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Intravitreal triamcinolone acetonide as primary treatment for diffuse diabetic macular edema: A prospective noncomparative interventional case series

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PURPOSE. *To evaluate the efficacy and safety of one intravitreal injection of 25 mg of triamcinolone acetonide as primary treatment for diffuse diabetic macular edema.*

METHODS. *Intravitreal triamcinolone acetonide injection was performed in 30 eyes with previously untreated diabetic macular edema. The main outcome measures were logMAR visual acuity (VA) and central macular thickness (CMT) at 1, 3, and 6 months. A secondary outcome was intraocular pressure progression.*

RESULTS. *Visual acuity results for 30 eyes that had a follow-up of at least 6 months are presented. Twenty of them were followed up to 10.1±2.38 months. Preoperatively, VA was 0.54±0.27. At 1, 3, and 6 months follow-up, VA was 0.44±0.29 (p=0.001), 0.43±0.28 (p=0.001), and 0.45±0.29 (p=0.006), respectively. Preoperatively, CMT was 417.3±143.5 µm. At 1, 3, and 6 months follow-up, CMT was 277.3 +74.0 µm (p<0.0001), 279.6±94.4 µm (p<0.0001), and 297.07±114.87 µm (p=0.002), respectively. For the 20 eyes with a follow-up of 10.1±2.38 months, VA was 0.5±0.25 and 0.50±0.32 at baseline and at the last follow-up visit, respectively (p>0.05). Preoperatively, intraocular pressure (IOP) was 15.13±1.48 mmHg. IOP was 18.26±2.71 mmHg, 20.07±4.27 mmHg, and 20.4±6.18 mmHg, at 1, 3, and 6 months, respectively (p<0.0001). Four eyes underwent uncomplicated filtrating surgery for intractable glaucoma.*

CONCLUSIONS. *Intravitreal triamcinolone as primary treatment effectively increases VA and reduces CMT due to diffuse diabetic macular edema. Longer follow-up and randomized clinical trial are warranted. Safety results highlight the need to further study the relationship between triamcinolone and intraocular pressure. (Eur J Ophthalmol 2006; 16: 129-33)*

KEY WORDS. *Intravitreal triamcinolone, Diabetic macular edema*

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INTRODUCTION

Diabetic macular edema (DME) is the main cause of visual impairment in diabetic patients (1). Its treatment is based mainly on laser photocoagulation. The Early Treatment Diabetic Retinopathy Study (ETDRS) trial showed that focal laser photocoagulation is beneficial for eyes with clinically significant DME (2). However, for diffuse DME, this treatment has had limited results. It has been showed (3, 4) that VA decreased by ≥3 lines in 24.6% of the eyes with diffuse DME treated with grid laser photocoagulation. The aim of our study was to investigate, in a prospective noncontrolled interventional case series, the efficacy and

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safety of one intravitreal injection of triamcinolone acetonide (IVTA) for previously untreated diffuse DME.

METHODS

Patients and study population

Patients were included if they had diffuse DME on biomicroscopy with no sign of vitreomacular traction on either biomicroscopy or optical coherence tomography (OCT) examination in at least one eye, a baseline best-corrected visual acuity (BCVA) better than 20/200, and no history of previous focal or grid laser treatment in the macular region. Diffuse macular edema was defined by macular thickening on biomicroscopy, involving the center of the macula, with few or no macular exudates, and generalized breakdown of the inner blood–retina barrier, with diffuse fluorescein leakage involving most of the macular area on fluorescein angiography. Patients with a history of glaucoma or ocular hypertension were excluded from the study. Also excluded were patients with ≥1 disc diameter of capillary closure on fluorescein angiography and patients who had undergone cataract or vitreous surgery. All of the patients were fully informed about the experimental character of the treatment and signed an informed consent. Two weeks before IVTA injection all the patients underwent BCVA measurement with refraction using ETDRS refraction charts (Light House), an ophthalmic examination including slit-lamp biomicroscopy, applanation tonometry, fundus examination with a contact lens, fluorescein angiography (FA) (Topcon Imagenet System), and optical coherence tomography (Stratus OCT 3, Carl Zeiss Meditec AG, Jena, Germany).

