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

Marco A. Bonini-Filho,1 Rodrigo Jorge,1 José C. Barbosa,2 Daniela Calucci,3 Jose A. Cardillo,5 and Rogério A. Costa1,5

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.

RESULTS. Twenty-eight patients (28 eyes) completed the 24-week study. Central macular thickness was significantly reduced in the IVI group compared with the STi group at 2, 4, 8, 12, and 24 weeks after treatment (P < 0.01).

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.

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.

Patient Eligibility and Baseline Evaluation

Patients were included if they had (1) refractory diffuse DME (defined herein as clinically significant DME [by biomicroscopic evaluation]) and lens status were evaluated.

Visual outcomes at baseline in mean intraocular pressure (mm Hg) was seen at 1, 2, 4, 8 ± 1, 12 ± 2 and 24 ± 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 compared with the STi group at 2, 4, 8, 12, and 24 weeks after treatment (P < 0.01).

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.

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Ophthalmic evaluation was performed by the same retinal specialist (JAC, DC) were kept masked throughout the study period. 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.

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rathy); (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 (HbA1C) 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 vision chart 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 an applanation tonometry, undilated and dilated slit lamp biomicroscopic examination (including lenticular status using the Lens Opacity Classification System III), and indirect fundus examination. Stereoscopic digital color fundus photography and fluorescein angiography were performed with an ultrarolution (3072 × 2048) fundus camera system (UVi-60/EyeQ Pro; Canon, Tokyo, Japan). Third-generation OCT evaluation (Stratus Tomograph, 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. In addition, all OCT evaluations were performed in the afternoon (between 1 and 6 PM). 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 OCT 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.

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 (Triamcinolona 40 mg/mL; Ophthalmos, 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 Ancorettace Clinical Study Group. 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.

### Follow-up Examinations and Outcome Measures

Patients were scheduled for follow-up examinations at weeks 1, 2, 4, 8 ± 1, 12 ± 2, and 24 ± 2 after treatment. At these visits, patients’ BCVA was determined, and they underwent a complete ophthalmologic 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
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., 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., 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. 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. 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. 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., whereas Massin et al. have reported only a trend toward improvement in visual acuity 3 months after intravitreal injection. About STi for refractory diffuse DME, Bakri and Kaiser 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
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. In fact, Inoue et al. have recently showed that intravitreal injection of TA leads to much higher vitreous concentrations of the steroid (1.29 ± 0.41 µg/mL) than STi (<0.001 µg/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. However, in spite of multiple photocoagulation attempts, some eyes remain refractory to treatment, 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. 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. as well as Frank et al. 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. 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.

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

References