INTRAVITREAL INJECTION VERSUS SUBTENON INFUSION OF TRIAMCINOLONE ACETONIDE DURING CATARACT SURGERY IN PATIENTS WITH REFRACTORY DIABETIC MACULAR EDEMA

CLÉCIO TAKATA, MD,* ANDRE MESSIAS, MD, PHD,*
MARCO S. FOLGOSA, MD,* LEVY R. LUCENA, MD,*
DANIEL R. LUCENA, MD, PHD,* INGRID U. SCOTT, MD, MPH,†
RODRIGO JORGE, MD, PHD*

Purpose: The purpose of this study was to compare the effectiveness of intravitreal injection (IVT) versus posterior subtenon infusion (STI) of triamcinolone acetonide performed during phacoemulsification cataract surgery in eyes with refractory diffuse diabetic macular edema.

Methods: Twenty-four eyes of 24 patients with refractory diffuse diabetic macular edema scheduled to undergo phacoemulsification cataract surgery were randomly assigned to receive either a 4-mg IVT (n = 12) or a 40-mg STI (n = 12) of triamcinolone acetonide during cataract surgery. Comprehensive ophthalmic evaluation, including best-corrected visual acuity, intraocular pressure, and central macular thickness measured with optical coherence tomography, was performed at baseline and at 1, 4, 8 ± 1, 12 ± 2, and 24 ± 2 weeks postoperatively.

Results: Ten patients from the IVT group and 9 patients from the STI group completed the 24-week study visit. Mean baseline best-corrected visual acuity (logarithm of the minimum angle of resolution) was 20/259 and 20/222 in the IVT and STI groups, respectively ($t = 0.41$; $P = 0.3407$). A significant improvement in best-corrected visual acuity was observed only in the IVT group at 4 weeks (mean difference ± standard error, improved to 20/116; $P = 0.0437$), 8 weeks (20/110; $P = 0.0355$), and 12 weeks (20/121; $P = 0.0471$) postoperatively. There was no significant change from baseline in mean intraocular pressure in either group. Mean ± standard error baseline central macular thickness was 474.1 ± 42.4 μm and 490.8 ± 70.8 μm in the IVT and STI groups, respectively ($t = 0.21$; $P = 0.5807$). The central macular thickness reductions after surgery at all study follow-up visits were significantly greater in the IVT group than in the STI group ($P < 0.05$).

Conclusion: These data suggest that IVT is more effective than STI of triamcinolone acetonide for the management of refractory diffuse diabetic macular edema in eyes undergoing phacoemulsification. Further investigation of a larger number of patients with longer follow-up is necessary to confirm these findings.

RETINA X:1–1, 2010

Macular edema is a leading cause of decreased visual acuity in patients with diabetic retinopathy.[1,2] Moreover, patients with diabetic retinopathy have a higher risk for macular edema onset or worsening after cataract surgery than patients without diabetic retinopathy.[3–5] This susceptibility is related to

From the *Department of Ophthalmology, Otorhinolaryngology and Head and Neck Surgery, School of Medicine of Ribeirão Preto, USP, Ribeirão Preto, Brazil, and the †Departments of Ophthalmology and Public Health Sciences, Penn State College of Medicine, Hershey, Pennsylvania.

Supported by Fundação de Amparo à Pesquisa do Estado de São Paulo Grant 2006/55080-5.

The authors declare no conflict of interest.

Reprint requests: Rodrigo Jorge, MD, PhD, Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto, Avenida Bandeirantes 3900, Ribeirão Preto, SP 14049-900, Brazil; e-mail: rjorge@fmrp.usp.br

the association between perioperative inflammation and breakdown of the blood–retinal barrier, especially in patients with previous microvascular changes secondary to diabetic retinopathy.[6–8] To decrease the risk of macular edema worsening after cataract surgery, preexisting diabetic macular edema (DME) is generally treated before cataract surgery.[9]

Laser photocoagulation is the standard of care treatment for DME, based on findings of the Early Treatment Diabetic Retinopathy Study (ETDRS) and recent clinical trials.[10,11] However, because visual acuity improvement after laser treatment is observed infrequently, and because of the frequent recurrence or persistence of DME (refractory DME) after laser treatment, particularly in eyes presenting with angiographically diffuse macular edema,[12–16] there is a need for alternative treatments for the management of DME. In addition, for some patients with significant cataract, precise visualization of posterior pole structures may not be possible, so that pharmacological therapy with intravitreal agents may be preferable to laser treatment.

