The Response Pattern of Intravitreal Triamcinolone Injection for Non-AMD Macular Edema

Patama Bhurayanontachai MD*,
Mansing Ratanasukon MD*, Arinda Ma-a-lee MS**

** Retina Unit, Department of Ophthalmology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand*
*** Epidemiology Unit, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand*

Objective: *To determine the pattern of functional and anatomical responses after intravitreal triamcinolone (IVTA) for macular edema in diabetic retinopathy, retinal vein occlusion, uveitis, and macular telangiectasia.*
Material and Method: *A Retrospective interventional study was carried out between January 2004 and July 2006. Thirty-eight eyes from 36 patients who had undergone an IVTA injection for macular edema from etiologies other than age-related macular degeneration (non-AMD macular edema) were included in the present study. Visual improvement and retinal thickness were the main outcomes. Potential complications, including increased intraocular pressure (IOP), intraocular bleeding, and postoperative endophthalmitis were also recorded.*
Results: *The mean pre-operative logarithm of Minimum Angle of Resolution (logMAR) visual acuity (VA) was 1.0 with an average macular thickness of 463.2 $\pm$ 141.4 microns and mean IOP of 12.9 $\pm$ 2.7 mmHg. The macular thickness rapidly decreased in the first week after an injection with a trough at two months ($p < 0.001$) and began to rise thereafter. The overall VA started to improve significantly at one month and lasted for two months. The IOP significantly increased from the mean baseline during the first two months in 31.6%, which could be controlled only by the medication. No other serious complications were observed.*
Conclusion: *IVTA has the potential to improve both functional and anatomical outcomes in non-AMD macular edema. The decrease in macular thickness occurs from one week after an injection but the visual function improves more slowly and has a short-time effect.*

Keywords: *Intravitreal triamcinolone, Macular edema, Diabetic, Retinal vein occlusion, Intraocular pressure*

J Med Assoc Thai 2009; 92 (1): 58-63
Full text. e-Journal: *http://www.mat.or.th/journal*

Macular edema is one of the leading causes of visual deficit, which is frequently found in patients with diabetic retinopathy; retinal vein occlusion; Irvine-Gass syndrome and chronic posterior uveitis. For diabetic macular edema, the Early Treatment Diabetic Retinopathy Study (ETDRS) has demonstrated that focal retinal photocoagulation can reduce moderate visual loss from clinically significant macular edema (CSME)[1]. The Central Retinal Vein Occlusion Study (CVOS) Group also showed some improvement in vision after macular grid photocoagulation[2]. However, the treatment unavoidably causes direct retinal burns and sometimes absolute scotoma. Furthermore, cystoid macular edema (CME) tends to be resistant to macular grid photocoagulation. Studies have illustrated the benefit of intravitreal triamcinolone acetonide (TA) injection particularly in patients with CME and massive subretinal exudates[3-6]. Therefore, this present study has been undertaken to analyze the response pattern after intravitreal TA injection for macular edema caused by the conditions other than age-related macular degeneration.

Correspondence to: Bhurayanontachai P, Retina Unit, Department of Ophthalmology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla 90110, Thailand. Phone: 074-451-380, Fax: 074-429619, E-mail: tpatama @hotmail.com

Material and Method

After the approval of the Ethics Committee of Songklanagarind Hospital, the medical records of 37 patients were reviewed. The present study examined patients who had previously undergone an intravitreal injection of TA at Songklanagarind Hospital between January 2004 and July 2006. The inclusion criteria for this analysis were patients of 18 years of age or older with macular edema caused by diabetic retinopathy, retinal vein occlusion (RVO), posterior uveitis, or Irvine-Gass syndrome. The diagnosis of macular edema was made clinically by slit-lamp biomicroscopy of the fundus. If an optical coherence tomography (OCT) is also performed, the retinal thickness should be more than 220 microns. Types of retinal vein occlusion included central retinal vein occlusion (CRVO), hemiretinal vein occlusion (HRVO), and branch retinal vein occlusion (BRVO). The retinal features of CSME in diabetic retinopathy were defined by one of the following: a retinal edema was located at or within 500 microns of the center of the macula; hard exudates were at or within 500 microns of the center if associated with thickening of the adjacent retina; or there was a zone of retinal thickening larger than one disc area if located within one disc diameter of the fovea. Those patients who had previous surgery, except for cataract extraction, were excluded from the study. TA solution (Kanolone-F®, L.B.S. Laboratory, Bangkok, Thailand) was prepared in a concentration of 4-mg/0.1 ml and was injected in phakic and pseudophakic eyes at 4.0 and 3.5 mm, respectively, from the limbus under a sterile condition in the operating theater. Postoperatively, patients were instructed to take routine postoperative medication (neomycin and gramicidin eye drop and chloramphenicol eye ointment) and were allowed to resume normal activities. Follow-up examinations were performed at one week, one month, and at 2- to 3-month intervals thereafter. If a second injection of TA or an injection of anti-vascular endothelial growth factor was required then the patient's data was collected up to the last visit before re-injection.

