

Intravitreal Injection Versus Sub-Tenon's Infusion of Triamcinolone Acetonide for Refractory Diabetic Macular Edema: A Randomized Clinical Trial

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PURPOSE. To compare the effectiveness of posterior sub-Tenon's infusion (STi) and intravitreal injection (IVI) of triamcinolone acetonide (TA) for treatment of refractory diffuse diabetic macular edema.

METHODS. Thirty-six phakic diabetic patients with refractory diffuse diabetic macular edema were prospectively enrolled. Patients randomly received either 40 mg STi or 4 mg IVI of TA. Comprehensive ophthalmic evaluation was performed at baseline and 1, 2, 4, 8 $\pm$ 1, 12 $\pm$ 2 and 24 $\pm$ 2 weeks after treatment. Macular morphologic changes detected by optical coherence tomography and visual acuity, intraocular pressure, and lens status were evaluated.

RESULTS. Twenty-eight patients (28 eyes) completed the 24-week study. Central macular thickness was significantly reduced in the IVI group when compared with the STi group at 2, 4, 8, 12, and 24 weeks after treatment ($P < 0.01$). Mean visual acuities (in logarithm of the minimum angle of resolution [logMAR]) at week-4, -8, and -12 follow-up examinations were significantly higher in the IVI group (0.74, 0.75, and 0.82, respectively) when compared with the STi group (0.88, 0.88, and 0.90, respectively; $P < 0.01$). A significant change from baseline in mean intraocular pressure (mm Hg) was seen at weeks 4 (± 3.21) and 8 (± 3.35) in STi the group ($P < 0.01$), and at week 8 (± 2.78) in the IVI group ($P < 0.05$). No patient had cataract progression during the study.

CONCLUSIONS. Although the number of patients and length of follow-up in this preliminary study were limited, the changes in central macular thickness and visual acuity observed after treatment suggest that IVI TA may be more effective than STi for the management of refractory diffuse diabetic macular edema. Further studies are needed to confirm these preliminary findings. (*Invest Ophthalmol Vis Sci.* 2005;46:3845-3849) DOI: 10.1167/iovs.05-0297

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Macular edema is the main cause of visual impairment in diabetic patients.¹ Based on observations of the Early Treatment Diabetic Retinopathy Study (ETDRS) Group, diabetic macular edema (DME) has been classified as clinically significant if well-defined, specific clinical features² are associated with retinal thickening at or within 1 disc diameter of the center of the macula or with definitive hard exudates in this region. For such a subgroup of patients, a clear benefit of focal laser photocoagulation has been demonstrated.² However, the uncommonness of clinically significant visual acuity recovery as well as recrudescence or persistence of DME after appropriate laser treatment, particularly in eyes presenting angiographically diffuse macular edema,^{2,3} has led investigators to seek alternative treatments for the management of DME.

Among alternative treatments currently under investigation for DME, the administration of triamcinolone acetonide (TA), either by intravitreal injection (IVI)⁴⁻¹¹ or by sub-Tenon's infusion (STi),^{12,13} has demonstrated somewhat promising results for the management of diffuse DME, whether refractory or primary. Although both routes of TA administration have already been reported for the management of refractory DME, as far as we are aware, there have been no studies comparing them in a clinical scenario. Therefore, we conducted a randomized, prospective study to compare the efficacy and safety of STi and IVI of TA for refractory, diffuse DME.

METHODS

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local institutional review board, and all participants gave written, informed consent before entering in the study. All patients evaluated at the Retina Section of the Department of Ophthalmology, School of Medicine of Ribeirão Preto, with a diagnosis of refractory diffuse DME in at least one eye between February and July 2004 were invited to participate in the study. Throughout the study, measurement of best corrected visual acuity (BCVA) was performed by a single certified examiner (JAC) before any other study procedure. Ophthalmic evaluation was performed by the same retinal specialist (RJ) and stereoscopic fundus photography, fluorescein angiography, and third-generation optical coherence tomography (OCT) were performed by the same experienced certified ophthalmic technician (DC). Examiners (JAC, DC) were kept masked throughout the study period. Study data were collected and interpreted by RAC and processed by JCB, who were also unaware of the patients' study treatment procedure assignment.