Among pharmacological treatments currently under investigation for DME, intravitreal injection (IVT) of triamcinolone acetonide (TA)[13–19] and of antiangiogenic agents such as bevacizumab,[20–26] pegaptanib,[27] and ranibizumab[28] has been reported to be associated with favorable remodeling of the macular architecture and visual acuity improvement in primary DME.[6–17] However, in cases of refractory DME, antivascular endothelial growth factor agents have been reported to have a very transient and subtle effect on best-corrected visual acuity (BCVA) improvement and central macular thickness (CMT) reduction, especially compared with intravitreal triamcinolone.[20] In view of these results, and considering the inflammatory reaction triggered by cataract surgery, we conducted a randomized, prospective study to compare the morphologic and visual acuity outcomes associated with a single intravitreal versus subtenon infusion (STI) of TA during cataract surgery for the management of 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 into the study. All patients evaluated in the Retina Section of the Department of Ophthalmology, School of Medicine of Ribeirão Preto, with a diagnosis of cataract and refractory DME in at least 1 eye between September 2007 and February 2009 were invited to participate in the study.

Throughout the study, measurements of BCVA with ETDRS and CMT using third-generation optical coherence tomography (OCT) were performed before other study procedures by a masked certified examiner. Ophthalmic evaluation, fundus photography, and fluorescein angiography were performed by two retina specialists (C.T. and M.S.F.) who were aware of treatment assignment. Study data were collected, interpreted, and analyzed by two other masked investigators (R.J. and A.M.).

Patient Eligibility and Baseline Evaluation

A total of 24 patients with refractory diffuse DME and cataract in at least 1 eye based on clinical examination and fluorescein angiography were identified. If both eyes were eligible for treatment, the eye with worse visual acuity was included. Nineteen out of 24 patients were ultimately included in the analyses (2 patients from the IVT group and 3 patients from the STI group missed 2 consecutive study visits and were excluded from analyses).

Inclusion Criteria

1. Refractory DME (defined herein as the presence of "clinically significant macular edema"—as per ETDRS criteria—despite at least 1 session of macular laser photocoagulation performed at least 3 months earlier) and diffuse fluorescein leakage involving the foveal center and most of the macular area on fluorescein angiography
2. Best-corrected visual acuity between 0.3 logarithm of the minimum angle of resolution (logMAR) (20/40) and 1.6 logMAR (20/800)
3. Central subfield macular thickness >300 μm on OCT
4. Presence of cataract with grade 2 or higher nuclear opalescence[29] and sufficient to impede adequate grid laser retreatment

Exclusion Criteria

1. Aphakic or pseudophakic eyes
2. Glycosylated hemoglobin (HbA1C) level $>10\%$
3. History of glaucoma or ocular hypertension [defined as an intraocular pressure (IOP) >22 mmHg]
4. An ocular condition (other than diabetes) that, in the opinion of the investigator, might affect macular edema or alter visual acuity during the course of the study (e.g., retinal vein occlusion, uveitis or other ocular inflammatory disease, neovascular glaucoma)
5. Systemic corticosteroid therapy
6. Uncontrolled hypertension (according to guidelines of the seventh report of the Joint National

Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure)
7. Any condition affecting follow-up or documentation

Each patient received a detailed ophthalmologic examination including measurement of BCVA according to a standardized refraction protocol using a retroilluminated Lighthouse for the Blind distance visual acuity test chart (using modified ETDRS charts 1, 2, and R), applanation tonometry, undilated and dilated slit-lamp biomicroscopic examination, indirect fundus examination, and color fundus photography and fluorescein angiography.

Cataract grading was performed according to the Lens Opacity Classification System III,[29] which consists of slit-lamp evaluation of the lens opacity giving scores, in a decimal scale, for nuclear color, nuclear opalescence, cortical cataract, and posterior subcapsular cataract. For intraocular lens power measurement, keratometry was done with a Topcon autorefractor (KR8800, Topcon, Tokyo, Japan), and axial length was measured using Alcon OcuScan RXP A-Scan Biometry (Alcon, Fort Worth, TX).

Third-generation OCT evaluation (Stratus Tomographer, Model 3000, Carl Zeiss Ophthalmic Systems Inc., Humphrey Division, Dublin, CA) was performed in all patients and consisted of 6 linear 6.00-mm scans orientated at intervals of 30° and centered on the foveal region. To optimize accuracy of OCT data, automatic delineation of the inner and outer boundaries of the neurosensory retina generated by OCT built-in software was verified for each of the six scans using the "retinal thickness (single eye)" analysis protocol.[30] Central macular thickness values were automatically calculated because the average thickness of a central macular region 1,000 μm in diameter centered on the patient's foveola by built-in OCT3 software using the "retinal thickness/volume" analysis protocol. Good reproducibility of these measurements using this method and the feasibility of this method to monitor and detect DME[31] and macular edema after cataract surgery[32] have been described elsewhere.

Treatment Assignment

Each patient was randomly assigned to receive either 1 IVT of 4 mg/0.1 mL of TA or an STI of 40 mg/1 mL of TA at the conclusion of phacoemulsification cataract surgery, which was performed within 1 week of baseline. Patients assigned to intravitreal triamcinolone constituted the IVT group, and those assigned to subtenon triamcinolone infusion constituted the STI group.

