Posterior Juxtascleral Infusion of Modified Triamcinolone Acetonide Formulation for Refractory Diabetic Macular Edema: One-Year Follow-Up

Daniele Veritti, Paolo Lanzetta, Laura Perissin, and Francesco Bandello

PURPOSE. To evaluate prospectively the efficacy and safety of posterior juxtascleral infusion of a new formulation of triamcinolone acetonide for refractory diffuse diabetic macular edema.

METHODS. This was an interventional case series. Twenty-two consecutive eyes of 18 patients with refractory diffuse diabetic macular edema were included in the study. Each patient underwent a complete ophthalmic examination, including optical coherence tomography (OCT) and digital fluorescein angiography (FA). All patients received a suspension of 40 mg triamcinolone acetonide, 20 mg sodium chondroitin sulfate, and 15 mg sodium hyaluronate (1.5 mL), delivered posteriorly through a conjunctival and Tenon’s incision. All patients completed the 1-year follow-up.

RESULTS. On average, studied eyes received 1.5 treatments. Mean preoperative foveal thickness (±SD) and visual acuity (±SD) were 474.2 ± 136.6 μm and 0.6 ± 0.37 logarithm of the minimal angle of resolution (logMAR), respectively. The central foveal thickness was significantly reduced from baseline at every follow-up visit (P < 0.001). Mean (±SD) reductions in macular thickness were 136 ± 108 μm at 1 week and 128 ± 122 μm after 1 year of follow-up. Mean (±SD) improvement in visual acuity at 12 months was 0.15 ± 0.21 logMAR (P = 0.008). Visual acuity improvement of one or more lines and three or more lines were observed in 14 (63.6%) and 6 (27.3%) eyes, respectively. Seven eyes (31.8%) required topical treatment due to a significant intraocular pressure increase.

CONCLUSIONS. Posterior juxtascleral infusion of a new formulation of triamcinolone acetonide is an effective treatment for diffuse diabetic macular edema unresponsive to conventional grid laser photocoagulation. A randomized, larger study is warranted. (Invest Ophthalmol Vis Sci. 2009;50:2391–2397) DOI:10.1167/iovs.08-2518

Diabetic macular edema (DME) represents the major cause of decreased visual acuity in diabetic patients. Approximately 29% of patients with a disease duration of 20 years or more are affected by macular edema.2 The Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated a significant benefit of focal laser photocoagulation for the treatment of clinically significant macular edema.3 However, diffuse macular edema, resulting from a generalized breakdown of the inner blood-retinal barrier, has a poor prognosis despite grid laser photocoagulation.4–6 Lee and Olk7,8 have reported that visual acuity improved in 14.5% of eyes, did not change in 60.9%, and decreased in 24.6%, 3 years after initial grid treatment in patients with this condition. Thus, other treatment modalities for diffuse DME are being evaluated.

Clinical studies have already shown that intravitreal injection of triamcinolone acetonide (TA) reduces macular edema and improves visual acuity.9–15 However, intravitreal injections involve specific and considerable risks, including acute infectious endophthalmitis and pseudoendophthalmitis.14,16–19 Therefore, other routes of administration could be considered. Therapeutic doses of the drug could reach the posterior segment via transscleral absorption, after periocular administration.20 Drug reflux after sub-Tenon infusion has been reported and may be responsible for the loss of efficacy compared with the intravitreal route.21

In the present study, TA was mixed with sodium chondroitin sulfate and sodium hyaluronate to improve the viscosity of the medication. The higher viscosity and the biochemical properties of the suspension may control drug reflux, improve the drug-sclera contact time and influence steroid diffusion through the scleral barrier.

The purpose of this study was to evaluate prospectively the efficacy and safety of the posterior juxtascleral infusion of this TA formulation on macular thickness and visual acuity in eyes with diffuse DME unresponsive to grid laser treatment.

METHODS

The study protocol adhered to the tenets of the Declaration of Helsinki and was approved by the local institutional review board. Written, informed consent was obtained from all the participants before they were enrolled in the study. The Patients were recruited and enrolled at the Department of Ophthalmology, University of Udine, from March 2005 to September 2006 and were followed up for 12 months. This study involved the off-label use of drugs.

