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CLINICAL INVESTIGATION

Efficacy and Retention Times of Intravitreal Triamcinolone Acetonide for Macular Edema

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Abstract

Purpose: To evaluate the retention of intravitreal triamcinolone acetonide (TA) particles and the efficacy of TA therapy for patients with cystoid macular edema in branch retinal vein occlusion (BRVO) or diabetic macular edema (DME). We monitored the TA particles until absorption from the vitreous cavity was complete. The correlation between the intravitreal retention time of TA and its efficacy was evaluated based on central macular thickness (CMT).

Results: The intravitreal TA retention time was a mean 141.8 ± 139.6 days in BRVO patients and 114.5 ± 59.6 days in DME patients. Patient age and retention time were negatively correlated ($r = -0.46$; $P = 0.013$). At 6 months posttreatment the mean CMT decreased from 544.1 ± 143.7 to 322.4 ± 131.9 μm in BRVO patients and from 454.5 ± 119.0 to 371.2 ± 209.4 μm in DME patients. Retention time and CMT reduction were positively correlated in BRVO patient ($r = 0.56$, $P = 0.02$) but not in DME patients ($P = 0.06$).

Conclusions: Intravitreal TA reduced the CMT in BRVO and DME patients over 6 months. The retention time was longer in younger individuals. The efficacy of the therapy depended on the intravitreal TA retention time observed clinically in BRVO patients. Biomicroscopic examination of intravitreal TA is useful for evaluation of its efficacy. **Jpn J Ophthalmol** 2008;52:122–126 © Japanese Ophthalmological Society 2008

Key Words: branch retinal vein occlusion, central macular edema, diabetic macular edema, intarvitreal triamcinolone injection, drug retention time

Introduction

Macular edema is the leading cause of visual loss in branch retinal vein occlusion (BRVO) and diabetic retinopathy. Grid laser photocoagulation has been shown to be efficacious for treating macular edema in BRVO;[1] however, some eyes are resistant to treatment and have a poor visual outcome. Diabetic macular edema (DME) has two subtypes, focal macular edema and diffuse macular edema. The former can be treated by the application of focal laser photocoagulation to microaneurysms, but in the latter the efficacy of grid laser photocoagulation is limited.[2–4]

Recent studies have suggested that intravitreal triamcinolone acetonide (TA) may be a therapeutic option for macular edema in various fundus diseases including uveitis,[5] BRVO,[6–8] and DME.[9,10] The efficacy of TA tends to diminish in a few months, and macular edema may recur.[11] However, there is no pharmacodynamic parameter that indicates the efficacy of TA in human eyes.

The purpose of the current study was to investigate the clinical course of TA for cystoid macular edema (CME) due to BRVO and DME and the correlation between its efficacy and the intravitreal TA retention time.

Patients and Methods

Twenty-nine patients (29 eyes) with CME due to BRVO (17 eyes of 17 patients) or DME (12 eyes of 12 patients) examined at St. Luke's International Hospital, Tokyo, between January 2004 and October 2005 were included in this study. The follow-up periods ranged from 6 to 27 months (mean, 13 months). The patient ages ranged from

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38 to 80 years (mean, 62.8 ± 9.9) in BRVO and from 42 to 72 (mean, 60.5 ± 7.9) in DME. The mean preoperative period of persistent CME in the 17 eyes with BRVO and the 12 eyes with DME was approximately 5 months (range, 3–20 months). Three eyes with BRVO and three eyes with DME had been treated with grid laser photocoagulation more than 5 months before treatment with TA. Posterior vitreous detachment (PVD) was observed in six eyes with BRVO and in two eyes with DME. There was no evidence of vitreomacular traction in any of the 29 eyes. The best-corrected visual acuity (BCVA) converted to the logarithm of minimal angle of resolution (logMAR) was within 0.3–1.0 (decimal visual acuity, 0.1–0.5). The central macular thickness (CMT) was more than 250 μm in all 29 eyes.