For the IVT group, 4 mg of preservative-free TA (Triancinolona 40 mg/mL, Ophthalmos, São Paulo, Brazil) was used, and for the STI group, 1 mL (40 mg) of the same triamcinolone formation was infused into the subtenon space, using a technique described elsewhere.[15] The phacoemulsification procedure included the following steps: 3.0 clear cornea incision, "stop and chop" phacoemulsification technique (Legacy, Alcon), type 7B foldable intraocular lens (Alcon) insertion, and 1 nylon 10.0 stitch to close the clear cornea incision.

All treatments were performed by the same physicians under sterile conditions (L.R.L., phaco surgery; R.J., triamcinolone injections). In addition, 1 drop of ciprofloxacin 0.3% every 3 hours was used postoperatively for 2 weeks.

Follow-Up Examinations and Outcome Measures

Patients were scheduled for follow-up examinations at weeks 1, 4, 8 ($\pm$1), 12 ($\pm$2), and 24 ($\pm$2) after surgery. At these visits, patients' BCVA was determined after ETDRS refraction, and they underwent complete ophthalmic examination using the same procedures as at baseline, with the exception of fluorescein angiography, which was performed only at the final (week 24) follow-up visit.

Primary outcome measures were 1) macular remodeling on OCT (changes in CMT) and 2) changes in ETDRS BCVA from baseline. Secondary outcomes included the presence of changes in IOP and occurrence of complications.

Statistical Analysis

Intraindividual differences from baseline of BCVA (logMAR) and IOP at the four follow-up periods after treatment (e.g., BCVA − BCVA at baseline) were calculated to analyze the effect of treatment on visual acuity during follow-up, whereas a quotient between CMT values at the four periods after treatment and the baseline (CMT/CMT at baseline) was used for macular thickness comparisons. In intragroup comparison, a statistically significant effect was defined as a difference from zero for intraindividual BCVA and IOP mean differences, and in a factor of 1 for intraindividual CMT. Intergroup comparison was done by comparing the intraindividual differences or ratios between groups with a nonpaired *t*-test. Statistical analyses were performed using JMP software, version 7.0.2 (SAS Institute Inc., Cary, NC).

Results

Between September 2007 and February 2009, 19 patients completed the 24-week study period (Figure 1). Seven eyes (n = 3, IVT group; n = 4, STI group)

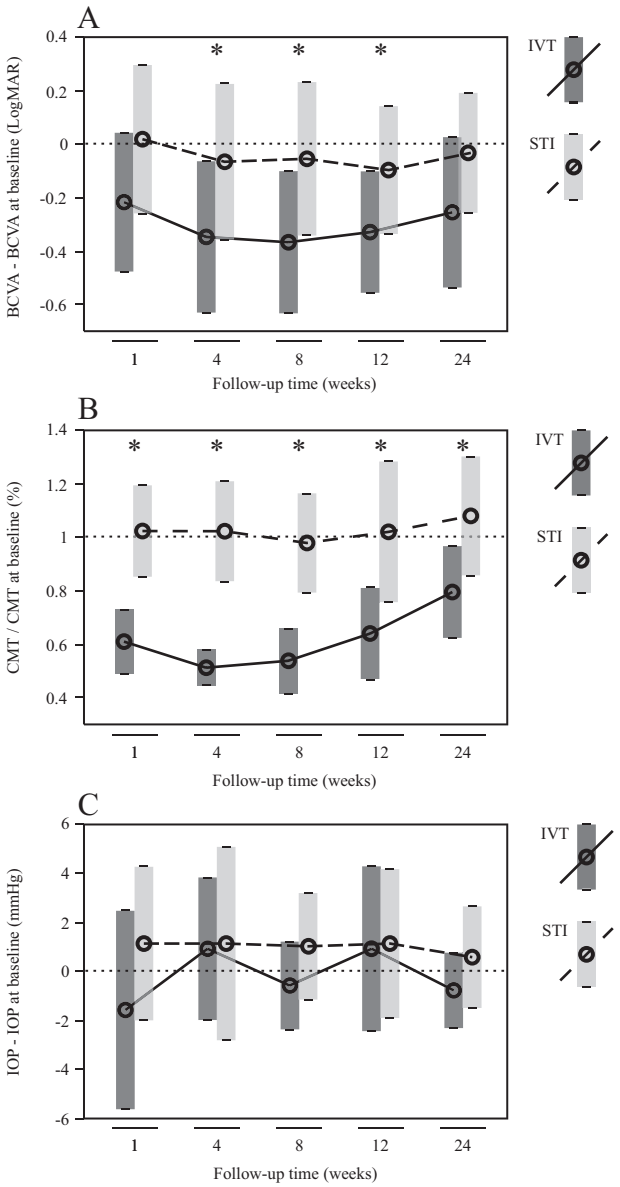

Fig. 1. A. Circles represent means, and error bars represent the 95% confidence limits of the intraindividual differences of BCVA (logMAR). **B.** Intraindividual ratio of CMT (%). **C.** Intraindividual differences of IOP (mmHg) versus follow-up time in weeks. Full lines connect means in the IVT group, and dashed lines connect means in the STI group; asterisks indicate significant difference between groups (*$P < 0.05$).

had proliferative diabetic retinopathy treated by panretinal photocoagulation at least 6 months before initial evaluation. Five patients (2 from the IVT group and 3 from the STI group) missed 2 consecutive visits and were excluded.