The main outcomes of the evaluation were an improvement of vision and a decrease in retinal thickness after a single injection of TA. Visual acuity was converted to a logarithm of Minimum Angle of Resolution (logMAR) and the central foveal thickness was measured by an OCT (Stratus OCT III, version 4, Carl-Zeiss, Dublin, CA). The secondary outcome recorded was the post-operative complications such as endophthalmitis, vitreous hemorrhage, increased intraocular pressure, and retinal detachment. Differences between the preoperative and postoperative values were tested with the use of Student's t-test, the Chi-square test, or Wilcoxon rank-sum test. A p-value of 0.05 or less would be considered to indicate a statistical significance.

Results

Demographics

From 37 medical records, one patient was excluded from the study because of an incomplete follow-up. The baseline demographic features of the 38 eyes from 36 patients are shown in Table 1. There was an even representation between genders with a median age of 60.5 years (range, 24-75 years) and an over representation of the left eye (65.8%) in laterality. The etiology of macular edema, in the present study, were diabetic macular edema (DME) in 21 eyes (55.3%); macular edema from all types of retinal vein occlusion (RVO) in 14 eyes (36.8%); refractory Irvine-Gass syndrome, uveitis-associated macular edema, and retinal telangiectasia in one eye (2.6%) each. Twenty eyes (52.6%) of the DME group and four eyes (10.5%) of the RVO group had received more than one section of macular grid photocoagulation prior to the TA injection with a mean interval of the last treatment at 13.7 $\pm$ 7.6 weeks (range 4-29 weeks), but they were all refractory to the laser treatments. No patient had taken steroid or non-steroidal anti-inflammatory drops at the time of the present study. All patients had a minimum follow-up of two months with the median time of seven months (range 2-24 months).

Baseline OCT, VA, and IOP

Pre-operative logMAR visual acuity (VA) ranged from 0.3-2.0 (median 1.0, mean 1.02). The average macular thickness was 463.2 $\pm$ 141.4 microns (range 250-818) and the mean IOP was 12.9 $\pm$ 2.7 mmHg. The baseline macular thickness in the RVO group (512.3 $\pm$ 132.5 microns) was significantly higher ($p = 0.04$) than in DME group (417.2 $\pm$ 116.4 microns). There was no statistical difference of baseline VA and IOP between the subgroups.

Post-injection results

The macular edema started to decrease dramatically in the first week ($p = 0.003$) with a mean macular thickness of 322.5 $\pm$ 96.7 microns following an injection. The response reached a trough of 261.9 $\pm$ 80.0 microns at two months ($p < 0.001$) and slowly rose thereafter, to 329.0 $\pm$ 102.1 microns at six months (Fig. 1). None of the patients with uveitis, refractory

Table 1. Baseline clinical characteristics of the patients with non-AMD macular edema

Characteristics	n (%)
Median age in years (range)	60.5 (24-75)
No. (%) of male patients	21 (55.3)
No. (%) of left eye	25 (65.8)
No. (%) of lens status:	
Phakic	33 (86.8)
Pseudophakic	5 (13.2)
No. (%) of diagnosis:	
Diabetic macular edema	21 (55.3)
Central retinal vein occlusion	3 (7.9)
Hemiretinal vein occlusion	4 (10.5)
Branch retinal vein occlusion	7 (18.4)
Irvine-Gass syndrome	1 (2.6)
Posterior uveitis	1 (2.6)
Macular telangiectasia	1 (2.6)
No. (%) of patients with systemic disease:	
Diabetes mellitus	16 (42.1)
Hypertension	6 (15.8)
Diabetes mellitus + Hypertension	10 (26.3)
Mean duration of visual symptom in weeks (range)	25.6 $\pm$ 17.5 (2-59)
Median VA in logMAR (range)	1.0 (0.3-2.0)
Mean IOP in mmHg	12.9 $\pm$ 2.7
Mean macular thickness in microns (range)	463.2 $\pm$ 141.4 (250-818)

VA = visual acuity; logMAR = logarithm of Minimum Angle of Resolution; IOP = intraocular pressure; mmHg = millimeters of mercury

Irvine-Gass syndrome, and macular telangiectasia gained VA better than 20/50. In 11 eyes (28.9%), macular edema was completely resolved but the visual acuity was still less than 20/40. Seven out of ten patients were in the RVO group, three were in the DME group, and one was a patient with Irvine-Gass syndrome.