Exclusion criteria included a history of glaucoma or ocular hypertension, a response to steroid therapy, poorly controlled diabetes (HbA1c, >10%), severe hypertension or severe nephropathy, ischemic maculopathy or macular degeneration, or intraocular surgery during follow-up or within 4 months before the administration of intravitreal TA. To exclude the steroid responders, elevations of intraocular pressure (IOP) were assessed in all patients before administration of intravitreal TA by a test treatment with topical 0.1% betamethasone sodium phosphate (Rinderon A, Shionogi, Osaka, Japan) three times a day for 1 month, based on the report of Armaly.[12] We followed all patients for longer than 6 months after administration of the first single injection of intravitreal TA.

Main Outcome Measures

Examinations were performed at baseline, 1 and 2 days every week for 1 month, and then every month until the final examination. The main outcome measures were CMT with optical coherence tomography (OCT) (Stratus OCT, Carl Zeiss- Humphrey, Dublin, CA, USA), BCVA (logMAR) for distance vision, and the intravitreal retention time of TA crystals observed by biomicroscopy with a three-mirror contact lens. IOP was measured by Goldmann applanation tonometry. At each follow-up, the CMT was measured with the Stratus OCT after maximal pupillary dilation with 1% tropicamide and 2.5% phenylephrine hydrochloride (Mydrin-P, Santen, Osaka, Japan). The macular thickness was calculated automatically by computer software from the aggregate data from multiple radial scans. During examinations patients were asked to fixate on the target illumination in order to obtain images of the same part of the macula at every visit.

Procedures

The outpatient treatment was performed in an operating room. Local anesthesia consisted of application of 0.4% oxybuprocaine hydrochloride eyedrops (Benoxil, Santen) followed by disinfection with ×16 povidone–iodine solution (Isodine, Meiji Seika, Tokyo, Japan). We prepared 0.1 ml of sterilized TA suspension, which contained 4 mg of TA (Kenacort, Bristol-Myers-Squibb, New York, NY, USA) by the following procedure. We removed the supernatant, which contains a preservative, from a 1-ml TA (40-mg) vial and then washed the TA crystals with balanced salt solution (BSS, Alcon Laboratories, Fort Worth, TX, USA) and filtered them through a 0.22-μm Millipore filter (MILLEX GS, Billerica, MA, USA). The entire content of the vial was drawn into a 2.5-ml syringe, then washed by filtered BSS five times. Finally, a 1.0-ml suspension of 40 mg of TA was prepared. The 0.1-ml suspension containing 4 mg of TA was injected into the vitreous cavity, using a sharp 27-gauge needle with a 1-ml tuberculin syringe, through the inferotemporal pars plana (4 mm from the limbus in phakic eyes and 3.5 mm in pseudophakic eyes). After injection, the eyes were patched with Ofloxacin ointment (Tarivid, Santen) overnight. Postoperatively, oral Cefdinir (Cefzon, Astellas, Tokyo, Japan) was prescribed for 4 days, and Levofloxacin eyedrops (Cravit, Santen) were also applied four times daily for 1 month.

Statistical analyses were performed with Microsoft Excel 2000 (Microsoft, Redmond, WA, USA) and Stat Mate III (ATMS, Tokyo, Japan). Data were compared by using the Wilcoxon rank test, the Mann-Whitney *U* test, and Spearman's rank correlation test. A P value of <0.05 and a correlation coefficient ≥ 0.4 were considered significant.

This pilot study was designed as a prospective, interventional case series, and was carried out at St. Luke's International Hospital, Tokyo, Japan. The study followed the tenets of the Declaration of Helsinki. Before treatment, all patients provided informed consent after receiving a detailed explanation about the aim of the study and possible complications.

Results

The mean CMT at baseline was 544.1 ± 143.7 μm in BRVO patients and 454.5 ± 119.0 μm in DME patients. The CMT decreased from 544.1 ± 143.7 to 234.7 ± 92.5 μm (P = 0.000003) at 1 month and to 322.4 ± 131.9 μm (P = 0.0002) at 6 months in BRVO patients, and from 454.5 ± 119.0 to 261.0 ± 78.1 μm (P = 0.0004) at 1 month and 371.2 ± 209.4 μm (P = 0.15) at 6 months in DME patients. The change in the CMT in each eye is shown in Fig. 1.