Baseline characteristics are summarized in Table 1. There were no significant differences between groups regarding age, sex, severity of diabetic retinopathy, number of previous focal or grid laser sessions, or lens opacity scores (Table 2). The outcome measures are discussed in the following sections.

Central Macular Thickness

Central macular thickness (mean ± standard error) at baseline was 474.1 ± 42.4 μm in the IVT group and 490.8 ± 70.8 μm in the STI group ($t = 0.21$; $P = 0.5807$). In the IVT group, CMT was significantly reduced from baseline at week 1 to week 24 after treatment. The maximal CMT reduction was observed at week 4: 54% ± 17%. In contrast, no significant changes in CMT were observed in the STI group (Table 3; Figure 1). Intergroup comparison of CMT changes showed statistically significant differences between the two groups at all follow-up periods (Table 3; Figure 1).

At baseline, CMT ranged from 306 μm to 667 μm in the IVT group and 262 μm to 871 μm in the STI group. Six of 10 eyes from the IVT group showed CMT ≤250 μm or a reduction to 50% of the baseline at 1 week after treatment (Table 4), whereas this was not observed in any eye from the STI group. Furthermore, 10, 9, 4, and 6 of 10 eyes from IVT showed CMT <250 μm or a reduction to 50% of the baseline at weeks 4, 8, 12, and 24, respectively; this was seen in only 2 eyes from the STI group (Table 4).

Best-Corrected Visual Acuity

Mean ± standard error BCVA at baseline was 1.11 ± 0.10 logMAR (20/200) in the IVT group and 1.04 ± 0.13 (20/200) in the STI group ($t = 0.41$; $P = 0.3407$). Best-corrected visual acuity was significantly better than at baseline at weeks 4, 8, and 12 after treatment in the IVT group. The maximal BCVA improvement was observed at week 8: 0.37 ± 0.11 logMAR (as an example, this would be equivalent to an improvement from 20/150 to 20/63). In contrast, no statistically significant BCVA improvement was observed in the STI group (Table 3; Figure 1). Intergroup comparisons of BCVA changes showed significantly better visual acuity outcomes in the IVT group compared with the STI group at 4 ($P = 0.0437$), 8 ($P = 0.0355$), and 12 ($P = 0.0471$) weeks after treatment (Table 3; Figure 1).

As an example, at the fourth week after treatment, 6 of 10 eyes from the IVT group showed a BCVA improvement to baseline of ≥2 lines, whereas this was seen in 4 of 9 eyes from the STI group. The same picture was observed at the other follow-up periods (Table 4), confirming the tendency of better visual function results in the IVT group, as shown by the BCVA group means comparison.

Table 1. Patient Demographic Data and Baseline Characteristics

	IVT	STI
Age (mean ± SD)	66.7 ± 5.1	60.8 ± 10.4
Sex	6 male/4 female	4 male/5 female
Duration of diabetes (years) (mean ± SD)	18.2 ± 10.9	19.2 ± 3.2
Treatment regimen (n)	4 no-insulin/6 insulin	3 no-insulin/6 insulin
Diabetic retinopathy classification	7 moderate NPDR 3 DR inactivated by PRP	5 moderate NPDR 4 DR inactivated by PRP
Macular edema duration (months) (mean ± SD)	16.6 ± 9.9	18.1 ± 9.3
Number of laser (grid) sections (mean ± SD)	1.2 ± 0.4	1.11 ± 0.3

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

Intraocular Pressure

Mean IOP at baseline was 14.0 ± 1.3 mmHg in the IVT group and 13.7 ± 1.4 mmHg in the STI group, and there was no statistically significant change in IOP in any follow-up period in the IVT or STI group (Table 3; Figure 1). Moreover, only 1 eye showed an IOP increase of >10 mmHg compared with baseline (IOP = 23 mmHg; baseline IOP = 11 mmHg). This was observed at week 12 in the IVT group, with IOP returning to 16 mmHg at week 24. No IOP increase >10 or >25 mmHg was otherwise observed.

