Original Article

Different Dosages of Intravitreal Triamcinolone Acetonide Injections for Macular Edema Secondary to Central Retinal Vein Occlusion

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Abstract

Purpose: To study the effect of intravitreal injections of triamcinolone acetonide (TA) for the treatment of macular edema secondary to central retinal vein occlusion (CRVO) in a sample of Chinese patients from Shaanxi province.

Methods: The 50 eyes from 50 patients were separated into three TA treatment groups: 17 patients were given 4 mg/0.1 ml, 19 patients were given 8 mg/0.2 ml, and 14 patients were given 16 mg/0.4 ml. Patients were followed up for 12 months. Foveal thickness, intraocular pressure (IOP), and best-corrected visual acuity (BCVA) were measured.

Results: Macular edema responded well both anatomically and functionally to the TA injections. After the initial intravitreal injection, macular edema recurred at 2–4 months in the low-dose group (4 mg), at 3–5 months in the medium-dose group (8 mg), and at 6-9 months in the high-dose group (16 mg). No significant difference in BCVA or in foveal thickness were observed between the first intravitreal injection and the re-injection. There was no increase in IOP after re-injection of 16 mg TA, if the patient did not have an elevated IOP after the initial intravitreal injection of 4/8 mg TA.

Conclusion: A low dosage of TA (4 mg) administered via intravitreal injection might be useful as an initial treatment for macular edema secondary to CRVO. A higher dosage of TA (16mg) can be used if there is no IOP elevation with the initial TA injection. (***Eye Science 2012; 27:152–157***)

Keywords: triamcinolone acetonide; intravitreal injection; macular edema; central retinal vein occlusion

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Central retinal vein occlusion (CRVO) is the second most common retinal vascular disease after diabetic retinopathy[1]. Visual loss may result from macular ischemic damage and/or edema. Early treatment should be required to improve visual acuity because only 30% of macular edema associated with CRVO could be resolved by themselves over time, and long-standing macular edema could result in irreversible photoreceptor damage[2,3].

Anti-VEGF medications (Ranibizumab and Bevacizumab) have achieved excellent effects except in cases of severely ischemic retina[4,5]. Patients may need repeated intravitreal injections of bevacizumab to maintain the efficacy, because the effect of a single injection could only last for approximately two months in most patients. Laser photocoagulation is less effective for patients with macular edema associated with CRVO compared with other approaches[6,7].

Intravitreal triamcinolone acetonide (IVTA) injection, a less traumatic treatment, has gradually become a popular treatment of patients who suffered from macular edema secondary to CRVO. It has been shown that TA injection is effective to reduce edema and improve visual acuity in CRVO patients, yielding more remarkable effects in non-ischemic than in ischemic CRVO[8–12].

In most clinical situations, the efficacy (extent and duration) of IVTA injection depends on the dose of TA and the presence of retinal ischemia[8]. The effect of IVTA injection (4 mg) lasted approximately 2 to 4 months, and about 6 to 8 months at a dosage of 20

mg[12]. Repeated IVTA injections are possibly required, however, the efficacy to reduce the retinal thickness and increase the visual acuity may be lowered after repeated injections[13,14].

Despite its apparent established efficacy, the proper dose or administration route of TA has been uncertain and, therefore, a rational medical management strategy is still to be determined. This study is designed to evaluate the effects and side-effects of different dosages of TA intravitreal injections in the treatment of macular edema secondary to CRVO in Northwest Chinese population.

Patients and methods

This study was performed according to the Declaration of Helsinki of the World Medical Association. The protocol was approved by the Institutional Review Board of Xi'an No.4 Hospital and informed consent was obtained from the patients. A total of 57 eyes from 57 consecutive patients in outpatient clinics between September 2007 and September 2009 were included in the prospective observational clinical trial. Patients with macular edema due to nonischemic CRVO duration from onset to injection of ≤ 6 months, no neovascular complication, no macular ischemia, no previous treatment for CRVO and without any other eye disease that would affect the prognosis were included in this study. Seven eyes (12%) with nonischemic CRVO which were converted to ischemic CRVO during 12-month were excluded in this study. Therefore, 50 eyes from 50 patients (29 male and 21 female) were considered for the study. The age ranged from 46 to 70 years (mean 58.2 years), and the time from onset of macular edema to IVTA injection was ≤ 3 months in 31 patients and >3 months in 19 patients.