Intervention procedure

IVTA injections were performed as previously described (5). All the patients were given topical beta-blockers twice a day (Timoptol 0.5%) for the follow-up period.

Outcome measures

The main outcome measures were the change in ETDRS logMar VA and CMT variation measured by OCT. The proper average ETDRS visual acuity was computed by converting the value to the logMAR equivalent and then taking the average of the logMAR values (6). All statistical calculations were performed using logMAR values for visual acuity. CMT was calculated using commercially available equipment (Stratus OCT, Zeiss, Dublin, CA).

Statistical analysis

Results are presented as means ± SD. Statistical evaluation of the data was performed using a t-test coupled for the means.

RESULTS

Between July 2003 and August 2004, 30 eyes of 21 consecutive diabetic patients were treated with IVTA. There were 7 women and 14 men, for a total of 30 eyes. Mean (SD) age of the patients was 65.3 (8.31) years (median, 64.5 years; range, 50 to 82 years). BCVA and intraocular pressure (IOP) measurements were available for all the patients at 1, 3, and 6 months after IVTA injection.

OCT measurements were available in all the eyes at 1 month, in 86% (26 out of 30) of the eyes at 3 months, and in 57% (17 out of 30) of the eyes at 6 months. The mean ETDRS logMar VA, CMT, and IOP before and after IVTA injections are presented in Table I. There were statistically significant differences in VA, CMT, and IOP after IVTA injection when compared with pretreatment values up to the 6 months follow-up visit. Overall at the 6 months follow-up visit VA increased in 17 (56.6%) of the 30 eyes (Tab. II) with a mean of 1.1±1.83, 1.06±1.95, and 0.93±2.01 ETDRS lines at 1, 3, and 6 months follow-up visit. For 20 eyes a mean follow-up of 10.1±2.38 months (median, 9; range, 7 to 16) was available. For this group of patients mean VA was 0.499±0.252 and 0.501±0.321 at baseline and at the last follow-up visit, respectively (Tab. III). CMT for this group of patients was not available. VA increased in 10 (50%) of 20 eyes with a mean of 0.35±2.68 ETDRS lines (Tab. II).

Increase in VA was not statistically significant in the subgroup of 20 eyes ($p>0.05$).

During the study period mean IOP was significantly higher with respect to the baseline as shown in Table I. IOP was higher than 21 mmHg in 5 (16.7%), 9 (30%),

and 7 (23.3%) of the 30 study eyes at 1, 3, and 6 months follow-up visit. Of the 7 eyes with IOP higher than 21 mmHg at 6 months, IOP could be normalized adding a carbonic anhydrase inhibitor (dorzolamide) to the beta-blocker in 3 eyes. In four eyes of two patients IOP exceeded 40 mmHg and could not be compensated by medical therapy. These patients underwent uncomplicated filtrating surgery and IOP was normalized. Postoperative infectious endophthalmitis did not occur in any of the study eyes. Mild increase in cataract formation was observed in three patients; however, no grading or estimation of the impact of cataract formation on final visual acuity were assessed in this study.

DISCUSSION

DME is the most common cause of visual loss in patients with diabetes mellitus (1, 7-9). The ETDRS (8) demonstrated the beneficial effect of laser photocoagulation on preventing visual loss in eyes with diffuse DME. However, macular edema may persist in some eyes despite laser treatment. Moreover, laser photocoagulation may result in some complications such as accidental photocoagulation of the fovea, choroidal neovascularization, and submacular fibrosis (9, 10). To date, numerous reports demonstrated that triamcinolone acetonide has no known toxicity when injected in vitrectomized or nonvitrectomized eyes (11-13). It is accepted that in DME there is a breakdown of the blood–retina barrier, and that prostaglandins and VEGF may play a part in this process (14). Both prostaglandins and VEGF might be inhibited by corticosteroid (14, 15). In our study, we found a significant improvement in VA and a significant decrease in CMT at 6 months follow-up. Further analysis of VA in the subgroup of 20 eyes with a mean follow-up of 10.1 months still showed an improvement in VA although not statistically significant. This last result could be considered a trend toward decrease in VA for follow-up longer than 6 months. Our results are in line with