Table 2. Number of Eyes Classified With Scores of 1 to 5 by the Cataract Grading According to the Lens Opacity Classification System III[26] for the IVT and STI Groups

Group	ID	NO	NC	P	C	Summed Score
IVT	7	2	2	4	2	10
IVT	9	2	2	4	2	10
STI	6	2	2	3	3	10
STI	8	4	4	1	1	10
IVT	2	4	4	1	2	11
IVT	6	2	2	4	3	11
STI	1	2	2	5	2	11
STI	3	4	4	1	2	11
STI	4	2	2	4	3	11
STI	9	4	4	1	2	11
IVT	1	3	3	4	2	12
IVT	3	4	4	1	3	12
IVT	10	4	4	1	3	12
STI	2	4	4	2	2	12
STI	5	4	4	1	3	12
IVT	5	4	4	2	3	13
IVT	8	4	4	1	4	13
STI	7	4	4	3	2	13
IVT	4	5	5	2	2	14

NO, nuclear opalescence; NC, nuclear color; P, posterior subcapsular; C, cortical.

Discussion

Previous studies from our group have suggested that IVT of TA may be more effective than STI of TA for the management of refractory diffuse DME.[20,33] However, Choi et al[34] have reported positive effects on CMT and BCVA after STI of TA in patients with DME. In addition, Kim et al[35] reported that STI of TA at the end of cataract surgery reduced the amount of CMT increase in patients with diabetes 1 month after surgery. Subtenon infusion also has the advantage of being less invasive, whereas IVT has been reported to be associated with immunosuppression and endophthalmitis.[36] All these factors taken together led us to proceed with this comparative study.

An alternative to perioperative treatment of DME with TA would be preoperative treatment with the same drug, either IVT or STI, and then perform surgery 8 weeks to 12 weeks after OCT-documented regression of CMT. However, there are 2 major concerns regarding this strategy: 1) preoperative IVT TA may lead to ocular immunosuppression[36] and may, therefore, augment the risk of endophthalmitis after cataract surgery in this subset of patients with diabetes, and 2) patients would require 2 procedures and additional visits. Although preoperative bevacizumab could be tried before cataract surgery and would not carry the risk of immunosuppression, previous results from our group show only subtle effects on CMT reduction, especially in refractory DME cases.[20]

Comparatively, a more favorable macular remodeling was observed with intravitreal triamcinolone compared with subtenon as early as 4 weeks postoperatively, and it persisted up to week 24. Therefore, the overall results of this study suggest that one IVT of triamcinolone may be associated with greater beneficial effects on vision and macular remodeling than a single subtenon injection of TA for the short-term

Table 3. Mean Visual Acuity, CMT, and IOP Values by Study Visit in IVT and STI Groups

	Group IVT			Group STI		
Study Period	VA (logMAR ± SEM)	CMT (μm ± SEM)	IOP (mmHg ± SEM)	VA (logMAR ± SEM)	CMT (μm ± SEM)	IOP (mmHg ± SEM)
Baseline	20/259	474.1 ± 42.4	14.0 ± 1.3	20/222	490.8 ± 70.8	13.8 ± 1.4
1 week	20/156	275.5 ± 21.1	12.4 ± 1.0	20/230	489.1 ± 67.4	14.9 ± 1.7
4 weeks	20/116	231.5 ± 10.9	14.9 ± 1.3	20/189	515.0 ± 89.9	14.9 ± 1.8
8 weeks	20/110	239.0 ± 16.4	13.4 ± 0.9	20/194	487.2 ± 85.1	14.8 ± 1.3
12 weeks	20/121	288.0 ± 35.1	14.9 ± 1.4	20/176	496.3 ± 83.6	14.9 ± 1.5
24 weeks	20/143	370.7 ± 45.0	13.2 ± 0.9	20/204	541.3 ± 90.0	14.3 ± 1.3

SEM, standard error of the mean; VA, visual acuity.

management of refractory diffuse DME in patients undergoing cataract surgery.

Changes in CMT observed in the IVT group in this study are consistent with those reported previously by our group in patients with refractory DME not undergoing cataract surgery[15]; mean CMT reduction of 59% (182.93 μm) at 4 weeks versus 49% (232.5 μm) in this study, 36% (136.7 μm) at 12 weeks[15] versus 36.25% (170.8 μm) in this study, and 12% (55.07 μm) at 24 weeks[15] versus 20.7% (97.7 μm) in this study. Lam et al[37] also reported significant reductions in CMT after cataract surgery and peroperative TA IVT in patients with refractory DME: 24.5% (110 μm), 26.3% (118 μm), and 9.1% (41 μm) reductions in mean macular thickness by 1, 3, and 6 months of follow-up, respectively.