Patient Eligibility and Baseline Evaluation

Patients were included if they had (1) refractory diffuse DME (defined herein as clinically significant DME [by biomicroscopic evaluation]² were unresponsive to focal laser photocoagulation [performed at least 3 months before evaluation], and had generalized breakdown of the inner blood-retina barrier with diffuse fluorescein leakage involving the foveal center and most of the macular area on fluorescein angiog-

raphy); (2) Snellen logarithm of the minimum angle of resolution (logMAR) BCVA equivalent of 20/40 or worse; and (3) central macular thickness (CMT) greater than 300 μm on optical coherence tomography (OCT). Exclusion criteria were (1) aphakic or pseudophakic eyes, (2) glycosylated hemoglobin ($\text{HbA}_{1\text{C}}$) rate above 10%, (3) history of glaucoma or ocular hypertension, (4) loss of vision as a result of other causes, (5) systemic corticoid therapy, (6) severe systemic disease, or (7) any condition affecting follow-up or documentation.

During the inclusion period of the study, refractory diffuse DME was identified in at least one eye of 47 patients based on clinical and angiographic evaluation. Thirty-six of the 47 patients were included in the study. Each patient received a detailed ophthalmologic examination, including measurement of BCVA according to a standardized refraction protocol using a retroilluminated Lighthouse for the Blind (New York, NY) distance visual acuity test chart (using modified ETDRS charts 1, 2, and R), as well as applanation tonometry, undilated and dilated slit lamp biomicroscopic examination (including lenticular status using the Lens Opacity Classification System III¹⁴), and indirect fundus examination. Stereoscopic digital color fundus photography and fluorescein angiography were performed with an ultraresolution (3072 $\times$ 2048) fundus camera system (UVi-60/EyeQ Pro; Canon, Tokyo, Japan). Third-generation OCT evaluation (Stratus Tomographer, model 3000; Carl Zeiss Ophthalmic Systems Inc., Humphrey Division, Dublin, CA) was also performed in all patients and consisted of six linear 6.00-mm scans oriented at intervals of 30° and centered on the foveal region. To minimize bias generated by OCT data, we verified the automatic delineation of the inner and outer boundaries of the neurosensory retina generated by the OCT built-in software for each of the six scans using the retinal thickness (single eye) analyses protocol, and new acquisitions were repeated if necessary.¹⁵ In addition, all OCT evaluations were performed in the afternoon (between 1 and 6 PM).^{16,17} For this study, CMT measurements (defined as the average thickness of a central macular region 1000 μm in diameter centered on the patient's foveola) automatically generated by built-in OCT3 software in the retinal thickness (both eyes) analysis protocol were used. Good reproducibility of these measurements using this method and its feasibility for monitoring morphologic changes in diabetic eyes have been described elsewhere.^{8,18,19}

If both eyes were eligible for treatment, the eye with the worse visual acuity was included. For patients who agreed to participate in the study, the initial evaluation was used as the baseline.

Treatment Assignment

Each patient was randomly allocated to receive either an STi or an IVI of TA within 72 hours of baseline. Randomization was performed in the operating room just before injection. The patients were treated in groups of two. As the first patient was prepared for treatment, the anesthesiologist was asked to pick up one of two identical opaque envelopes, one containing the designation for *sub-Tenon's*, whereas the other contained the designation for *intravitreal* administration of TA. The second patient was automatically assigned with the second envelope.

For both STi-TA and IVI-TA, a vial of 1 mL containing 40 mg of preservative-free TA (Triamcinolone 40 mg/mL; Ophthalmo, São Paulo, Brazil) was used. All treatments were performed by the same retinal specialist (MBF) using topical anesthesia under appropriate sterile conditions, and 0.3% ciprofloxacin was instilled four times daily for 1 week after the procedure. For STi-TA, 1 mL (40 mg) of the suspension was delivered posteriorly through a small (1.0–1.5 mm) conjunctival and Tenon's incision that was made in the superotemporal quadrant midway between the superior and lateral rectus muscles, 8 mm posterior to the limbus, through a curved blunt cannula similar to that used by The Anecortave Acetate Clinical Study Group.²⁰ For IVI-TA, 0.1 mL (4 mg) of the suspension was injected in the vitreous cavity with a 29.5-gauge needle inserted in the inferotemporal quadrant 3.5 mm posterior to the limbus.