The mean baseline BCVA (logMAR) was 0.55 ± 0.27 in BRVO and 0.55 ± 0.25 in DME. The BCVA (logMAR) improved to a mean of 0.32 ± 0.25 at 1 month (P = 0.0002), 0.33 ± 0.24 at 3 months (P = 0.0001), and 0.29 ± 0.22 at 6 months (P = 0.00006) in BRVO and 0.39 ± 0.32 at 1 month (P = 0.002), 0.36 ± 0.34 at 3 months (P = 0.005), and 0.42 ± 0.33 at 6 months (P = 0.12) in DME.

The TA particles were dispersed in the vitreous for a few days after injection, and then they aggregated and embedded in the inferior vitreous gel. During follow-up, we found that the size of the aggregated TA particles in the vitreous cavity decreased at each examination. TA particles were gradually absorbed and finally disappeared from the vitreous (Fig. 2). These particles were visible for 141.8 ± 139.6

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days (range, 7–448 days) in BRVO patients and 114.5 ± 59.6 days (range, 23–196) days in DME patients, based on biomicroscopy with a Goldmann three-mirror contact lens.

Age and Intravitreal Retention Time of TA

Age and the intravitreal retention period of TA particles were significantly and negatively correlated (r = –0.45; P = 0.013) (Fig. 3).

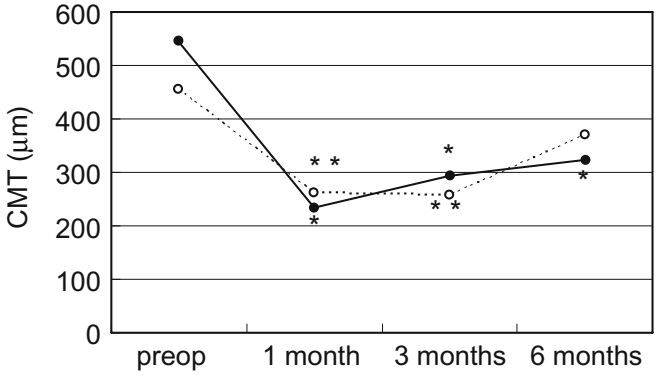

Figure 1. Changes in the mean central macular thickness (*CMT*) in diabetic macular edema (DME) and branch retinal vein occlusion (BRVO) patients after intravitreal injection of 4 mg triamcinolone acetonide. CMT was significantly decreased for up to 6 months in BRVO patients compared with the preoperative (*preop*) value. *P < 0.01 (BRVO); **P < 0.01 (DME). ○, DME; ●, BRVO.

Intravitreal Retention Periods between BRVO and DME

There was no significant difference in the intravitreal retention time of TA particles between the BRVO and DME groups (P = 0.48).

CMT and Intravitreal Retention Time of TA

We assessed the relationship between the reduction ratio of CMT from baseline to 6 months after treatment and the intravitreal retention time of TA particles. The CMT reduction ratio and the TA retention period were positively correlated in the BRVO group (r = 0.56; P = 0.02) but not in the DME group (P = 0.06) (Fig. 4).

BCVA for Distance Vision and Intravitreal Retention Time of TA

Improvement in the BCVA for distance vision from baseline and the intravitreal retention period of TA were significantly positively correlated in the BRVO group (r = 0.54; P = 0.02) but not in the DME group (P = 0.16) (Fig. 5).