Intravitreal injection was conducted under sterile conditions in the operating room. Povidone-iodine was applied before injections. Under the operating microscope, paracentesis was performed into the anterior chamber and some aqueous fluid was aspirated by using a 26-gauge needle to decrease the volume of the eye. A portion of 0.1 ml of TA (40 mg/1.0 ml suspension, Erba CO. Italy) was injected slowly through the inferior pars plana 4 mm posterior to the limbus via a 27-gauge needle. An anterior chamber paracenthesis was performed again and mannitol intravenous injection was given immediately to control the increased intraocular pressure (IOP>40 mmHg). Topical antibiotic was used in all of the patients for 3 days.

The 50 eyes from 50 patients were separated into 4 mg treatment group (n=17), 8 mg treatment group (n=19) and 16 mg treatment group (n=14). They were given 4 mg/0.1 ml, 8 mg/0.2 ml and 16 mg/0.4 ml of TA intravitreal injections respectively, and followed up for 12 months.

All of the patients underwent a complete ophthalmological evaluation (including best-corrected visual acuity testing, IOP, anterior and posterior segment examinations), fundus photography and optical coherence tomography (OCT, Carl Zeiss Ophthalmic Systems Inc, California, USA) at baseline and at 1, 3, 5, 7, 9 and 12 months after the first injection. Flourescein angiography (FA) was performed every 3 months. IOP was measured by noncontact tonometer+ central corneal thickness measurements at monthly intervals after the first injection for 6–10 months if an IOP was ≥ 24 mm Hg[15]. For eyes requiring repeated steroid injections, a similar follow-up procedure was employed.

Nonischemic CRVO was defined as the area of retinal nonperfusion capillary was < 10 disc areas on FA[16]. Pressure elevation was defined as an IOP ≥ 24 mm Hg.

Statistical analysis was performed by SPSS statisti cal software (version 11.5; SPSS, Chicago, IL). The data obtained were analyzed with frequency and descriptive statistics. Nonparametric Wilcoxon test was applied to test the differences between measurements at baseline and measurements obtained during follow-up. *Chi*-square was used to test the differences among different dose groups, and Mann–Whitney U test was used to analyze the differences between macular edema due to CRVO duration from onset to injection of≤3 months and those patients >3 months. The level of significance was 0.05 (2 sided) in all statistical testing.

Results

There was no statistical significance in the foveal thicknesses among 3 groups before IVTA injections

(P=0.866). Macular edema associated with CRVO responded well anatomically and functionally to IVTA injections at 1 month after the first injection. Visual acuity increased from 0.11±0.05 to 0.39±0.15, from 0.12±0.04 to 0.39±0.15 and from 0.11±0.04 to 0.44±0.12 in the 4 mg, 8 mg and 16 mg groups, respectively (Figure 1). Foveal thickness decreased from 664±93 μm to 228±78 μm, from 683±108 μm to 240±107 μm and from 683±145 μm to 176±14 μm in the 4 mg, 8 mg and 16 mg groups, respectively (Figure 2). Statistical significance was observed both in the improvement of visual acuity and the decrease of foveal thicknesses in each group (P<0.01). The reduction of foveal thickness in the 16 mg group was better than those in the 4 mg and 8 mg groups (P=0.006), while there was no significant difference in the increase of visual acuity among the 4 mg, 8 mg and 16 mg groups at 1 month after the first injection (P=0.490). There were no significant differences either in the increase of visual acuity (P=0.515) or in the reduction of foveal thickness (P=0.851) among the three groups at 3 month after the first injection. As a consequence of re-injections in some eyes, however, no significant differences were found in foveal thickness (P=0.800) and visual acuity (P=0.878) among the three groups at 12 month after the first injection.

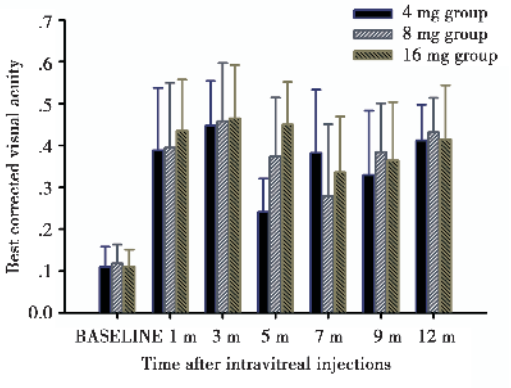

Figure 1 Comparison of mean ± SD values of BCVA between measurements at baseline and measurements obtained during follow ± up among different doses groups. m = month.