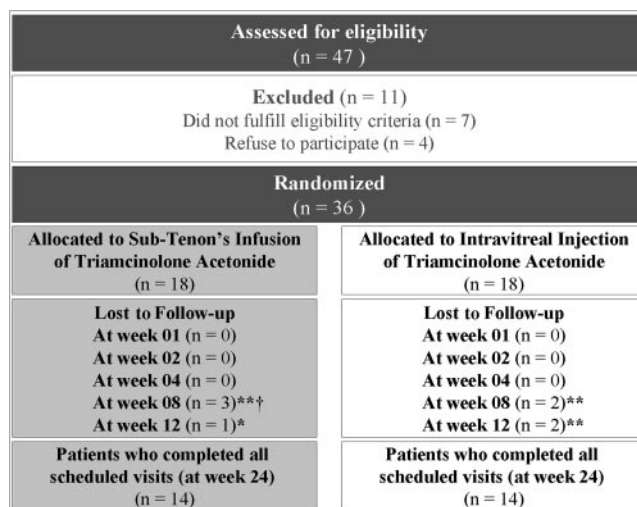


FIGURE 1. Flow of patients through the study (*withdrew; †died of a stroke).

Follow-up Examinations and Outcome Measures

Patients were scheduled for follow-up examinations at weeks 1, 2, 4, 8 $\pm$ 1, 12 $\pm$ 2, and 24 $\pm$ 2 after treatment. At these visits, patients' BCVA was determined, and they underwent a complete ophthalmic examination and OCT evaluation using the same procedures as at baseline. In addition, stereoscopic color fundus photography and fluorescein angiography were performed at the week-24 (final) visit.

The primary outcome measure was the macular morphologic changes induced by treatment as monitored by OCT, by measuring CMT. Secondary outcome measures were changes in BCVA (logMAR ETDRS values), intraocular pressure, and cataract progression.

Statistical Analysis

To study the effect of both routes of TA administration at different periods of the study, an analysis of variance was used, with a split-plot design, considering the group factor as the main effect (group STi and group IVI), and the seven periods (including baseline) as the subplot factor. The Tukey test was used for multiple comparisons at 5% level of significance ($P < 0.05$).

RESULTS

Between February 2004 and January 2005, 28 patients completed the 24-week study period (Fig. 1). Twenty of the eyes ($n = 9$, STi group; $n = 11$, IVI group) of these patients had proliferative diabetic retinopathy that had been treated by panretinal photocoagulation at least 6 months before the treatment procedure of the study. Baseline characteristics by group are summarized in Table 1. Eight patients had bilateral refractory diffuse DME and the eligible eye with worse visual acuity was included in the study.

Outcome Measures

The analysis of variance showed significant interaction between groups and periods considering retinal thickness measurements ($F = 17.37$; $P < 0.01$). Figure 2 shows a significant reduction ($P < 0.01$) in CMT in the IVI group at 2, 4, 8, 12, and 24 weeks after treatment when compared with the STi group. Separate within-group analysis showed significant reduction in CMT in the IVI group 2, 4, 8, 12, and 24 weeks after injection when compared with baseline. In the STi group, changes in

TABLE 1. Baseline Characteristics

Variable	Group	
	STi	IVI
Age (y)		
Mean	61.48	62.72
± 1 SD	15.19	13.99
Gender (n, %)		
Male	6 (42.9)	7 (50)
Female	8 (57.1)	7 (50)
Systolic blood pressure (mm Hg)		
Mean	135.1	130.5
± 1 SD	12.76	11.58
Diastolic blood pressure (mm Hg)		
Mean	79.7	75.9
± 1 SD	9.2	9.8
Duration of diabetes (y)		
Mean	14.8	15.2
± 1 SD	9.31	9.76
Treatment regimen for diabetes (n, %)		
No insulin	4	3
Insulin	10	11
HbA1c (%)		
Mean	8.68	8.96
± 1 SD	0.83	0.82
Status of DR (n, %)		
Moderate NPDR	1 (7.1)	—
Severe NPDR	4 (28.6)	3 (21.4)
DR inactivated by PRP	9 (64.3)	11 (78.6)
Duration of macular edema (mo)		
Mean	11	14
± 1 SD	5.82	6.55
Grid sessions (n)		
Mean	1.57	1.86
± 1 SD	0.75	0.95

DR, diabetic retinopathy; HbA1c, glycosylated hemoglobin; NPDR, nonproliferative diabetic retinopathy; PRP, panretinal photocoagulation.

