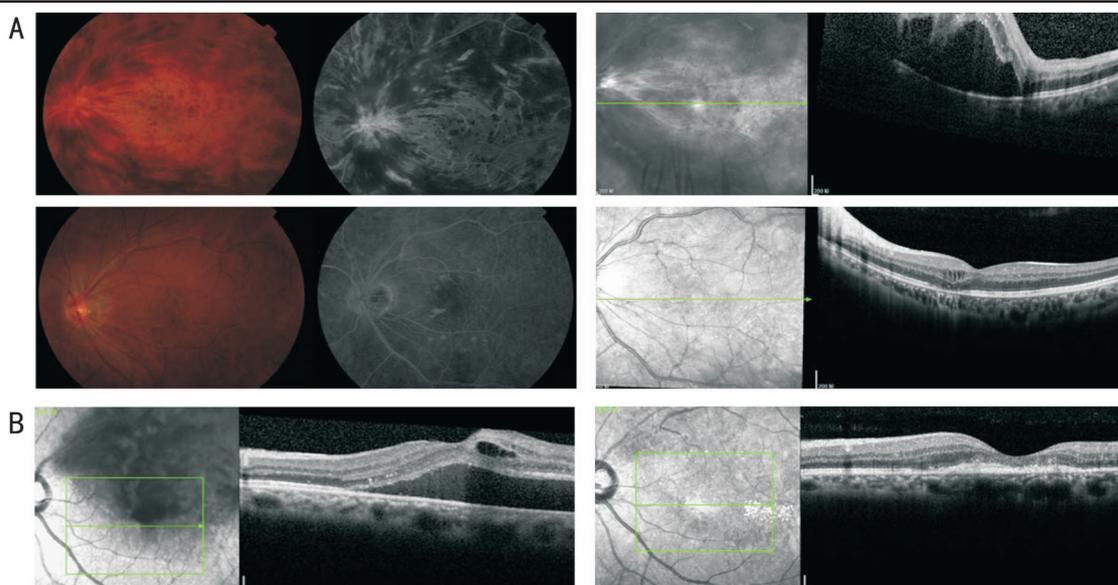
Parameters	Group I	Group II	P
N1			
Mean	2.3	2.9	0.151
Range	1-5	1-5	
SD	1.1	1.0	
N2			
Mean	0.9	1.7	<0.001
Range	0-2	1-2	
SD	0.4	0.4	
Duration (mo)			
Mean	7.1	11.6	0.001
Range	1-24	3-24	
SD	4.3	3.1	
Cataract	0 (0)	4 (16.7)	0.018
Raised intraocular pressure	4 (21.1)	5 (20.8)	1.000

N1: No. of injection of ranibizumab; N2: No. of injection of TA.

fovea. In Group II, 14 subjects had subfoveal exudates at baseline but 7 of them disappeared at final stage. Ten subjects had no subfoveal exudates at baseline but 4 of them had new subfoveal exudates appeared at final stage (Figure 2). Totally 29.17% subjects in Group II with subfoveal exudates, had final vision outcome less than 45 letters. Subfoveal exudates at final stage had significant relationship with vision outcome,  $P < 0.01$  (Table 3).

## DISCUSSION

A few studies has reported the use of combination therapy with ranibizumab and Ozudex. The combination therapy was found effective in treating macular edema due to RVO and reduced the injection times and economic bounden than ranibizumab injection alone<sup>[9-11]</sup>. Ozurdex has shown fewer side effects than TA, but it is still unavailable in many country and is much more expensive than TA. In this study, we collected 2 groups of RVO subjects after sequential therapy with ranibizumab and TA. All the subjects got stable CFT < 300 µm for more than 6mo after last treatment. The average ranibizumab injection times was 2.3 in Group I and 2.9 in Group II, which was much lower than that in ranibizumab injection alone (8-9 in the first year and another 6-7 in the second year when patients were



**Figure 2 Photos of fundus of patients with RVO before and after treatment** A: One 36 years old patient suffered CRVO with high CFT (1036  $\mu\text{m}$ ) and SFT (636  $\mu\text{m}$ ) at baseline, started combined treatment (ranibizumab $\times$ 5+TA $\times$ 2) 6wk from onset, gained good vision improvement from 30 letters at baseline to 78 letters BCVA at final stage, a few non-perfusion area in fluorescein fundus angiography; B: One 52 years old patient suffered BRVO without HE under fovea at baseline, gained 56 letters BCVA at final stage with new appeared HE under fovea.

**Table 3 HE characteristics** *n* (%)

Groups		Baseline HE status	Final HE status
Group I ( <i>n</i> =19)	+	5 (26.32)	0 (0)
	-	14 (73.68)	19 (100)
Group II ( <i>n</i> =24)	+	14 (58.33)	11 (45.83)
	-	10 (41.67)	13 (54.17)

HE: Hard exudates.

treated with 6+ PRN protocol)<sup>[12]</sup>. The TA injection times was 0.9 in Group I and 1.7 in Group II. It was the first time that the total injection times of ranibizumab and TA was reported in the sequential therapy, which got the anatomic cure of macular edema. The working times of TA was 2.6mo (range 2-4mo), which was shorter than Ozurdex (range 3-6mo) as reported<sup>[4,9-10]</sup>. But the side effects were quite few in patients received 2 mg TA injection once. As to subjects who received TA injection twice, the side effects was not higher than that in Ozurdex injection as reported<sup>[4,9-10]</sup>, because the second TA injection was given 6mo after the first injection and the dosage was 2 mg/0.05 mL each time. The sequential therapy with ranibizumab and TA injection as described in this study was safe and workable for macular edema from RVO. The less TA injection was related to the shorter duration of the whole treatment in Group I.