Inclusion and Exclusion Criteria

Patients were included in the study if they (1) were older than 18 years of age; (2) had refractory diffuse DME, defined as clinically significant macular edema (as classified by the ETDRS)8 with a generalized breakdown of the inner blood-retinal barrier and diffuse fluorescein leakage involving the foveal center and most of the macular area on fluorescein angiography, unresponsive to adequate laser photocoagulation performed at least 3 months before evaluation (Fig. 1); (3) had central foveal thickness (CFT) greater than 300 μm on optical coherence.
tomography (OCT); and (i) had best corrected visual acuity (BCVA) between 0.2 and 1.3 logarithm of the minimum angle of resolution (logMAR). Exclusion criteria were (1) presence of vitreomacular traction or epiretinal membrane, (2) history of uncontrolled glaucoma (defined as intraocular pressure ≥ 25 mm Hg despite treatment) or low-tension glaucoma, (3) history of systemic or ocular corticosteroid medication within 6 months before the baseline evaluation, (4) active intraocular inflammation or systemic infection, (5) glycosylated hemoglobin (HbA1c) rate above 10%, and (6) loss of vision as a result of other causes.

**Baseline Evaluation, Follow-up, and Retreatment**

During the inclusion period 22 eyes of 18 patients were enrolled in the study. Each patient received a complete ophthalmic examination, including measurement of BCVA, Goldmann applanation tonometry, undilated and dilated slit lamp biomicroscopic examination. The measurement of best corrected logMAR visual acuity was obtained with the ETDRS charts and standardized procedures. Color fundus photography and fluorescein angiography (FA) were performed (TRC 50 IX camera and acquisition software Imagenet 2000; Topcon Optical Co., Tokyo, Japan). OCT scans were obtained with a third-generation OCT equipment (Stratus Tomograph, model 3000; Carl Zeiss Meditec, Inc., Humphrey Division, Dublin, CA). OCT evaluation consisted of six linear 6-mm scans oriented at intervals of 30° and centered on the foveal region. The retinal thickness was computed automatically with the system’s OCT retinal mapping software. CFT was defined as the average thickness of the six scans of the central macular region. All scans were reviewed before considering the use of the automatic measurement of macular thickness. This method has been described as feasible for monitoring morphologic changes in diabetic eyes and with a good reproducibility. Patients were scheduled for follow-up examinations at week 1 and months 1, 3, 6, 9, and 12 after treatment. At these follow-up times, the patients underwent a complete ophthalmic evaluation and OCT examination using the same procedures as at baseline. FA was performed every 3 months. Re-injection was considered at 3-month intervals at the physician’s discretion based on OCT (CFT ≥500 μm), VA, and FA findings. The patients were followed-up for potential side effects secondary either to the surgical procedure or to the steroid treatment. At the end of the infusion, the presence or absence of drug reflux was recorded. Intraocular pressure and HbA1c rate were also monitored during follow-up.

**Drug Preparation and Route of Administration**

All patients received a suspension of 40 mg TA, 20 mg sodium chondroitin sulfate, and 15 mg sodium hyaluronate (1.5 mL) delivered in a posterior juxtascleral injection. In brief, after topical anesthesia (2% lidocaine) and 5% povidone iodine application, a small conjunctival and Tenon’s incision (7 mm posterior and superotemporal to the limbus) was made in the bare sclera. With a curved, blunt cannula the medication was infused into the posterior juxtascleral space. Subsequently, the cannula was slowly withdrawn, with gentle pressure maintained by a sterile swab along the path of the cannula. Afterward, the surgical incision was cauterezed, and topical antibiotic was instilled.

**Outcome Measures**

The primary outcome measure was the macular morphologic changes after treatment and monitored by OCT measurement of CFT. Standardized change in macular thickness (SCMT) was calculated with the formula of Chan and Duker: SCMT = (baseline CFT − final CFT)/(baseline CFT − normal CFT). Normal CFT was taken as 182 μm for StratusOCT. However, the thickness in some patients dropped below 182 μm during the study. In these cases, the minimum value obtained during the follow-up was considered normal. Secondary outcome measures were changes in BCVA (logMAR ETDRS values), intraocular pressure, and HbA1c rate.