The mean VA improved by two or more lines from month one to three, which slightly declined after three months (Fig. 2). The lower logMAR value in Fig. 2 implied the better vision. The difference between the baseline VA and the VA seen after six months was not statistically significant ($p = 0.08$). The refractory response in vision improvement, despite the resolving in OCT findings, occurred in those patients with thick macular exudation.

The mean IOP is shown in Fig. 3. Twelve eyes (31.6%) had an increased IOP during the follow-up at various times; most of which occurred between one and three months. All of these patients were successfully treated by 0.5% timolol maleate eye drop. No endophthalmitis, vitreous hemorrhage, or retinal detachment was reported.

Five patients eventually needed more than one injection of TA and another five patients turned to bevacizumab injections but the data after the second injection was not counted in the present study results. Cataract surgery was performed in three eyes during the follow-up period to achieve the highest visual gain. The operations in these cases were carried out after the fifth month visit of all patients.

Discussion

Persistent macular edema, particularly if bilateral, is associated with reduced visual acuity and limited daily activities of the patients. Laser photocoagulation can accelerate a resolution of the edema but a good response does not occur in all cases. The benefit of intravitreal TA has been addressed in papers concerned with the treatment of unresponsive macular edema to the conventional macular grid photocoagulation[3,5,6], however, the exact mechanism remains unclear. There has been a major hypothesis for the mechanism of intravitreal corticosteroid action in inhibiting leukocyte recruitment, thereby, reducing the retinal capillary permeability from blood-retinal barrier (BRB) breakdown

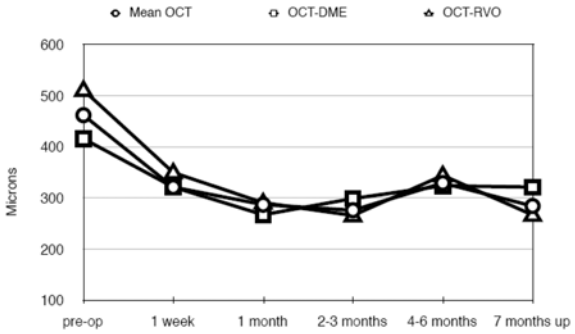

Fig. 1 Central macular thickness (microns) after intravitreal injection of triamcinolone acetonide

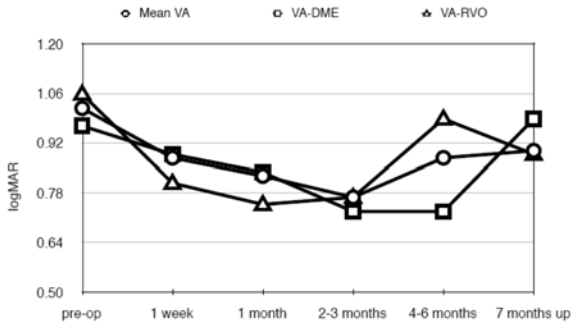

Fig. 2 Visual acuity in logarithm of minimum angle of resolution (logMAR) after intravitreal injection of triamcinolone acetonide

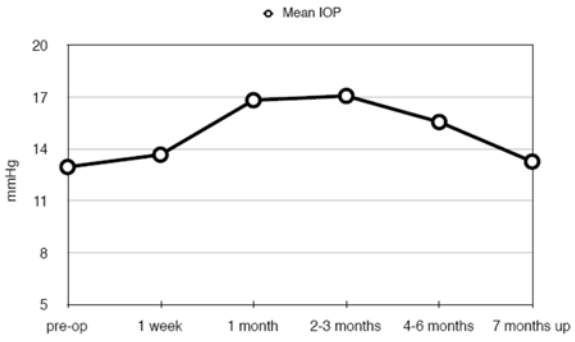

Fig. 3 Intraocular pressure (mmHg) after intravitreal triamcinolone acetonide injection

and inhibiting the metabolic pathway of vascular endothelial growth factor (VEGF)[7].

From the present study, an intravitreal TA injection for macular edema that is caused by conditions other than AMD provides significant benefits with the onset of a response in macular thickness and VA improvement at one week and one month, respectively. This implies that VA or a functional response after the treatment of the edematous retina improves at a slower rate than does the anatomical response.