Treatment of macular edema is imperative to improve the vision. A study revealed that approximately 30% of the cases resolved spontaneously over a long interval, often with neuroretinal or pigment epithelial scarring and atrophy<sup>[13]</sup>. In one study, the times taken for resolution of macular edema in untreated nonischemic CRVO with macular edema averaged 23mo compared to 29mo for ischemic CRVO<sup>[14]</sup>. Postponing

treatment for more than 3mo would adversely affect the collaterals, and caused more damage to the macula. Therefore, early treatment with intravitreal injection is suggested<sup>[15-16]</sup>. In this study, we found that Group I started treatment 6.7wk after onset (range 4-15wk, 70% before 6wk), Group II started treatment 22wk after onset (range 6-56wk). Perhaps because retinal anatomic changes of shorter duration are more likely to be reversible compared with more chronic changes in the retinal architecture. So early treatment with intravitreal injection is related with good vision outcome. Six weeks from onset was suggested to start an intravitreal injection.

Age had been found as a definite factor across both disease entities (CRVO and BRVO) for predicting visual acuity outcomes, with younger age associated with a gain in 15 or more in visual acuity letter score in SCORE-BRVO trial (with larger sample size)<sup>[17]</sup>. In this study, the age was younger in Group I than that in Group II (46.4y vs 57.5y). Younger patients may have better visual acuity outcomes due to generally healthier ocular tissue with improved likelihood for recovery following an acute insult such as a RVO: for example, irreparable damage to photoreceptors may be associated with age.

Visual loss in RVO commonly occurs as a result of macular edema, the formation of which has been described by Gass and others<sup>[18-19]</sup>. The degree of accompanying capillary endothelial damage then determines location of the extracellular fluid collection. If the capillary damage is mild, serous exudation may be confined to the inner retinal layers without the formation of cystoid spaces. If the capillary damage is moderate, and particularly if the deeper plexus of retinal capillaries is affected, the serous fluid extends posteriorly and laterally, where it accumulates in the inner nuclear layer (INL) and outer

ple-xiform layer (OPL). As the severity of leakage increases, cystoid spaces may form in the more superficial retinal layers; conversely, in some cases, leakage may be of sufficient severity to breach the external limiting membrane of the outer retina, leading to SRF accumulation. So, the presence of SRF had been considered as a sign of severity of RVO and worse vision outcome. But, in BRAVO and CRUISE study, it was reported that SRF presence did not portend a poor outcome in patients treated with ranibizumab for whom SRF was eliminated in almost all by month 3<sup>[20]</sup>. We confirmed the same conclusion in this study, as the presence of SRF had no difference between Group I and Group II and actually all the SRF eliminated before the third month. Young patients with high CRF and SRF at baseline could gain VA better than 78 letters after treatment (Figure 2).

Macular HE is common in retinal vascular disease such as RVO and diabetic retinopathy. More attention was paid on the HE in diabetic retinopathy than that in RVO. It has been reported that HE severity was associated with worse visual outcomes, but the vision was affected by the presence of HE in field close to central macular<sup>[21]</sup>. It was confirmed by Sasaki *et al*<sup>[22]</sup> that the involvement of the central macular region was associated with poor VA but not total HE. The location of HE was an important determinant of visual function. It is easier to judge if the exudates presence or absence in clinic than quantitative analysis. So, in this study, we analysed the relationship of presence of HE under the central fovea with vision outcome in RVO. We found that no matter the subfoveal exudates presence or not, all of them disappear at the final stage in Group I. But 45.83% subjects in Group II had subfoveal exudates at final stage. In this study, we confirmed that presence of subfoveal exudates at final stage had significant relationship with vision outcome. In Group I, 5 subjects with subfoveal exudates at baseline disappear at final stage after treatment. In Group II, 7 subjects with subfoveal exudates at baseline disappear at the final stage after treatment but new HE appeared in 4 subjects even after combined inject and TA. Ranibizumab injection alone had been confirmed helpful in reducing HE<sup>[23-24]</sup>. In this study, we found that combined injection reduced subfoveal HE quite well in Group I but not in Group II. Response ability was different in this two groups which may determine the result. Younger age, shorter duration from onset to treatment should also be considered as reasons for better response ability in Group I.

In conclusion, we found that younger patients and earlier treatment will help to get better vision outcome. Final stage subfoveal exudates had significant relationship with vision outcome. No relationship existed between the baseline CFT, SFR and the vision outcome. But the main shortage of this study is the small sample. Further observation should be taken in a larger samples.

## ACKNOWLEDGEMENTS

**Conflicts of Interest:** Qin YW, None; Yu J, None; Zhang Q, None.

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