**Statistical Analysis**

The sample size was found to detect a 60-μm difference in CFT (SD 100 μm). With α = 0.05 (two-sided) and a power of 80%, the calculated sample size was at least 22 eyes. Repeated-measures ANOVAs, with Greenhouse-Geisser correction and a significance level of 5%, were conducted to assess whether there were differences between average values. Serial comparisons of pretreatment and posttreatment outcomes were performed with paired t tests or the Wilcoxon matched-pairs nonparametric test according to whether the distributions were gaussian or nongaussian. In serial comparisons, the null hypothesis was rejected for $P < 0.008$ (Bonferroni correction: $P < 0.05/6 = P < 0.008$).

**RESULTS**

Twenty-two eyes of 18 patients fulfilled the inclusion criteria, and each patient completed the 12-month study period. Baseline characteristics are summarized in Table 1. On average, the studied eyes received 1.5 ± 0.6 treatments (range, 1–3). A single infusion was given in 54.5% of eyes. No drug reflux was observed in any procedure.

**Changes in Central Foveal Thickness**

The changes in CFT are summarized in Table 2 and Figure 2. A repeated-measures ANOVA, with Greenhouse-Geisser correction, was conducted to assess whether there were differences between the average CFT values. Results indicated that macular thickness changed significantly ($F_{2,89} = 9.02$, $P < 0.001$). Serial comparison between baseline and posttreatment values demonstrated that the decrease in the mean CFT was significant at each follow-up time ($P < 0.0005$). The propor-

![Figure 1](https://iovs.arvojournals.org/pdfaccess.ashx?url=/data/journals/iovs/932959/) FA of two selected cases. Lower (A) and higher (B) ends of the extent of the prior photocoagulation spectrum.
Table 1. Patients’ Characteristics

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
<th>n = 22</th>
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<tbody>
<tr>
<td>Female sex, n (%)</td>
<td>7 (31.8)</td>
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<tr>
<td>Age (mean ± SD), y</td>
<td>64.2 ± 11.9</td>
</tr>
<tr>
<td>Diabetes duration (mean ± SD), y</td>
<td>16.8 ± 14.2</td>
</tr>
<tr>
<td>Insulin treatment, n (%)</td>
<td>10 (45.4)</td>
</tr>
<tr>
<td>Phakic, n (%)</td>
<td>14 (63.6)</td>
</tr>
<tr>
<td>Prior laser treatments for macular edema (mean ± SD), n</td>
<td>2.2 ± 0.4</td>
</tr>
<tr>
<td>Time since last laser for macular edema (mean ± SD), mo</td>
<td>9.4 ± 3.9</td>
</tr>
<tr>
<td>Prior pan retinal photocoagulation, n (%)</td>
<td>17 (77.3)</td>
</tr>
<tr>
<td>HbA1c (mean ± SD) %</td>
<td>7.4 ± 1.3</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>27.3 ± 4.4</td>
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<tr>
<td>Systolic blood pressure (mean ± SD), mm Hg</td>
<td>136.7 ± 16.7</td>
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<tr>
<td>Diastolic blood pressure (mean ± SD), mm Hg</td>
<td>79.2 ± 10.8</td>
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<tr>
<td>Central foveal thickness (mean ± SD), μm</td>
<td>474.2 ± 136.6</td>
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<tr>
<td>Visual acuity (mean ± SD), logMAR</td>
<td>0.6 ± 0.37</td>
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<tr>
<td>Intraocular pressure (mean ± SD), mm Hg</td>
<td>15.7 ± 3.8</td>
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HbA1c, glycosylated hemoglobin rate; BMI, body mass index.