The IOP was higher than 21 mmHg in three eyes, detected at 1, 3, or 8 weeks after treatment. Those eyes were treated with topical antiglaucomatous medications only from 2 to 16 weeks. No eye required cataract surgery during follow-up. Three eyes developed a minimal subcapsular cataract with no clinically relevant adverse effects on visual acuity. No study participant developed other complications

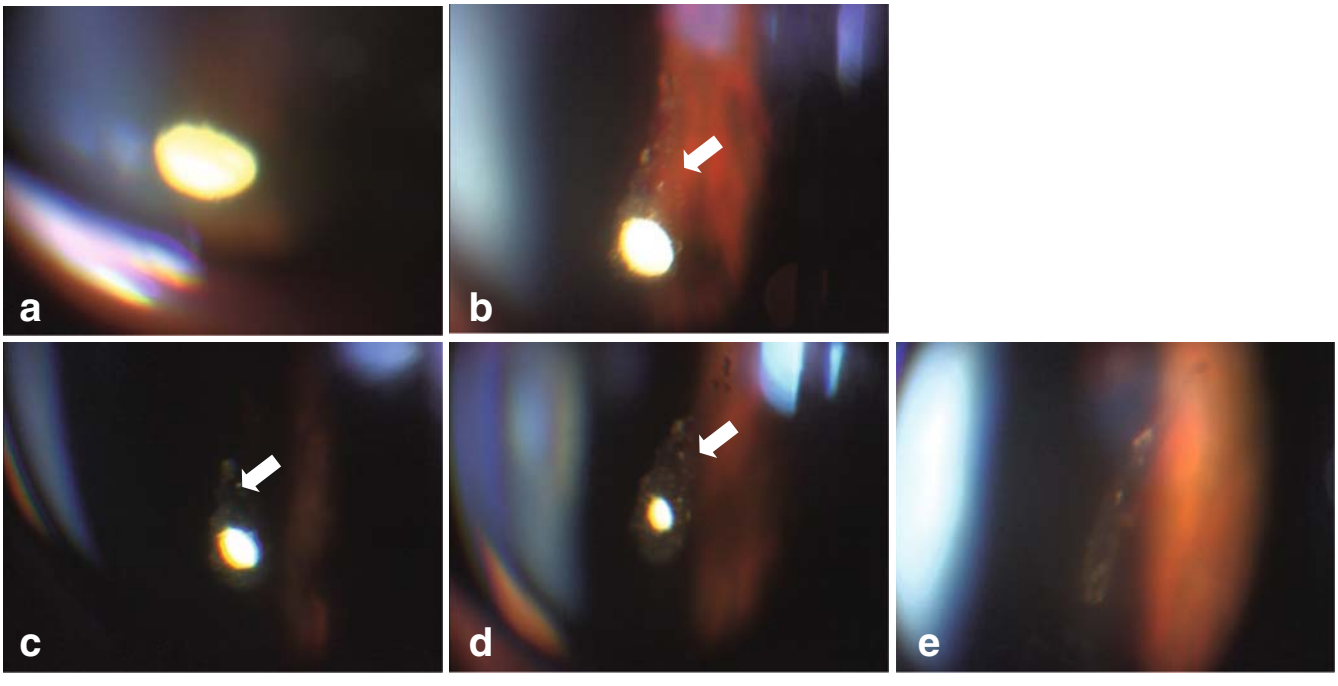

Figure 2a–e. Changes in the size of an triamcinolone acetonide (TA) particle in the vitreous. The particle was observed in the inferior vitreous cavity of a 38-year-old man. It was gradually absorbed and decreased in size 1 week (**a**) and 3 (**b**), 10 (**c**), 12 (**d**), and 15 months (**e**) after injection of intravitreal TA. The TA particle was visible in the vitreous gel for up to 12 months (*arrows*).