The results revealed that 64.7%, 57.9% and 50% of the CRVO patients undergoing IVTA injections in the 4 mg, 8 mg and 16 mg groups experienced recurrent edema at 2–4, 3–5 and 6–9 months after the initial injection, respectively. Repeated injections of TA were performed at 3 to 5 months in the 4mg group (4 to 6 months in the 8 mg group) or later after the first injection, and there were no significant differences in the increase of visual acuity and reduction of retinal thickness between the initial injection and the re-injections (P>0.05). Kaplan-Meier survival analysis showed that the need for additional injections was significantly greater in the 4 mg group than in the 16 mg intravitreal group (P<0.01, Figure 3).

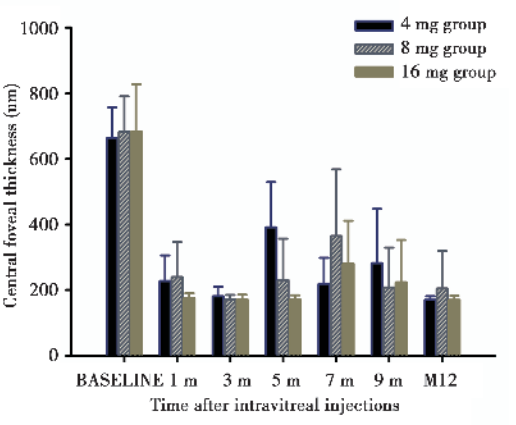

Figure 2 Comparison of mean ± SD values of central foveal thickness between measurements at baseline and measurements obtained during follow ± up among different doses groups by optical coherence tomography. m = month.

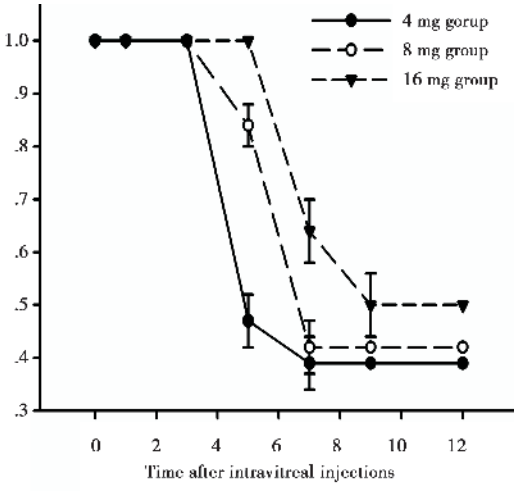

Figure 3 Kaplan ± Meier survival plots of eyes requiring reinjection of TA after the planned 12 ± month follow ± up among three different doses groups. The survival curve in the 16 mg group was significantly better than that in the 4mg group.

The patients with macular edema due to CRVO duration from onset to injection of ≤3 months were also compared with those patients >3 months.A greater BCVA improvement was noted in patients ≤ 3 months than those > 3 months, but there was no significant difference in the increase of BCVA and reduction of retinal thickness ($P > 0.05$).

In this study, 6 patients (35.3%) in the 4 mg group, 8 patients (42.1%) in the 8mg group and 6 patients (43%) in the 16 mg group experienced IOP elevation, occurring at 1 to 2 months after the first IVTA injection. The most notable IOP elevation was found at 3 months in the 4/8 mg groups, 2–3 months and 5–6 months in the 16 mg group, respectively. The duration of TA induced-IOP elevation was longer at a dose of 16 mg than that at doses of 4/8 mg (approximately 7–9 months vs. 3–6 months) (Figure 4). Younger males (< 50 years) with CRVO had a higher risk of refractory IOP, especially at 5–6 months after the injections of 16 mg TA.

Elevated IOP was controllable in most cases with 1–2 anti-glaucoma medications on average. Seven patients required the addition of anti-glaucoma medication. Four patients need system anti-glaucoma medication and finally received argon laser trabeculoplasty (2 eyes) or anti-glaucoma operation (2 eyes).