To the best of our knowledge, there is no study regarding CMT changes after cataract surgery and subtenon TA treatment for refractory DME. For this reason, we will compare our results with those of previous studies in which TA STI was not used in the cataract surgery scenario. Central macular thickness changes in this study are consistent with previous data from our group in patients with refractory DME: on average, no significant reduction in CMT was observed at any study period in both studies.[14] The same tendency was observed if data were analyzed on a subject level, by looking for reductions of CMT to 250 μm or to 50% of the baseline value (Table 4) and its association with BCVA improvements of at least 2 ETDRS chart lines. Here, just 1 patient at week 4 and 2 patients at week 8 showed BCVA improvement associated with reduction in CMT in the STI group. In this group, half of the patients did not have improvements in CMT and BCVA during all follow-up visits after surgery. In fact, other studies also report a limited effect of subtenon triamcinolone on CMT in patients with DME.[38,39]

Beneficial effects of IVT compared with STI with respect to change in visual acuity were noted at 4, 8, and 12 weeks after surgery. In the IVT group, visual acuity improvement from baseline was noted at weeks 4 (0.35 logMAR), 8 (0.37 logMAR), and 12 (0.33 logMAR). Similarly, Habib et al[40] also reported significant visual improvement in visual acuity 2 months after cataract surgery and perioperative IVT of 4 mg of TA in patients with refractory DME. In the study of Habib et al,[40] 50% of patients had visual acuity >6/

Table 4. Number of Patients Who Showed CMT Reduction to 250 μm or Less or Reduction to 50% of the Baseline, With or Without Visual Acuity Improvement of 2 Lines

Follow-Up Time (Weeks)	Group	CMT <250 μm or <50% of Baseline and BCVA Improvement ≥2 Lines	CMT <250 μm or <50% of Baseline and No Improvement in BCVA	CMT ≥250 μm and ≥50% of Baseline and BCVA Improvement ≥2 Lines	CMT ≥250 μm and ≥50% of Baseline and No Improvement in BCVA
1	IVT	2	4	1	3
	STI	0	0	3	6
4	IVT	6	4	0	0
	STI	1	1	3	4
8	IVT	6	3	0	1
	STI	2	0	2	5
12	IVT	2	2	4	2
	STI	2	0	1	6
24	IVT	2	4	0	4
	STI	1	1	0	7

12. Indeed, >50% of the patients (6 of 10) showed improvement of at least 2 ETDRS chart lines and CMT reduction at 4 and 8 weeks after surgery. Other comparative studies, outside the cataract surgery scenario, also showed BCVA improvement 4, 8, 12, and 24 weeks after IVT.[20,23,33]

To our knowledge, there is no published study of visual acuity after cataract surgery and perioperative STI of TA in patients with refractory DME. In this study, the overall analysis showed no improvement in BCVA compared with baseline at any study point after surgery and STI of TA, even after cataract removal. However, 3 patients at weeks 1 and 4, 2 patients at week 8, and 1 patient at week 12 had BCVA improvement, despite having no reduction in CMT. Consequently, the gain in visual acuity verified in these patients probably resulted from cataract removal. Finally, a small subgroup of patients had a reduction in CMT but no improvement in visual acuity (Table 4). These patients may have had permanent photoreceptor damage secondary to chronic macular edema. Despite our data, other investigators have reported significant improvement in BCVA 1 month[41,42] and 3 months after STI of TA.[34]

The risk of IOP elevation associated with IVT and STI of TA has been reported in previous studies.[15,20,43] In our study, there was no significant IOP increase in either group. The absence of the hypertensive effect of TA may be explained by a hypotensive effect of cataract surgery. In fact, several studies have pointed out a significant reduction in IOP after uneventful cataract surgery in healthy patients without diabetic retinopathy,[44–46] and this hypotensive effect may have counteracted the hypertensive effect of IVT and STI TA.

In conclusion, in the scenario of refractory DME and cataract surgery, a single intraoperative IVT of 4 mg of TA seems to be more effective for the short-term management of refractory diffuse DME than 1 STI of 40 mg of the same drug. Our results are limited as a result of factors such as small sample size, suboptimal follow-up rate (80% of patients completed the 24-week follow-up), and limited length of follow-up. Further investigation is needed to allow more precise conclusions about the use of triamcinolone for DME in patients who undergo cataract surgery.

Key words: intravitreal injection, subtenon infusion, triamcinolone acetonide, cataract surgery, refractory diabetic macular edema, diabetic retinopathy, retina, vitreous.