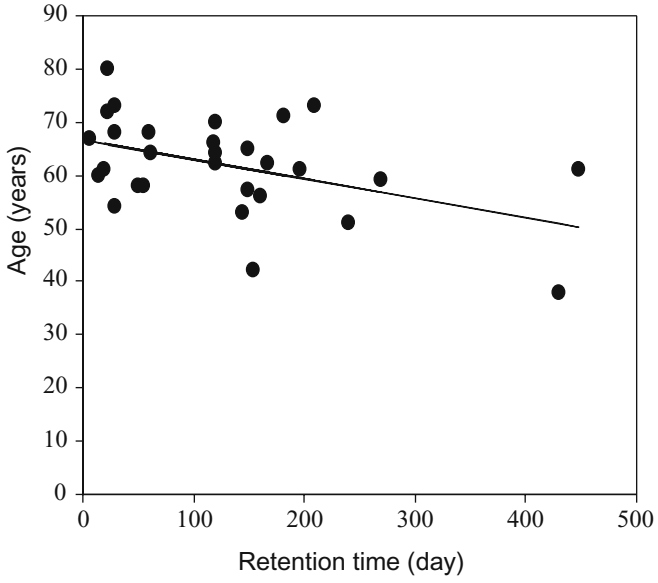

Figure 3. Relationship between patient age and the intravitreal retention times of TA. Age and intravitreal retention times of TA particles were negatively correlated in all patients with DME and BRVO in this study ($r = -0.45$; $P = 0.013$).

described in the literature such as panophthalmitis, pseudoophthalmitis, steroid glaucoma, retinal detachment, or vitreous hemorrhage.

Discussion

Corticosteroids administered topically or systemically have long been used to treat many ocular pathologies. TA is a long-acting corticosteroid that inhibits the arachidonic acid pathway, downregulates the production of vascular endothelial growth factor, a known vascular permeability factor, and stabilizes the blood-retinal barrier. Intravitreal injections of TA have been investigated as treatment for CME due to BRVO,[6–8] DME,[9,10] and other ocular diseases.[13–15] However, the efficacy of intravitreal TA diminishes over time, and CME occasionally recurs. We need to recognize the relation between the efficacious status of intravitreal TA and its therapeutic value, and when reinjection or other treatment should be carried out.

In the current study, intravitreal TA particles remained in young patients for longer periods than in older ones. The intravitreal retention period of TA depended solely on age,

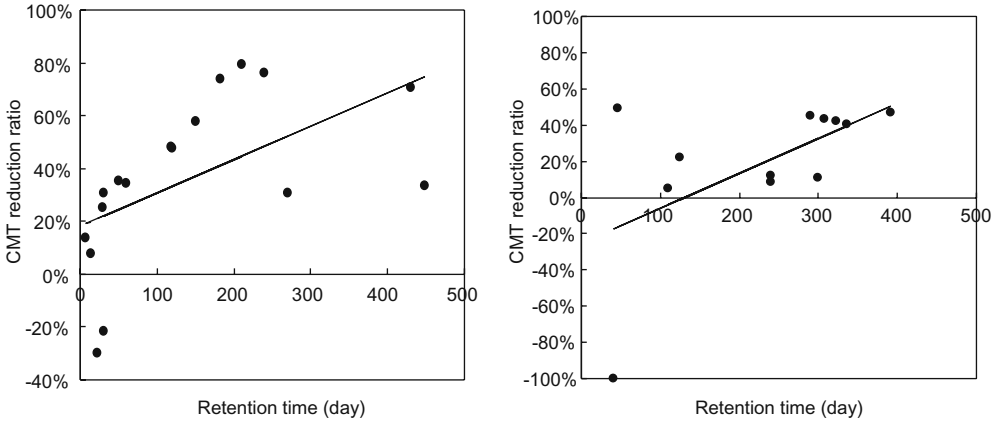

Figure 4. Relationship between the CMT reduction ratio and intravitreal retention times of TA. The CMT reduction ratio and intravitreal retention period were positively correlated in BRVO patients ($r = -0.56$; $P = 0.02$) (*left*) but not in DME patients ($P = 0.06$) (*right*).