CMT from baseline were not significant at any time point (Fig. 2; Table 2).

Significant interaction between groups and periods, using the same analysis of variance, was also verified for logMAR BCVA ($F = 11.30$; $P < 0.01$). Figure 3 shows significant improvement in visual acuity in the IVI group 4, 8, and 12 weeks after treatment, when compared with the STi group. Separate within-group analysis showed significant improvement in logMAR BCVA from baseline in IVI group 4, 8, and 12 weeks after treatment. There was no significant change in BCVA from baseline in the STi group (Table 2).

No interaction between groups and periods was observed for intraocular pressure (IOP) values using two-way analysis of variance ($F = 0.56$; $P > 0.05$). There was no difference in IOP between the two groups at the different time points during the study period (Fig. 4; Table 2). However, separate within-group analysis revealed a significant increase in IOP from baseline 4 and 8 weeks after infusion in the STi group ($P < 0.01$) and 8 weeks after injection in IVI group ($P < 0.05$). During the 24-week period of the study, no cataract progression was observed in patients subjected to either STi or IVI of TA.

DISCUSSION

In our study, IVI TA was more effective in reducing abnormally thickened macular retina than was STi of the steroid, in the short term. Comparatively, significant improvement in macular remodeling began at 2 weeks after treatment and persisted

until 24 weeks after the intravitreal procedure. In the absence of any additional study comparing both routes of TA administration for DME, within-group analysis was used in the sequence for CMT and visual acuity comparisons with previous reports. Induced morphologic macular changes observed in the IVI group are in agreement with those previously reported by Martidis et al.,⁵ who reported 55%, 58%, and 38% reductions in macular thickness by 1, 3, and 6 months of follow-up, respectively, as well as by Massin et al.,⁸ who also demonstrated short-term significant reduction in CMT, both after 4 mg intravitreal TA injection for refractory diffuse DME. In the latter, however, macular edema recurred, and retinal thickness reduction was no longer significant 24 weeks after injection.⁸ Our study still showed significant reduction in CMT at week 24, and a clear trend of CMT toward the baseline measurements was seen (Fig. 2). Using STi, we retrieved only one study commenting on OCT data in TA-treated DME. Ohguro et al.¹³ reported reduced retinal thickness in three eyes after trans-Tenon's infusion of 12 mg of TA. However, this was an uncontrolled study including vitrectomized eyes, in which the vitreous pharmacokinetics of the steroid may be different from nonsurgical eyes.

Beneficial effects of intravitreal injection of TA compared with STi with respect to change in visual acuity were noted starting with the week-4 examination and persisted up to the week-12 examination. In the IVI group, visual acuity improvement from baseline was noted for the same study periods. Similarly, Martidis et al.⁵ have demonstrated a functional visual response at 1 and 3 months with a mean improvement of 2.4 Snellen lines. A highly significant short-term visual acuity improvement in DME eyes has also been demonstrated by Sutter et al.,⁹ whereas Massin et al.⁸ have reported only a trend toward improvement in visual acuity 3 months after intravitreal injection. About STi for refractory diffuse DME, Bakri and Kaiser²¹ have recently demonstrated significant improvement in visual acuity 1 month after STi of TA during a 12-month study. In our study, we could find no significant changes in visual acuity from baseline in patients subjected to STi of TA.