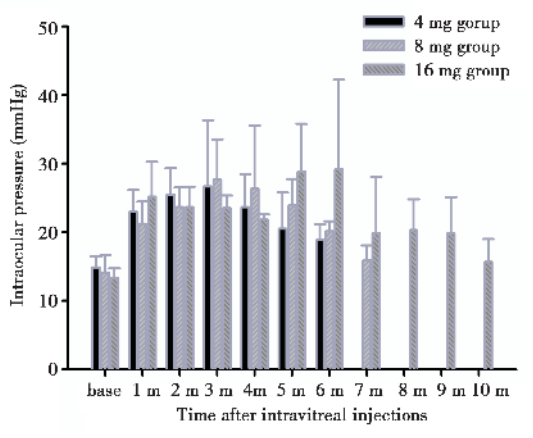

Figure 4 IOP measurements at before (Baseline) and monthly intervals after IVTA injection for 6–10 months were recorded (mean ± SD). The highest IOP was measured at 3 months in the 4/8mg groups, 2–3 months and 5–6 months in the 16mg group, respectively. The duration of TA–induced ocular hypertension was 3–4 months longer in the 4mg group, 5–6 months in the 8mg group, 7–9 months in the 16mg group, respectively. m=month.

In the 4/8mg groups, if the CRVO patients undergoing the first IVTA injection experienced recurrent edema and no elevated IOP, 16 mg TA was used in the second injection. There was no significant increase in IOP after the re-injection. Otherwise, if the patients receiving the first IVTA injection had recurrent edema and IOP elevation, which could be controlled by 1–2 anti-glaucoma medications, 4 mg TA was used in the second injection. The recurrence of elevated IOP could also be controlled by 1–2 anti-glaucoma medications.

Cataract progression was detected in 4 patients (23.5%) in the 4mg group, 6 (31.6%) in the 8mg group and 5(35.7%) in the 16mg group. Nine (34%) of the eyes with nonischemic CRVO were converted to ischemic CRVO during 12 months, and the incidence of neovascular glaucoma was 0% in cases with nonischemic CRVO. No other complications related to TA injections were observed.

Discussion

Blood-retinal barrier breakdown mediated by multiple cytokines such as VEGF was upregulated in hypoxic retina since central retinal vein occlusion greatly facilitates the extravasation of fluid, proteins and other large molecules. In this manner, macular edema results from central retinal vein occlusion, and tends to be a chronic course which is difficult to cure. If it persisted for > 8 months, it will cause permanent diminution of vision due to the disruption of microscopic intraretinal connections and the intracellular damage of visual elements[17]. TA, as a corticosteroid suspension, has been shown to reduce the breakdown of blood-retinal barrier after intravitreal application, and used to treat macular edema associated with various retinal diseases on account of its antiinflammatory, antiangiogenic, and blood-retinal barrier stabilizing effects[18,19].

It has been shown that the effect of 4 mg TA injected into the vitreous cavity lasts for about 3 months, and 20 mg of intravitreal TA endures for 6 to 9 months[20–22]. Therefore, it is possible that the recurrence of macular edema occurs when intravitreal TA is absorbed. In our study, the low dosage (4 mg) injection was more frequently delivered to compensate its shorter duration of the effect, and no marked