Response pattern of VA

The present study shows three lines of maximum visual improvement in three months, which is similar (two or more lines) to other clinical studies[8,9,10]. The vision starts to decline after three months and patients with diabetic macular edema tend to get longer favorable outcomes than those who have retinal vein occlusion. The insignificant difference between the baseline VA and the VA seen after six months can be explained from a rebound phenomenon of macular edema after a cessation of TA effect.

Response pattern of OCT finding

The OCT findings, in all patients, showed a rapid decrease in the central macular thickness within the first week following a TA injection but the values in most of the cases were still over 200 microns and a rebound effect occurred, especially if the re-injection was not timed correctly. Even though the macular edema in 11 of 38 eyes (seven in RVO group, three in DME group, one was Irvine-Gass syndrome) was finally resolved, the visual acuity was still less than 20/40. The negative impact on a compromised final vision, despite a normal OCT finding, was notably from an extensive macular exudation in DME patients and possibly from an ischemic process in other patients. Therefore, the normal OCT values ($\leq$ 200 microns) at the final follow-up may not guarantee good final visual acuity.

Although the median follow-up time was seven months, the treatment appears to have a rapid onset and short duration of pharmacologic effect. Re-injection of TA may be considered after three months following the first injection. The explanation for this temporary result could be that TA can reduce the vascular permeability, but does not eliminate the cause of the disease.

Using results from previous studies, intravitreal TA has been shown to be safe[11-13]. The only encountered significant adverse event was the elevation of IOP ($\geq$ 22 mmHg) in 31.6% of the patients but this appeared manageable. Another report described IOP increases to $\geq$ 24 mmHg in 40.4% of the patients[14].

A few patients consequently need cataract extractions after their five-month follow-up.

Given its retrospective nature, the present study does have several limitations including incomplete follow-up and lack of some OCT results for some patients. Most of the patients lacked fundus fluorescein angiographic findings because a diagnosis of macular edema is commonly made by a clinical fundal appearance. Although the indication of a fundus fluorescein angiography (FFA) in CSME, CRVO, and BRVO is to exclude the macular ischemia before performing a macular grid photocoagulation in suspicious cases, this indication is not generally used for an intravitreal TA injection.

Other studies have reported 4-week results as their first visit but the present study reveals the data as early as one week after the injection; giving a clearer treatment response pattern after the intravitreal TA injection. A prospective large-scale study is really needed to acquire more details of a subgroup analysis.

In conclusion, intravitreal triamcinolone has the potential to improve both functional and anatomical outcomes in non-AMD macular edema. The visual function improves slower than the decrease in macular thickness. The results also show a short-time effect. The IOP was significantly elevated but appeared manageable. A prospective large-scale study is really needed to acquire more details of subgroup analysis.

References

1. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985; 103: 1796-806.
2. The Central Vein Occlusion Study Group M. Report. Evaluation of grid pattern photocoagulation for macular edema in central vein occlusion. Ophthalmology 1995; 102: 1425-33.
3. Avitabile T, Longo A, Reibaldi A. Intravitreal triamcinolone compared with macular laser grid photocoagulation for the treatment of cystoid macular edema. Am J Ophthalmol 2005; 140: 695-702.
4. Khairallah M, Zeghidi H, Ladjimi A, Yahia SB, Attia S, Zaouali S, et al. Primary intravitreal triamcinolone acetonide for diabetic massive macular hard exudates. Retina 2005; 25: 835-9.
5. Cekic O, Chang S, Tseng JJ, Barile GR, Weissman H, Del Priore LV, et al. Intravitreal triamcinolone treatment for macular edema associated with central retinal vein occlusion and hemiretinal vein occlusion. Retina 2005; 25: 846-50.
6. Er H, Yilmaz H. Intravitreal cortisone injection for refractory diffuse diabetic macular edema. Ophthalmologica 2005; 219: 394-400.
7. Tamura H, Miyamoto K, Kiryu J, Miyahara S, Katsuta H, Hirose F, et al. Intravitreal injection of corticosteroid attenuates leukostasis and vascular leakage in experimental diabetic retina. Invest Ophthalmol Vis Sci 2005; 46: 1440-4.
8. Martidis A, Duker JS, Greenberg PB, Rogers AH, Puliafito CA, Reichel E, et al. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology 2002; 109: 920-7.
9. Goff MJ, Jumper JM, Yang SS, Fu AD, Johnson RN, McDonald HR, et al. Intravitreal triamcinolone acetonide treatment of macular edema associated with central retinal vein occlusion. Retina 2006; 26: 896-901.
10. Audren F, Erginay A, Haouchine B, Benosman R, Conrath J, Bergmann JF, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular oedema: 6-month results of a prospective controlled trial. Acta Ophthalmol Scand 2006; 84: 624-30.
11. McCuen BW, Bessler M, Tano Y, Chandler D, Machemer R. The lack of toxicity of intravitreally administered triamcinolone acetonide. Am J Ophthalmol 1981; 91: 785-8.
12. Hida T, Chandler D, Arena JE, Machemer R. Experimental and clinical observations of the intraocular toxicity of commercial corticosteroid preparations. Am J Ophthalmol 1986; 101: 190-5.
13. Young S, Larkin G, Branley M, Lightman S. Safety and efficacy of intravitreal triamcinolone for cystoid macular oedema in uveitis. Clin Experiment Ophthalmol 2001; 29: 2-6.
14. Smithen LM, Ober MD, Maranan L, Spaide RF. Intravitreal triamcinolone acetonide and intraocular pressure. Am J Ophthalmol 2004; 138: 740-3.