References

1. Klein R, Klein BE, Moss SE. Visual impairment in diabetes. Ophthalmology 1984;91:1–9.
2. Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. IV. Diabetic macular edema. Ophthalmology 1984;91:1464–1474.
3. Kim SJ, Equi R, Bressler NM. Analysis of macular edema after cataract surgery in patients with diabetes using optical coherence tomography. Ophthalmology 2007;114:881–889.
4. Chung J, Kim MY, Kim HS, Yoo JS, Lee YC. Effect of cataract surgery on the progression of diabetic retinopathy. J Cataract Refract Surg 2002;28:626–630.
5. Gupta A, Gupta V. Diabetic maculopathy and cataract surgery. Ophthalmol Clin North Am 2001;14:625–637.
6. Miyake K, Masuda K, Shirato S, et al. Comparison of diclofenac and fluorometholone in preventing cystoid macular edema after small incision cataract surgery: a multicentered prospective trial. Jpn J Ophthalmol 2000;44:58–67.
7. Matsunaga N, Ozeki H, Hirabayashi Y, Shimada S, Ogura Y. Histopathologic evaluation of the internal limiting membrane surgically excised from eyes with diabetic maculopathy. Retina 2005;25:311–316.
8. Cunha-Vaz J, Bernardes R. Nonproliferative retinopathy in diabetes type 2. Initial stages and characterization of phenotypes. Prog Retin Eye Res 2005;24:355–377.
9. Menchini U, Cappelli S, Virgili G. Cataract surgery and diabetic retinopathy. Semin Ophthalmol 2003;18:103–108.
10. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Early Treatment Diabetic Retinopathy Study research group. Arch Ophthalmol 1985;103:1796–1806.
11. Diabetic Retinopathy Clinical Research Network. A randomized trial comparing intravitreal triamcinolone acetonide and focal/grid photocoagulation for diabetic macular edema. Ophthalmology 2008;115:1447–1459.
12. Massin P, Audren F, Haouchine B, et al. Intravitreal triamcinolone acetonide for diabetic diffuse macular edema: preliminary results of a prospective controlled trial. Ophthalmology 2004;111:218–224; discussion 224–225.
13. Martidis A, Duker JS, Greenberg PB, et al. Intravitreal triamcinolone for refractory diabetic macular edema. Ophthalmology 2002;109:920–927.
14. Sutter FK, Simpson JM, Gillies MC. Intravitreal triamcinolone for diabetic macular edema that persists after laser treatment: three-month efficacy and safety results of a prospective, randomized, double-masked, placebo-controlled clinical trial. Ophthalmology 2004;111:2044–2049.
15. Bonini-Filho MA, Jorge R, Barbosa JC, Calucci D, Cardillo JA, Costa RA. Intravitreal injection versus sub-Tenon's infusion of triamcinolone acetonide for refractory diabetic macular edema: a randomized clinical trial. Invest Ophthalmol Vis Sci 2005;46:3845–3849.
16. Audren F, Lecleire-Collet A, Erginay A, et al. Intravitreal triamcinolone acetonide for diffuse diabetic macular edema: phase 2 trial comparing 4 mg vs 2 mg. Am J Ophthalmol 2006;142:794–799.
17. Karacorlu M, Ozdemir H, Karacorlu S, Alacali N, Mudun B, Burumcek E. Intravitreal triamcinolone as a primary therapy in diabetic macular oedema. Eye (Lond) 2005;19:382–386.
18. Margolis R, Singh RP, Bhatnagar P, Kaiser PK. Intravitreal triamcinolone as adjunctive treatment to laser panretinal photocoagulation for concomitant proliferative diabetic retinopathy and clinically significant macular oedema. Acta Ophthalmol 2008;86:105–110.
19. Vinten M, Larsen M, Lund-Andersen H, Sander B, La Cour M. Short-term effects of intravitreal triamcinolone on retinal vascular leakage and trunk vessel diameters in diabetic macular oedema. Acta Ophthalmol Scand 2007;85:21–26.