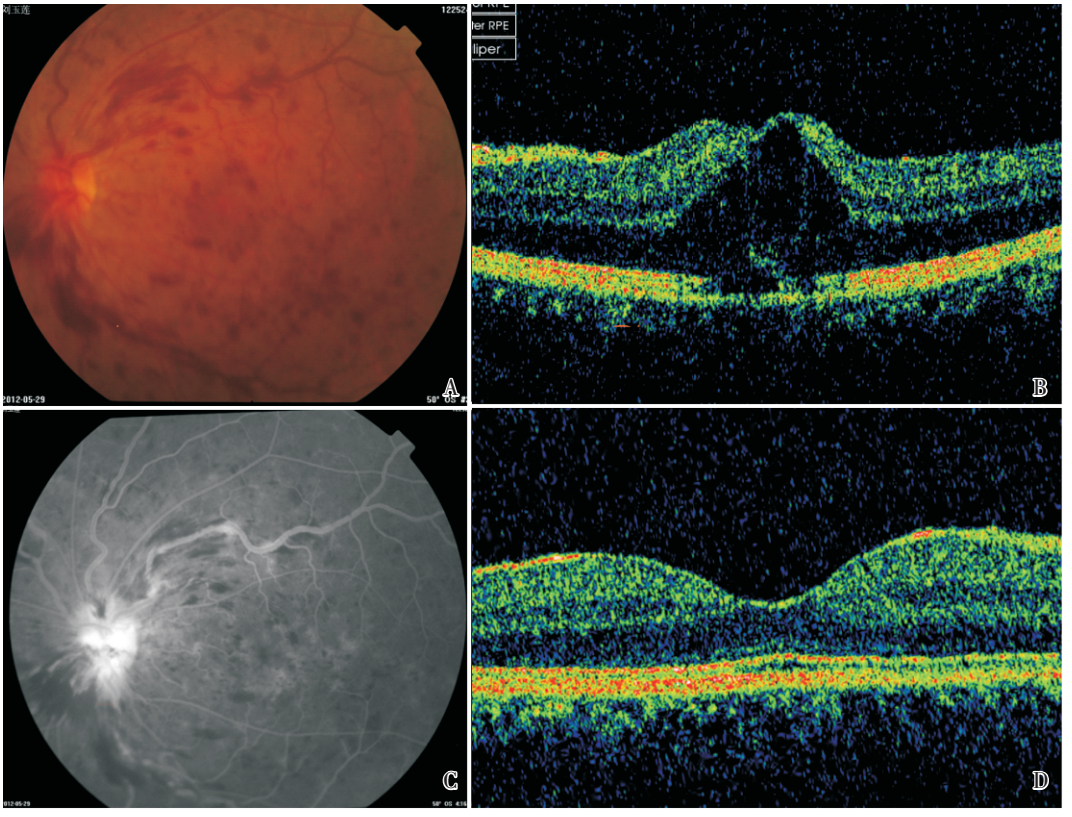

Figure 5 Fundus photography and OCT in a 57 year-old patient with CRVO. (A) Color fundus photography showed venous dilatation, tortuosity and scattered retina hemorrhage. (B) Pre ± injection OCT showed cystoid macular edema with central foveal thickness of 552 μm. (C) Fluorescein angiogram showed macular edema. (D) Post ± injection OCT showed decreased macular edema with central foveal thickness of 184 μm.

difference was noted regarding the increase in visual acuity and reduction of retinal thickness between the initial injection and the reinjections in CRVO patients.

The advantages of the higher dose injection include the longer duration of the effect, lower frequency of reinjections, lower risk of injection-associated infectious endophthalmitis, lower cost, and less burden for the patients. However, one disadvantage is that elevated IOP often lasted for 6 to 8 months. Another disadvantage is the higher incidence of significant IOP elevation happened in late stage, especially in young patients with a history of CRVO, indicating that patients should be followed-up for several months after intravitreal injection of 16 mg TA to detect a steroid-induced increase in IOP.

Besides the remarkable improvement in visual acuity and reduction of retinal thickness, intravitreal steroid can also relieve inflammation due to CRVO, promote recovery of visual functions by retinal cells and increase visual acuity in nonischemic CRVO[23].

In our study, IVTA decreased fluorescein leakage and no severe complications except a transient increase in IOP emerged.

During the acute phase after CRVO, extensive intraretinal hemorrhage that may involve with the macula and the foveal center constantly occurs. Under these circumstances, it is difficult to distinguish whether the BCVA improvement was caused by clearing of hemorrhage or by absorption of macular edema. Hence, these patients with macular edema due to CRVO duration of ≤3 months were compared with those patients >3 months. There was no significant difference in BCVA improvement and retinal thickness reduction.

In conclusion, low dosage IVTA injection could also be used as an initial treatment for macular edema secondary to CRVO. If those eyes without IOP elevation at the first IVTA injection thus required repeated IVTA injections, high dosage TA intravitreal injection should be considered. High dosage IVTA

possesses multiple advantages including longer duration of the effect, lower frequency of reinjections, lower risk of injection-related complications, lower cost, and less burden for patients. Especially, it can avoid longer duration of elevated IOP and higher incidence of significant IOP elevation in late stage.

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