European Journal of Ophthalmology / Vol. 14 no. 6, 2004 / pp. 543-549

Intravitreal triamcinolone acetonide injection as primary treatment for diabetic macular edema

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PURPOSE. *To evaluate the effectiveness of intravitreal triamcinolone injection on the course of diabetic macular edema.*
METHODS. *Forty-eight eyes of 48 diabetic patients were treated with 8 mg of intravitreal triamcinolone injection as the primary therapy for diabetic macular edema. The main outcome measures included best-corrected visual acuity, fundus fluorescein angio- graphy, macular edema map values of Heidelberg Retinal Tomograph II (HRT II), and intraocular pressures before and after intravitreal injection.*
RESULTS. *The visual acuity increased in 41 of 48 eyes (85.4%) during a mean follow-up time of 7.5 months. The mean baseline best-corrected logMAR (logarithm of minimal angle of resolution) value for visual acuities of the patients before intravitreal triamcinolone injection was 1.17±0.20. After treatment, it was 0.85±0.29 at 1 month, 0.73±0.30 at 3 months, and 0.74±0.31 at 6 months, and the differences were significant when compared with baseline values (for each, p<0.001). The mean edema map values significantly decreased by 36% at the 6-month examinations when compared with preinjection values (p<0.001). Average intraocular pressure rose 24.3%, 29.1%, and 11.8% from baseline at the 1-, 3-, and 6-month follow-up intervals. Intraocular pressure elevation exceeding 21 mmHg was observed in 8 of 48 eyes (16.6%), but was controlled with topical antiglaucomatous medications in all eyes.*
CONCLUSIONS. *Intravitreal triamcinolone application provides significant improvement in visual acuity of diabetic patients and clinical course of macular edema, and may therefore be a promising approach in the primary treatment of diabetic macular edema. (Eur J Ophthalmol 2004; 14: 543-9)*

KEY WORDS. *Intravitreal triamcinolone, Diabetic macular edema, Primary treatment*

Accepted: June 23, 2004

INTRODUCTION

Vascular changes in diabetic retinopathy are associated with increased permeability, lipid exudation, and macular edema. Leakage resulting in macular edema is the most common sight-threatening complication in diabetic patients (1-6). Although a breakdown of the inner blood-retinal barrier is accepted, the exact pathophysiologic mechanisms responsible for this disruption remain uncertain in diabetic macular edema (DME). The 3-year risk of moderate visual loss due to macular edema was 32% in the Early Treatment Diabetic Retinopathy Study (ETDRS). Focal macular laser photocoagulation has been shown to be effective in

 1120-6721/543-07$15.00/0

the treatment of DME in a large prospective multicenter randomized clinical trial of ETDRS (7). However, some treated eyes may be resistant to laser photocoagulation or else efficient laser treatment could not be performed due to diffuse macular edema. Therefore, the failure of laser photocoagulation in these eyes has prompted interest in other treatment modalities such as pars plana vitrectomy (8, 9) or treatment with protein kinase C inhibitors (10).

Triamcinolone acetonide has been used for intravitreal injection in vitrectomized (11) and nonvitrectomized eyes (12) and shown to reduce breakdown of the inner blood-retinal barrier and stabilize it (13). Although intravitreal triamcinolone (IVT) injection has recently been shown to be effective in macular edema of various etiologies (14-19), there are few studies showing the beneficial effect of IVT in DME (20-22). Therefore, the present study investigated the efficacy of IVT injection for primary treatment of DME by using Heidelberg Retinal Tomograph II (HRT II).

PATIENTS AND METHODS

Forty-eight eyes of 48 diabetic patients who underwent IVT injection as the primary treatment for DME were included in the present study. There were 29 women and 19 men, and the mean age of the patients was 58.4±7.8 years (range, 42-75 years). All patients had macular edema with hyperfluorescent leakage on fundus fluorescein angiography. The mean duration of DME was 8.8±4.3 months (range, 3-19 months). A detailed history of medication was obtained, and the patients were excluded from the study if they had uncontrolled systemic hypertension, severe renal dysfunction, nephrotic syndrome, dysproteinemias, or were receiving vasoactive drugs or antioxidant.