Table 2. OCT Changes

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>1 wk</th>
<th>1 mo</th>
<th>3 mo</th>
<th>6 mo</th>
<th>9 mo</th>
<th>12 mo</th>
</tr>
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<tbody>
<tr>
<td>CFT changes from baseline (mean ± SD), μm</td>
<td>-135.7 ± 108</td>
<td>-155 ± 106.6</td>
<td>-134.9 ± 114.9</td>
<td>-105.9 ± 105.5</td>
<td>-160.1 ± 131.5</td>
<td>-128 ± 121.5</td>
</tr>
<tr>
<td>95% Confidence interval</td>
<td>&lt;0.0001 t</td>
<td>&lt;0.0001 t</td>
<td>0.0001 w</td>
<td>0.0002 t</td>
<td>&lt;0.0001 t</td>
<td>0.0003 w</td>
</tr>
<tr>
<td>SCMT changes from baseline (mean ± SD), %</td>
<td>-47.4 ± 28.9</td>
<td>-53.3 ± 27.3</td>
<td>-48.3 ± 31.9</td>
<td>-37.5 ± 34.7</td>
<td>-51.9 ± 38.1</td>
<td>-42.6 ± 38.5</td>
</tr>
<tr>
<td>SCMT reduction ≥ 50%, n (%)</td>
<td>10 (45.4)</td>
<td>12 (54.5)</td>
<td>12 (54.5)</td>
<td>9 (40.9)</td>
<td>12 (54.5)</td>
<td>11 (50)</td>
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t, paired t-test; w, Wilcoxon matched-pairs nonparametric test.

Changes in Best Corrected Visual Acuity

The changes in logMAR BCVA are summarized in Table 3 and Figure 3. A further repeated-measures ANOVA, with Greenhouse-Geisser correction, was conducted to assess whether there were differences between the average BCVAs. Results indicated that logMAR BCVA changed significantly (F5,65 = 4.6, P = 0.006). Serial comparison between baseline and post-treatment values demonstrated that the improvement in mean BCVA was significant 1, 3, 9, and 12 months after treatment (P < 0.0008). At the end of the study, the mean improvement in BCVA was 0.15 logMAR. In 63% of eyes, the improvement was at least 1 ETDRS line, and in 27.3% cases, it was greater than 3 ETDRS lines. A BCVA reduction of more than 3 lines was noted in four cases during the follow-up time. Two cases were due to cataract progression, and in them, the BCVA returned to the previous value after cataract surgery. In the other two cases DME reappeared and then resolved with an additional juxtascleral TA injection after the 12-month follow-up.

Side Effects

Serial comparison analysis revealed a significant increase in IOP from baseline only 1 month after treatment (P = 0.007). In seven (31.8%) eyes, topical treatment was necessary because of a significant increase in intraocular pressure. In five cases, the increase in IOP resolved within 3 months and thus the medication was discontinued. In the remaining two cases, the topical treatment had to be administered for the entire study duration. In one case ptosis developed, and 3 of the 14 phakic eyes at baseline required cataract surgery. In all eyes a marked chemosis was observed immediately after the procedure and resolved without sequelae within 2 days. No cases of endophthalmitis were reported. Patients were also monitored for potential changes in HbA1c rates and blood pressure values. Hba1c rate data were collected for the entire study duration for 14 patients. A repeated-measures ANOVA indicated that average Hba1c rates did not change significantly (F5,65 = 1.35, P = 0.25).

Discussion

Macular edema is the main cause of visual impairment in diabetic eyes.25 In recent years, the intravitreal administration of TA has provided promising results for the treatment of refractory diffuse macular edema.12–15 Beer et al.26 observed that adequate concentrations of TA could provide therapeutic effects for approximately 3 months after 4-mg intravitreal TA injection. Audren et al.27 suggested a maximum-effect duration of 140 days, consistent with the duration of drug efficacy after intravitreal injection in previously published clinical trials.12–15 However, intravitreal TA injections carry considerable risk, including acute infectious endophthalmitis, pseudendophthalmitis, and iatrogenic retinal breaks.28 A recent review reported an estimated incidence rate of endophthalmitis after intravitreal administration of TA of 1.4% per injection (24/1739).19

Growing evidence is showing the usefulness of the transscleral pathway in delivering drug to the macular retina.20,29,30 The average 17-cm² surface area of the human sclera accounts for 95% of the total surface area of the globe and thus provides a large surface for drug diffusion.20 The human sclera is permeable to 70-kDa dextran and IgG of the same molecular weight.31 Therefore, TA with a molecular mass of approximately 400 Da, may easily penetrate the sclera by passive diffusion. Transscleral delivery of TA is routinely used for the treatment of various inflammatory eye diseases, and recently it has been proposed for the treatment of DME.32–39