TABLE I - MEAN + SD EARLY TREATMENT DIABETIC RETINOPATHY STUDY LOGMAR VISUAL ACUITY (VA), CENTRAL MACULAR THICKNESS (CMT), AND INTRAOCULAR PRESSURE (IOP) OF 30 EYES BEFORE AND AFTER INTRAVITREAL INJECTIONS OF TRIAMCINOLONE ACETONIDE

	Baseline	1 mo.	3 mo.	6 mo.
VA	0.544 ± 0.2660	436 ± 0.290 (p=0.001)	0.432 ± 0.277(p=0.001)	0.453 ± 0.294 (p=0.006)
CMT	417.3 ± 142.9	277.3 ± 73.9 (p<0.0001)	279.6 ± 94.4 (p<0.0001)	298.4 ± 107.9 (p=0.002)
IOP	15.13 ± 1.48	18.26 ± 2.72 (p<0.0001)	20.07 ± 4.28 (p<0.0001)	20.4 ± 6.18 (p<0.0001)

TABLE II - FREQUENCY DISTRIBUTION OF CHANGES IN VISUAL ACUITY FROM BASELINE BY FOLLOW-UP VISIT IN 30 EYES AFTER INTRAVITREAL INJECTION OF TRIAMCINOLONE ACETONIDE

	1 mo. (%)	3 mo. (%)	6 mo. (%)	Last follow-up, n = 20 (%)
≥3-line increase	5 (16.5)	6 (20)	6 (20)	3 (15)
No change	8 (26.5)	7 (23)	9 (30)	5 (25)
≥1-line increase	17 (57)	11 (37)	17 (57)	10 (50)
≤ 3-line decrease	0	1 (3)	1 (3)	4 (20)

TABLE III - MEAN ± SD LOGMAR VISUAL ACUITY (VA) AND INTRAOCULAR PRESSURE (IOP) OF 20 EYES BEFORE AND AFTER INTRAVITREAL INJECTIONS OF TRIAMCINOLONE ACETONIDE

	Baseline	Last follow-up (mean 10.1 months)
VA	0.499 ± 0.252	0.501 ± 0.321 (p>0.05)
IOP	15.15 ± 1.73	20.3 ± 6.3 (p<0.0001)

other authors and confirm for the first time that this treatment improves vision in this clinical situation or reduces foveal thickness (16). To date, IVTA has been used in the management of diffuse DME refractory to laser photocoagulation (4, 5, 17-19). Recently, Ozkiris used IVTA as primary treatment in patients with diffuse DME (20). The authors found that 85.4% of eyes improved VA with a mean of 3.1, 4.2, and 4.1 Snellen lines at 1-, 3-, and 6-month follow-up intervals, respectively, while VA was unchanged in the remaining 14.5% of eyes. Comparing our results with Ozkiris' study (20), one could argue that we had a less successful rate of VA improvement at the follow-up intervals (1.1, 1.06, 0.93 lines vs. 3.1, 4.2, and 4.1 lines at 1, 3, and 6 months, respectively) and overall a lower percentage (57% vs. 85%) of eyes whose VA increased at the 6-month follow-up visit. This is probably the consequence of the different methodology in measuring VA (ETDRS vs. Snellen charts) and different baseline logMar VA values (0.544±0.266 vs.1.17±0.20). In the present case series we did not take into consideration the medical history, which could affect negatively the macular thickness (21, 22). Elevation of IOP in our study deserves particular attention. We would be expected to observe a relatively small number of eyes whose IOP elevation was above 21 mmHg compared to other studies in which patients were left with no therapy until IOP did not reach 21 mmHg. Particular concern in our case series must be addressed to the two patients who needed a filtrating surgery about 6 months after IVTA injection in both eyes in order to normalize IOP. It is interesting to have two bilateral cases of intractable glaucoma. Possible reasons could be the dose of the drug we used or corticosteroid-induced ocular hypertension. Fifty percent of the patients treated with IVTA by Massin et al (19) had IOP values that exceeded 25 mmHg and they were all controlled by a single antiglaucomatous drug. Jonas et al (16, 23, 24) did not observe any intractable glaucoma in eyes with diffuse DME treated with one or more intravitreal injections of 25 mg triamcinolone acetonide. However, the same authors reported an overall incidence of glaucomatous filtrating surgery of about 1% (25-27). Further studies should be addressed to the exact mechanism for intravitreal triamcinolone to induce increase in IOP and if this increase is dose dependent.