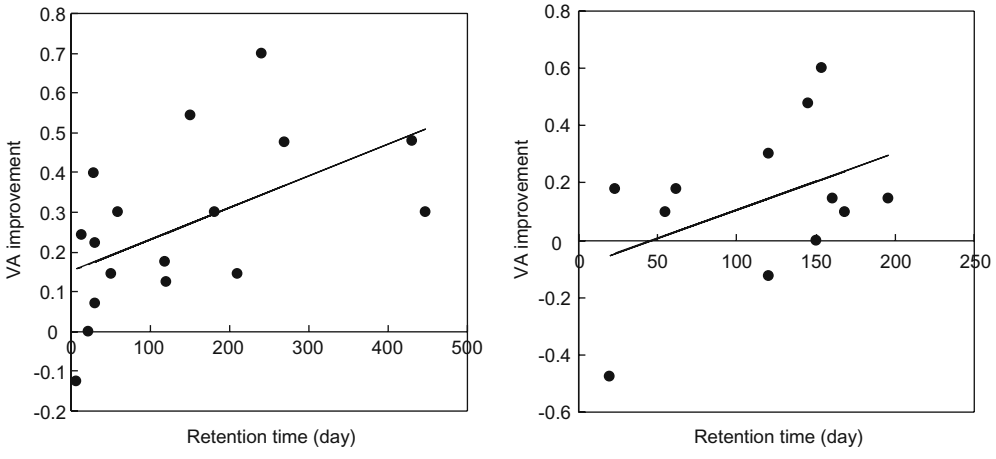

Figure 5. Relationship between improvement in visual acuity (*VA*) and intravitreal retention times of TA. Improvement in VA (logarithm of the minimal angle of resolution) and the intravitreal retention time were positively correlated in BRVO patients ($r = 0.54$; $P = 0.02$) (*left*) but not in DME patients ($P = 0.16$) (*right*).

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and it was unaffected by the disease, such as BRVO or DME, suggesting that the intravitreal retention period of TA may be related to age-related changes in the vitreous. Vitreous liquefaction progresses along with aging, which means that the volume of the gel decreases with age. Since TA particles were embedded in the vitreous gel and were gradually absorbed from the vitreous, a less liquefied vitreous would retain TA particles for longer periods.

There was a positive correlation between the CMT reduction ratio and the intravitreal retention period of TA in BRVO but not in DME, indicating that the presence of TA particles in the vitreous cavity might be a pharmacokinetic indicator of the clinical efficacy of intravitreal TA in BRVO, but not in DME. The different responses to intravitreal TA in these two diseases may be attributed to the more complicated metabolic etiology of DME than BRVO. A few studies on the pharmacokinetics of TA in the vitreous by various assessments have been reported.[16–19]

In previous studies, different doses of intravitreal TA ranging from 4 to 25 mg were administered. Spandau et al.[16] reported that the duration of the effect of intravitreal TA increased significantly with the dose of TA. The intravitreal retention time of TA depends on the status of the vitreous. Chin et al.[17] reported that the mean half-life of intravitreal TA was 2.89 days in nonvitrectomized rabbit eyes and 1.57 days in vitrectomized rabbit eyes. They reported TA in vitrectomized eyes to be eliminated 1.5 times faster than in nonvitrectomized rabbit eyes.[17] Beer et al.[11] reported that TA crystals were visible in the vitreous cavity for up to 101 days, and measurable concentrations of TA from the anterior chamber were expected to last for about 3 months in nonvitrectomized eyes of elderly patients. Audren et al.[18] hypothesized that in a pharmacokinetic model the maximum clinical duration of TA efficacy was 140 ± 17 days in human eyes. They administered another injection of TA before this time to avoid a relapse.[18]

In the current study, the TA particles were visible up to 141.8 ± 139.6 (range, 7–448) days after injection in eyes with BRVO and 114.5 ± 59.6 (range, 23–196) days after injection in eyes with DME, which is similar to the maximum duration of the effect of TA reported by Audren et al.[18] The current study clarified that the efficacy of TA persists as long as TA crystals are observed in the vitreous gel. Furthermore, the length of the therapeutic effect might depend on the status of the vitreous body, such as the presence of PVD or age-related liquefaction. From that standpoint, a younger patient with less vitreous liquefaction can expect a longer therapeutic effect from intravitreal injections of TA.

In conclusion, injections of intravitreal TA were beneficial for reducing CMT in BRVO and DME over 6 months. The therapeutic effect depended on the time that intravitreal TA was retained in the vitreous in eyes with BRVO. The intravitreal retention time was longer in younger individuals. We believe that the vitreous gel serves as a reservoir for TA, from which the drug is slowly released. Observation of residual particles of TA in the vitreous provides a pharmacokinetic indicator without laboratory measurement of the TA concentration.

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