20. Paccola L, Costa RA, Folgosa MS, Barbosa JC, Scott IU, Jorge R. Intravitreal triamcinolone versus bevacizumab for treatment of refractory diabetic macular oedema (IBEME study). Br J Ophthalmol 2008;92:76–80.
21. Takamura Y, Kubo E, Akagi Y. Analysis of the effect of intravitreal bevacizumab injection on diabetic macular edema after cataract surgery. Ophthalmology 2009;116:1151–1157.
22. Soheilian M, Ramezani A, Obudi A, et al. Randomized trial of intravitreal bevacizumab alone or combined with triamcinolone versus macular photocoagulation in diabetic macular edema. Ophthalmology 2009;116:1142–1150.
23. Bonini-Filho M, Costa RA, Calucci D, Jorge R, Melo LA Jr, Scott IU. Intravitreal bevacizumab for diabetic macular edema associated with severe capillary loss: one-year results of a pilot study. Am J Ophthalmol 2009;147:1022–1030.
24. Chen CH, Liu YC, Wu PCJ. The combination of intravitreal bevacizumab and phacoemulsification surgery in patients with cataract and coexisting diabetic macular edema. J Ocul Pharmacol Ther 2009;25:83–89.
25. Arevalo JF, Sanchez JG, Fromow-Guerra J, et al; Pan-American Collaborative Retina Study Group (PACORES). Comparison of two doses of primary intravitreal bevacizumab (Avastin) for diffuse diabetic macular edema: results from the Pan-American Collaborative Retina Study Group (PACORES) at 12-month follow-up. Graefes Arch Clin Exp Ophthalmol 2009;247:735–743.
26. Haritoglou C, Kook D, Neubauer A, et al. Intravitreal bevacizumab (Avastin) therapy for persistent diffuse diabetic macular edema. Retina 2006;26:999–1005.
27. Cunningham ET Jr, Adamis AP, Altaweel M, et al; Macugen Diabetic Retinopathy Study Group. A phase II randomized double-masked trial of pegaptanib, an anti-vascular endothelial growth factor aptamer, for diabetic macular edema. Ophthalmology 2005;112:1747–1757.
28. Chun DW, Heier JS, Topping TM, Duker JS, Bankert JM. A pilot study of multiple intravitreal injections of ranibizumab in patients with center-involving clinically significant diabetic macular edema. Ophthalmology 2006;113:1706–1712.
29. Chylack LT Jr, Wolfe JK, Singer DM, et al. The Lens Opacities Classification System III. The Longitudinal Study of Cataract Study Group. Arch Ophthalmol 1993;111:831–836.
30. Costa RA, Calucci D, Skaf M, et al. Optical coherence tomography 3: automatic delineation of the outer neural retinal boundary and its influence on retinal thickness measurements. Invest Ophthalmol Vis Sci 2004;45:2399–2406.
31. Goebel W, Franke R. Retinal thickness in diabetic retinopathy: comparison of optical coherence tomography, the retinal thickness analyzer, and fundus photography. Retina 2006;26:49–57.
32. Kim SJ, Belair ML, Bressler NM, et al. A method of reporting macular edema after cataract surgery using optical coherence tomography. Retina 2008;28:870–876.
33. Cardillo JA, Melo LA Jr, Costa RA, et al. Comparison of intravitreal versus posterior sub-Tenon's capsule injection of triamcinolone acetonide for diffuse diabetic macular edema. Ophthalmology 2005;112:1557–1563.
34. Choi YJ, Oh IK, Oh JR, Huh K. Intravitreal versus posterior subtenon injection of triamcinolone acetonide for diabetic macular edema. Korean J Ophthalmol 2006;20:205–209.
35. Kim SY, Yang J, Lee YC, Park YH. Effect of a single intraoperative sub-tenon injection of triamcinolone acetonide on the progression of diabetic retinopathy and visual outcomes after cataract surgery. J Cataract Refract Surg 2008;34:823–826.
36. Saidel MA, Berreen J, Margolis TP. Cytomegalovirus retinitis after intravitreous triamcinolone in an immunocompetent patient. Am J Ophthalmol 2005;140:1141–1143.
37. Lam DS, Chan CK, Mohamed S, et al. Phacoemulsification with intravitreal triamcinolone in patients with cataract and coexisting diabetic macular oedema: a 6-month prospective pilot study. Eye (Lond) 2005;19:885–890.
38. Diabetic Retinopathy Clinical Research Network; Chew E, Strauber S, Beck R, et al. Randomized trial of peribulbar triamcinolone acetonide with and without focal photocoagulation for mild diabetic macular edema: a pilot study. Ophthalmology 2007;114:1190–1196.
39. Entezari M, Ahmadieh H, Dehghan MH, Ramezani A, Bassirnia N, Anissian A. Posterior sub-tenon triamcinolone for refractory diabetic macular edema: a randomized clinical trial. Eur J Ophthalmol 2005;15:746–750.
40. Habib MS, Cannon PS, Steel DH. The combination of intravitreal triamcinolone and phacoemulsification surgery in patients with diabetic foveal oedema and cataract. BMC Ophthalmol 2005;5:15.
41. Bakri SJ, Kaiser PK. Posterior subtenon triamcinolone acetonide for refractory diabetic macular edema. Am J Ophthalmol 2005;139:290–294.
42. Toda J, Fukushima H, Kato S. Injection of triamcinolone acetonide into the posterior sub-tenon capsule for treatment of diabetic macular edema. Retina 2007;27:764–769.
43. Vasconcelos-Santos DV, Nehemy PG, Schachat AP, Nehemy MB. Secondary ocular hypertension after intravitreal injection of 4 mg of triamcinolone acetonide: incidence and risk factors. Retina 2008;28:573–580.
44. Pohjalainen T, Vesti E, Uusitalo RJ, Laatikainen L. Intraocular pressure after phacoemulsification and intraocular lens implantation in nonglaucomatous eyes with and without exfoliation. J Cataract Refract Surg 2001;27:426–431.
45. Jahn CE. Reduced intraocular pressure after phacoemulsification and posterior chamber intraocular lens implantation. J Cataract Refract Surg 1997;23:1260–1264.
46. Hata H, Yamane S, Hata S, Shiota H. Preliminary outcomes of primary phacoemulsification plus intraocular lens implantation for primary angle-closure glaucoma. J Med Invest 2008;55:287–291.