Previously conducted studies showed that intravitreal injection of TA may be more effective than posterior juxtascleral infusion for the treatment of refractory DME. Bonini-Filho et al.24 compared the effectiveness of posterior sub-Tenon infusion and intravitreal injection of TA in a randomized trial including 28 eyes with refractory diffuse DME. CFT was significantly reduced in the intravitreal injection group when compared with the sub-Tenon infusion group at 2 weeks, 1, 2, 3, and 6 months after treatment (P < 0.01). The authors supposed that this difference may be due in part to the reflux of...
the drug, which was noted in 21.4% of injections. This was also the case in the Anecortave Acetate Study, in which drug reflux was found in 55% of treatments.40 In a retrospective study on 85 eyes treated with posterior sub-Tenon TA and 41 eyes with intravitreal TA, Cardillo at al.33 concluded that in patients with diffuse DME, intravitreal injection of TA was more favorable than posterior sub-Tenon injection for the anatomic and functional aspect of improvement. On the contrary, other authors have found evidence of the benefit of sub-Tenon injection. Ozdek et al.32 evaluated retrospectively the efficacy of posterior sub-Tenon and intravitreal TA injections in DME refractory to conventional grid laser photocoagulation. The effect of 20 mg/0.5 mL sub-Tenon injection was less dramatic than that of intravitreal TA, although effective both functionally and anatomically with a duration effect of about 3 months. Similarly, Bakri and Kaiser36 showed that a 40-mg sub-Tenon injection was beneficial in improving or stabilizing visual acuity in patients with refractory DME. Over a 3-month period, Choi et al.37 compared a single 40-mg posterior sub-Tenon injection to intravitreal injection in 60 patients with DME and concluded that sub-Tenon administration had an effect comparable to that of the intravitreal route with lower risk of elevated IOP. In their recent study, Cellini et al.39 demonstrated that 3 months after administration, intravitreal and sub-Tenon injection of TA produce the same improvement in VA and an equally significant reduction in retinal thickness. The commonly reported advantages of periocular administration of TA versus intravitreal injection include a lower risk of IOP elevation and endophthalmitis. As regards the duration of the beneficial effect after a single sub-Tenon injection, most authors have not reported substantial advantages over the intravitreal route. Also of note is that most studies on periocular TA administration were evaluations of sub-Tenon injection, a simple procedure that requires only a drop or two of topical anesthetic. Posterior sub-Tenon infusion, as we applied in the present study, is undoubtedly a more invasive approach, which on the other hand would allow delivery of the drug to the desired position in direct contact with the globe posteriorly.41

In the present study, the drug was mixed with sodium chondroitin sulfate and sodium hyaluronate to enhance its