About the reasons for the different outcomes observed in our study, it should be noted that some reflux of TA (judged as *mild* [defined as TA reflux after infusion of at least 0.8 mL of the suspension] by the treating investigator), even if lessened by the technique used herein, occurred in three eyes submitted to STi. This fact may have contributed in part to a diminished effect observed in TA STi group. Although we used a

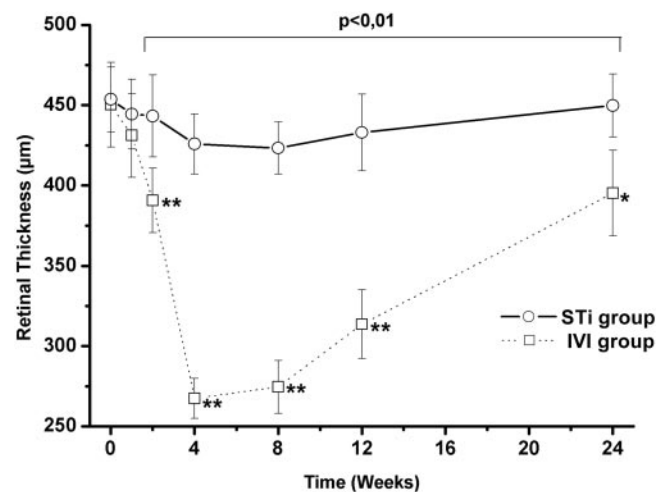


FIGURE 2. CMT after IVI and STi of TA by visit. Within-group significant changes from baseline, * $P < 0.05$; ** $P < 0.01$.

TABLE 2. Mean Visual Acuity, CMT, and IOP, by Study Visit

Study Period	Group STi-TA			Group IVI-TA		
	VA (logMAR $\pm$ SEM)	CMT (μ m $\pm$ SEM)	IOP (mm Hg $\pm$ SEM)	VA (logMAR $\pm$ SEM)	CMT (μ m $\pm$ SEM)	IOP (mm Hg $\pm$ SEM)
Baseline	0.9157 $\pm$ 0.0320	453.64 $\pm$ 20.26	14.57 $\pm$ 0.54	0.9371 $\pm$ 0.0427	450.36 $\pm$ 26.28	15.50 $\pm$ 0.63
1 week	0.9100 $\pm$ 0.0320	444.43 $\pm$ 21.73	15.42 $\pm$ 0.31	0.9300 $\pm$ 0.0347	431.21 $\pm$ 26.08	15.42 $\pm$ 0.54
2 weeks	0.9171 $\pm$ 0.0320	443.36 $\pm$ 25.43	15.50 $\pm$ 0.63	0.9014 $\pm$ 0.0347	390.79 $\pm$ 20.14	15.85 $\pm$ 0.43
4 weeks	0.8871 $\pm$ 0.0293	425.86 $\pm$ 18.74	17.78 $\pm$ 0.56	0.7400 $\pm$ 0.0293	267.43 $\pm$ 12.50	17.71 $\pm$ 0.39
8 weeks	0.8828 $\pm$ 0.0374	423.36 $\pm$ 16.26	17.92 $\pm$ 0.42	0.7514 $\pm$ 0.0240	274.50 $\pm$ 16.55	18.28 $\pm$ 0.98
12 weeks	0.9000 $\pm$ 0.0320	433.07 $\pm$ 23.87	16.35 $\pm$ 0.55	0.8286 $\pm$ 0.0240	313.64 $\pm$ 21.36	16.85 $\pm$ 0.43
24 weeks	0.9343 $\pm$ 0.0320	449.86 $\pm$ 19.70	15.71 $\pm$ 0.33	0.9186 $\pm$ 0.0240	395.29 $\pm$ 26.72	14.85 $\pm$ 0.65

CMT, central macular thickness; VA, visual acuity.

special designed cannula for STi, inadequate positioning of the drug next to the macular area may also be considered. Regarding retinal bioavailability of the drug, the use of the intravitreal route allows rapid delivery of TA to desired targeted tissue. In contrast, in STi, the drug has to cross the sclera and choroid, and inadequate penetration may contribute to the lower effectiveness of TA in reducing retinal thickness and in improving visual acuity in such scenario.²² In fact, Inoue et al.²³ have recently showed that intravitreal injection of TA leads to much higher vitreous concentrations of the steroid ($1.29 \pm 0.41 \mu\text{g/mL}$) than STi ($<0.001 \mu\text{g/mL}$).

Previous laser therapy for DME probably differed between patients and may have contributed to the different outcome observed. Focal treatment with laser photocoagulation has become the standard treatment for DME, contributing to maintenance of good long-term visual acuity for most treated patients as demonstrated by Chew et al.²⁴ However, in spite of multiple photocoagulation attempts, some eyes remain refractory to treatment,² which may lead to permanent retinal damage and loss of visual acuity secondary to sequelae of chronic macular edema. Therefore, during study design conception, we prefer to include in this first comparative trial patients with refractory DME.