Our study has several limitations. First, the follow-up time was relatively short, although visual and anatomic responses were apparent during the follow-up time. Second, this study has no control group, but it can be argued that the enrolled eyes serve as their own controls because the pre- and post-treatment visual acuities and CMT values of the same patients were compared.

In conclusion, in the present study, with a prospective, consecutive, non-comparative interventional case series study design, an intravitreal injection of triamcinolone resulted in an improvement in VA and CMT in patients with previously untreated diffuse DME. Limitations of these treatments include the risk of intractable IOP. Further studies should investigate if alternative and easily reversible forms of sustained drug delivery devices containing steroids may be an interesting alternative and which is the minimal dose ensuring the longest action with the least side effects (28-31).

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REFERENCES

1. Klein R, Klein BE, Moss SE. Visual impairment in diabetes. Ophthalmology 1984; 91: 1-9.
2. Early Treatment Diabetic Retinopathy Study Research Group. Photocoagulation for diabetic macular edema. Early Treatment Diabetic Retinopathy Study report number 1. Arch Ophthalmol 1985; 103: 1796-806.
3. Lee CM, Olk RJ. Modified grid laser photocoagulation for diffuse diabetic macular edema: long-term visual results. Ophthalmology 1991; 98: 1594-602.
4. Martidis A, Duker JS, Greenberg PB, et al. Intravitreal