ผลการรักษาภาวะจอตาบวมที่ไม่ได้เกิดจากจอตาเสื่อมในผู้สูงอายุ โดยการฉีด triamcinolone เข้าในน้ำวุ้นตา

ปฐมา ภูรยานนทชัย, แมนสิงห์ รัตนสุคนธ์, อารินดา มะอาลี

วัตถุประสงค์: เพื่อศึกษารูปแบบของการตอบสนองต่อการรักษาภาวะจอตาบวมจากสาเหตุต่าง ๆ เช่น จากภาวะเบาหวาน ขึ้นตา หลอดเลือดดำในจอตาอุดตัน และจากสาเหตุอื่น ๆ ด้วยการฉีด triamcinolone เข้าในน้ำวุ้นตา โดยประเมินทั้งด้านกายภาพ และระดับสายตา

วัสดุและวิธีการ: เก็บข้อมูลจากเวชระเบียนผู้ป่วยนอกที่ได้รับการรักษาจอตาบวมจากสาเหตุต่าง ๆ ที่ไม่ใช่จอตาเสื่อมในผู้สูงอายุ ด้วยการฉีด triamcinolone เข้าในน้ำวุ้นตา ตั้งแต่เดือนมกราคม พ.ศ. 2547 ถึงเดือนกรกฎาคม พ.ศ. 2549 นำมาวิเคราะห์ผลการรักษาโดยประเมินการตอบสนองจากการยุบบวมของจอตา และการเพิ่มขึ้นของระดับสายตา เป็นผลการศึกษาหลัก และบันทึกภาวะแทรกซ้อนจากการรักษาเป็นผลการศึกษารอง

ผลการศึกษา: รวบรวมผู้ป่วยได้ทั้งหมด 38 ตา จากผู้ป่วย 36 คน ก่อนการรักษาผู้ป่วยมีระดับสายตาเฉลี่ย 1 logMAR (VA = 20/200) ความหนาของจอตาเฉลี่ย 463.2 $\pm$ 141.4 ไมครอน และค่าความดันลูกตาเฉลี่ย 12.9 $\pm$ 2.7 มิลลิเมตรปรอท หลังจากฉีด triamcinolone เข้าในน้ำวุ้นตาพบว่าจอตายุบบวมลงอย่างมีนัยสำคัญภายใน 1 สัปดาห์ และลดลงจนถึงจุดต่ำสุด ที่ 2 เดือนหลังฉีด หลังจากนั้นจะค่อย ๆ บวมกลับขึ้นมาใหม่ ส่วนในด้านของระดับสายตานั้น พบว่ามีการตอบสนองที่ช้ากว่า คือ เริ่มดีขึ้นอย่างมีนัยสำคัญที่ 1 เดือน แต่อย่างไรก็ตาม เมื่อจอตาบวมกลับมาใหม่ ระดับสายตาก็จะแย่ลงช้าๆ อีกเมื่อพ้น 3 เดือนไปแล้ว ผลข้างเคียงที่พบได้คือ ภาวะความดันลูกตาสูง (ร้อยละ 31.6) ซึ่งมักเกิดใน 2 เดือนแรก แต่สามารถควบคุมได้ ด้วยการหยอดยา ไม่พบภาวะข้างเคียงที่รุนแรงอื่นใด

สรุป: การรักษาภาวะจอตาบวมด้วยการฉีด triamcinolone เข้าในน้ำวุ้นตา สามารถช่วยให้จอตายุบบวมและระดับสายตาดีขึ้นได้อย่างมีนัยสำคัญ แต่ผลการรักษาคงอยู่เพียงชั่วคราว ผลข้างเคียงที่พบไม่รุนแรงและสามารถรักษาได้