In diabetic patients, glycemic control, and blood pressure may affect macular thickness.²⁵ Therefore, we included in our study only diabetic patients with satisfactory glycemic and blood pressure control. Additional bias could be derived from temporal variation in DME as described by Sternberg et al.¹⁶ as well as Frank et al.¹⁷ To minimize this natural effect, OCT

evaluations were performed between 1 and 6 PM during baseline and follow-up visits.

The adverse effect observed in our study was the significant IOP increase from baseline observed 8 weeks after the procedure in both groups. In the STi group, IOP was also significantly higher at 4 weeks after infusion, when compared with baseline. This elevation is a known adverse event of corticosteroids administered topically or systemically in about one third of the general population.²⁶ In our study, at the week-24 follow-up visit, no patient needed antiglaucomatous therapy to maintain IOP within normal range nor did we observe cataract progression. However, the incidence of cataract progression and glaucoma may well increase with longer follow-up and additional TA treatments. No other injection- or infusion-related complications were observed, such as conjunctival ulceration, extraocular muscle palsy, retinal detachment, infectious or noninfectious endophthalmitis.^{27–29}

In conclusion, a single intravitreal injection of 4 mg of TA appears to be more effective for short-term management of refractory diffuse DME than does a single 40-mg STi infusion. However, we must bear in mind that our results should be analyzed with caution because of the small sample size and limited length of follow-up, as well as the large proportion that was lost to follow-up. Rather the findings should be used to bring to light the need for further studies to verify our preliminary findings. Moreover, the potential benefits of TA, whether by IVI or STi, if any, over additional laser therapy for the

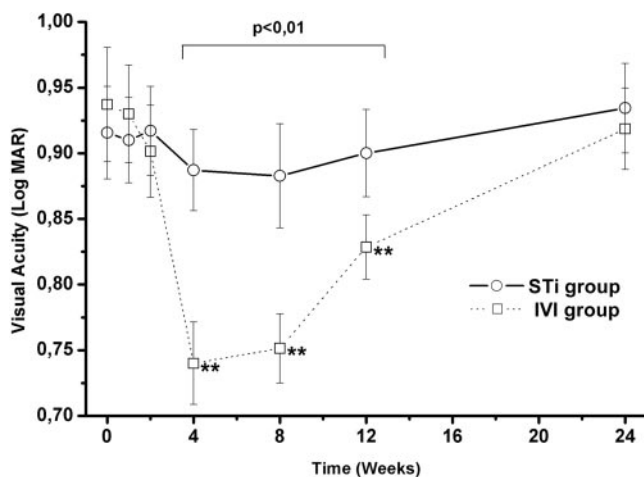


FIGURE 3. BCVA after IVI and STi of TA by visit. Within-group significant changes from baseline, * $P < 0.05$; ** $P < 0.01$.

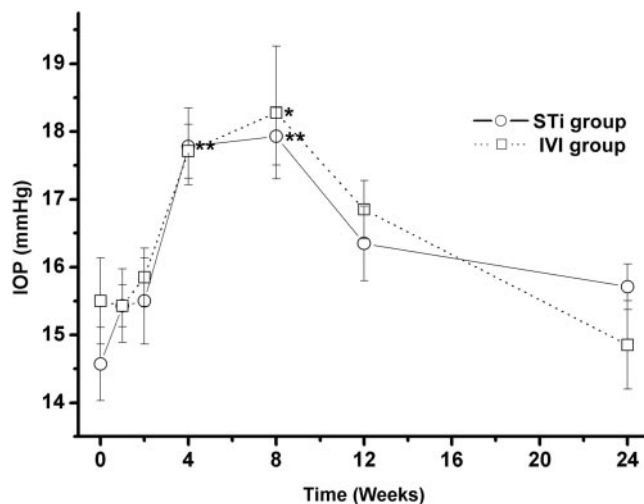


FIGURE 4. Intraocular pressure after IVI and STi of TA by visit. Within-group significant changes from baseline, * $P < 0.05$; ** $P < 0.01$.

management of refractory diffuse DME remains to be determined, particularly in the long term.

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