<table>
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<th>TABLE 3. Visual Acuity Changes</th>
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<tr>
<td>Follow-up</td>
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<tr>
<td>BCVA changes from baseline</td>
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<tr>
<td>(mean ± SD), logMAR</td>
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<tr>
<td>95% Confidence interval</td>
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<tr>
<td>P</td>
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<tr>
<td>BCVA improvement ≥ 1 ETDRS lines, n (%)</td>
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<tr>
<td>BCVA improvement ≥ 3 ETDRS lines, n (%)</td>
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<tr>
<td>BCVA loss ≥ 1 ETDRS lines, n (%)</td>
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<tr>
<td>BCVA loss ≥ 3 ETDRS lines, n (%)</td>
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<tr>
<td>Stable BCVA (change &lt; 1 ETDRS line), n (%)</td>
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BCVA, best corrected visual acuity; t, paired t-test; w, Wilcoxon matched-pairs nonparametric test.
density and viscosity, to avoid reflux and promote the drug persistence in the retromacular space. No drug reflux was noticed in any of the 34 injections. Sodium chondroitin sulfate and sodium hyaluronate were used for biochemical and biophysical reasons. Biocompatibility of proteoglycans has been shown when injected for the treatment of osteoarthritis, interstitial cystitis, and discogenic low back pain and during cataract surgery.42–44 Their usefulness has also been shown in the prodrug approach as a method for the controlled and targeted delivery of drugs.45 Chondroitin sulfate has an advantage in the solubilization of drugs, especially to help hydrophobic drugs traverse compartmental barriers, and extend the release time.45,46 Unfortunately, no data on pharmacokinetics of chondroitin sulfate within the sub-Tenon space are available yet. Similarly, no previous studies have been conducted on the beneficial effect of the addition of proteoglycans to TA. However, it is known that proteoglycans influence hydration, solute diffusion, and fluid movement through the sclera due to the hydrophilic nature of their extended glycosaminoglycan side chains.47 The scleral interfibrillar matrix is occupied by small leucine-rich proteoglycans, decorin and biglycan, containing dermatan and dermatan/chondroitin sulfate glycosaminoglycans, together with the large proteoglycan, aggrecan, which also carries keratan sulfate side chains.48 Thus, possible interactions between the glycosaminoglycans that carry TA and those of the scleral matrix may influence the drug diffusion through the sclera into the eye. Experimental measurements of scleral permeability derive from determinations of steady state flux. In the absence of a sustained-release system, the contact time between the drug and the sclera would be too short to permit the attainment of steady state flux. Thus, in vitro flux measurements may overpredict transscleral drug delivery in vivo.49 The new formulation used in the present study may increase the drug-sclera contact time, getting the in vivo scleral permeability properties closer to those measured in vitro.

The outcomes observed in our study compare favorably with previous trials, either those evaluating posterior juxtascleral infusion with Tenon capsule incision or those with subTenon injection. Our study showed significant reduction in CFT at any follow-up time (P < 0.001). One-week after TA infusion, mean reduction in CFT was 134 μm and the effect duration reaches approximately 6 to 9 months. One infusion only was given in 54.5% of eyes. A decrease in macular thickening of 50% or more was present in one half of the eyes at the end of the follow-up time. The eyes included in the study had diffuse refractory macular edema. Nevertheless, approximately one-third of the eyes showed an improvement of at least 3 ETDRS lines at the end of the follow-up period, and more than two-thirds showed some VA improvement. Our results also appear encouraging with respect to other reports on the use of intravitreous TA in similar conditions, especially with regard to the effect duration and side effects. Nevertheless, it should be considered that diabetic patients enrolled in a prospective study may be induced to tighten their metabolic control. It has been demonstrated that macular edema severity may correlate with diabetes control. Therefore, reduction of macular thickness and improvement of visual acuity may also follow more assiduous care of the disease and systemic risk factors. However, HbA1c rates did not change significantly in the treated patients as well as blood pressure values, suggesting that these elements did not have a major role in the outcome.

Although juxtascleral infusion of TA seems to be a safe procedure, possibilities of complications, such as elevation of IOP, orbital hemorrhage, ptosis, and periorbital abscesses, are not eliminated.36,39,49,50 Previous studies have reported that the main side effect of intravitreal TA is an elevation of the IOP, which occurred in 34.6% to 50% of eyes. In our study, posterior juxtascleral infusion of TA resulted in a IOP elevation in 7 (31.8%) eyes and it was transient in five cases. We did not observe any infectious complication or any effect of TA on coagulation. The limitations of the present study include the small sample size and the absence of a control group. How ever, HbA1c rates did not change significantly in the treated patients as well as blood pressure values, suggesting that these elements did not have a major role in the outcome.

In conclusion, posterior juxtascleral infusion of a new formulation of TA is an effective treatment for diffuse diabetic macular edema unresponsive to conventional grid laser photocoagulation. The limitations of the present study include the small sample size and the absence of a control group. However, the efficacy of the treatment, the extraocular delivery route, the effect duration, and the reduced incidence of serious adverse events suggest that posterior juxtascleral infusion of TA in a new formulation may be a promising treatment option.
that should be investigated in further randomized studies exploring its efficacy also in naïve diabetic macular edema, in combination with laser therapy and in macular edema secondary to other conditions.

References

41. Jockovich ME, Murray TG, Clifford PD, Moshefgi AA. Posterior juxtasceral injection of anecortave acetate: magnetic resonance