triamcinolone for refractory diabetic macular edema. Ophthalmology 2002; 109: 920-7.
5. Holladay JT. Proper method for calculating average visual acuity. J Refract Surg 1997; 13: 88-391.
6. Jonas JB, Kreissig I, Sofker A, Degenring RF. Intravitreal injection of triamcinolone for diffuse diabetic macular edema. Arch Ophthalmol 2003; 121: 57-61.
7. Ciulla TA, Amador AG, Zinman B. Diabetic retinopathy and diabetic macular edema: pathophysiology, screening and novel therapies. Diabetes Care 2003; 26: 2653-64.
8. Early Treatment Diabetic Retinopathy Study Research Group. Treatment techniques and clinical guidelines for photocoagulation of diabetic macular edema. ETDRS report number 2. Ophthalmology 1987; 94: 761-74.
9. Lewis H, Schachat AP, Haimann MH, et al. Choroidal neovascularization after laser photocoagulation for diabetic macular edema. Ophthalmology 1990; 97: 503-10; discussion 510-1.
10. Han DP, Mieler WF, Burton TC. Submacular fibrosis after photocoagulation for diabetic macular edema. Am J Ophthalmol 1992; 113: 513-21.
11. Machemer R, Sugita G, Tano Y. Treatment of intraocular proliferations with intravitreal steroids. Trans Am Ophthalmol Soc 1979; 77: 171-80.
12. McCuen BW II, Bessler M, Tano Y, et al. The lack of toxicity of intravitreally administered triamcinolone acetonide. Am J Ophthalmol 1981; 91: 785-8.
13. Kivilcim M, Peyman GA, El-Dessouky ES, Kazi AA, Cheema R, Hegazy H. Retinal toxicity of triamcinolone acetonide in silicone-filled eyes. Ophthalmic Surg Lasers 2000; 31: 474-8.
14. Schleimer RP. An overview of glucocorticoid anti-inflammatory actions. Eur J Clin Pharmacol 1993; 45 (Suppl): S3-7; discussion S43-4.
15. Wilson CA, Berkowitz BA, Sato Y, et al. Treatment with intravitreal steroids reduces blood-retina barrier breakdown due to laser photocoagulation. Arch Ophthalmol 1992; 110: 155-9.
16. Jonas JB, Degenring RF, Kamppeter BA, Kreissig I, Akkoyun I. Duration of the effect of intravitreal triamcinolone acetonide as treatment for diffuse diabetic macular edema. Am J Ophthalmol 2004; 138: 158-60.
17. Ciardella A P, Klancnik J, Schiff W, Barile G, Langton K, Chang S. Intravitreal triamcinolone for the treatment of refractory diabetic macular oedema with hard exudates: an optical coherence tomography study. Br J Ophthalmol 2004; 88: 1131-6.
18. Sutter FKP, 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: 2044-9.
19. 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: 218-24.
20. Ozkiris C, Evereklioglu K, Erkiliç N, Tamçelik E, Mirza. Intravitreal triamcinolone acetonide injection as primary treatment for diabetic macular edema. Eur J Ophthalmol 2004; 14: 543-9.
21. Bresnick GH. Diabetic macular edema: a review. Ophthalmology 1986; 93: 989-97.
22. Stratton IM, Kohner EM, Aldington SJ, et al. KPDS Group. UKPDS 50: risk factors for incidence and progression of retinopathy in type II diabetes over 6 years from diagnosis. Diabetologia 2001; 44: 156-63.
23. Jonas JB, Degenring R, Kreissig I, Akkoyun I. Safety of intravitreal high-dose reinjections of triamcinolone acetonide. Am J Ophthalmol 2004; 138: 1054-5.
24. Kreissig I, Degenring RF, Jonas J. Diffuse diabetic macular edema and intraocular pressure after intravitreal triamcinolone acetonide. Ophthalmologe 2004; 13: 153-7.
25. Jonas J B, Kreissig I, Degenring R. Treatment of edematous, proliferative and neovascular diseases by intravitreal triamcinolone acetonide. Klin Monatsbl Augenheilkd 2003; 220: 383.
26. Jonas J, Akkoyun I, Budde WM, Kreissig I, Degenring RF. Intravitreal reinjection of triamcinolone for exudative age-related macular degeneration. Arch Ophthalmol 2004; 122: 218-22.
27. Jonas JB, Kreissig I, Degenring R. Intraocular pressure after intravitreal injection of triamcinolone acetonide. Br J Ophthalmol 2003; 87: 24-7.
28. Behar-Cohen F. Drug delivery to target the posterior segment of the eye. Med Sci (Paris) 2004; 20: 701-6.
29. Eljrrat-Binstock E, Raiskup F, Frucht-Pery J, Domb AJ. Hydrogel probe for iontophoresis drug delivery to the eye. J Biomater Sci Polym Ed 2004; 15: 397-413.
30. Parkinson TM, Ferguson E, Febbraro S, Bakhtyari A, King M, Mundasad M. Tolerance of ocular iontophoresis in healthy volunteers. J Ocul Pharmacol Ther 2003; 19: 145-51.
31. Frucht-Pery J, Mechoulam H, Siganos CS, Ever-Hadani P, Shapiro M, Domb A. Iontophoresis-gentamicin delivery into the rabbit cornea, using a hydrogel delivery probe. Exp Eye Res 2004; 78: 745-9.