Before IVT injection, some eyes had received peripheral scatter laser photocoagulation to ablate ischemic areas or neovascularization, but no eyes received focal laser photocoagulation for DME. Intravitreal injection of triamcinolone acetonide (8 mg/0.2 ml) was offered as the first treatment of DME. All patients were fully informed about the experimental character of the treatment and informed consent was obtained from each patient. The study followed the tenets of Declaration of Helsinki. Baseline parameters were documented including best-corrected visual acuity, edema map values of HRT II, and intraocular pressure (IOP). Best-corrected visual acuity for each eye was ascertained before IVT applications, and then all eyes were tested with the same correction throughout the follow-up period. The proper average visual acuity was computed by converting the value to the LogMAR equivalent, and taking the average of the LogMAR values as described by Holladay (23). All statistical calculations were performed using LogMAR values for visual acuity. IVT injections were performed by the same surgeon (A.Ö.) under topical anesthesia. The standard, commercially available preparation of triamcinolone acetonide (Kenacort-A, Bristol-Myers Squibb, New York, NY) in a concentration of 40 mg/mL was used. First, the eye was anesthetized with topical instillation of proparacaine hydrochloride 0.5% and lidocaine 4%. The lid was prepped with povidone-iodine 5% applied directly to the eye, and triamcinolone acetonide was injected into the anterior vitreous 3.5 mm posterior to the limbus in pseudophakic eyes and 4.0 mm posterior to the limbus in phakic eyes with a tuberculin syringe and 27-gauge needle after a paralimbal paracentesis had been performed to decrease the volume of the globe. A cotton-tipped applicator was applied at the injection site immediately after the needle was removed to prevent drug egression from the needle track. Indirect ophthalmoscopy was used to confirm proper intravitreal localization of the suspension and perfusion of the optic nerve head. Topical ciprofloxacin drops were applied, and the patient was instructed to sit upright to ensure that the drug settled inferiorly. The IOP was measured 5 minutes afterwards.

The eyes were examined after 1 week and every 4 weeks thereafter unless IOP spikes required more frequent examinations. IOPs were measured by Goldmann applanation tonometer. Response to the treatment was monitored by visual acuity assessment, fundus fluorescein angiography, and HRT II. Potential corticosteroid- and injection-related complications were also recorded, if present.

The analysis of macular edema was performed using the HRT II Macula edema module. Edema map value of HRT II was used to evaluate the changes at the macula after IVT injection. The HRT II is a confocal laser scanning system that requires a series of optical section images at different locations of the focal plane. Technical details of the instrument have been

described elsewhere (24). The patient's macula was focused on the monitor screen by adjusting the location of the focal plane, the best focus being directly related to the subject's refractive error. The 670 nm wavelength diode laser was used to image the macula using a 15° by 15° field of view. The total scan depth was adjusted according to the thickness of the structure to be analyzed from 0.50 to 4.00 mm.

Statistical analysis

Results are presented as means ± SD. Statistical evaluation of the data was performed with two-way analysis of variance. A difference was considered statistically significant when p value was lower than 0.05.

RESULTS

The mean visual acuities, edema map values, and IOPs of the patients before and after IVT injection are presented in Table I. There were statistically significant differences in visual acuity after IVT injection when compared with pretreatment values (for each, $p<0.001$). After a mean follow-up period of 7.5 months, visual acuity increased in 41 of 48 eyes with a mean of 3.1±2.1, 4.2±2.3, and 4.1±2.4 Snellen lines at the 1-, 3-, and 6-month follow-up intervals, respectively. Visual acuity remained unchanged in seven eyes.

All eyes showed a reduction in macular edema map value after IVT injection. Mean edema map value decreased from a baseline value of 2.5±0.5 to a value of 1.6±0.3 at 6-month control examinations. Mean reduction of edema map values at 1, 3, and 6 months was 36%, 44%, and 36%, respectively, and the differences were statistically significant when compared with preinjection values (for each, $p<0.001$).

Average IOP rose 24.3%, 29.1%, and 11.8% from baseline at 1, 3, and 6 months, respectively. IOP elevation exceeding 21 mmHg was observed in 8 of 48 eyes (16.6%), but IOPs were under control with topical antiglaucomatous medications. After IVT injection, one eye exhibited cataract progression at 5 months and one eye developed a clinical picture simulating endophthalmitis with anterior chamber cellular reaction and vitritis. Visual acuity of the patient dropped to hand movements and cultures were negative for any organisms. After treatment with topical antibiotic and corticosteroid, the inflammation resolved in 2 weeks with recovery to visual acuity of 20/200.

DISCUSSION

DME is the most important cause of visual acuity impairment in patients with diabetes mellitus and may be localized or diffuse. The prognosis of diffuse macular edema is poorer when compared with focal edema (1, 5, 6). Although the exact pathophysiologic mechanisms responsible for DME remain uncertain, the disruption of the inner blood-retinal barrier is known to be associated with metabolic alterations affecting the retinal epithelium or retinal vascular endothelium (5, 6). The ETDRS (7) 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 (6). Moreover, laser photocoagulation may result in some complications such as choroidal neovascularization (25), exudative retinal detachment (26), and submacular fibrosis (27). Therefore, new approaches with promising results are needed in the treatment of DME.

TABLE I - MEAN ± SD LOGMAR VALUE FOR THE VISUAL ACUITIES, EDEMA MAP (EM) VALUES, AND IOP OF THE PATIENTS BEFORE AND AFTER INTRAVITREAL TRIAMCINOLONE INJECTION

Time	LogMAR value	EM value	IOP, mmHg
Preinjection	1.17±0.20	2.5±0.5	14.4±2.5
1 mo	0.85±0.29	1.6±0.4	17.9±4.3
3 mo	0.73±0.30	1.4±0.3	18.6±3.0
6 mo	0.74±0.31	1.6±0.3	16.1±2.9

IOP = Intraocular pressure

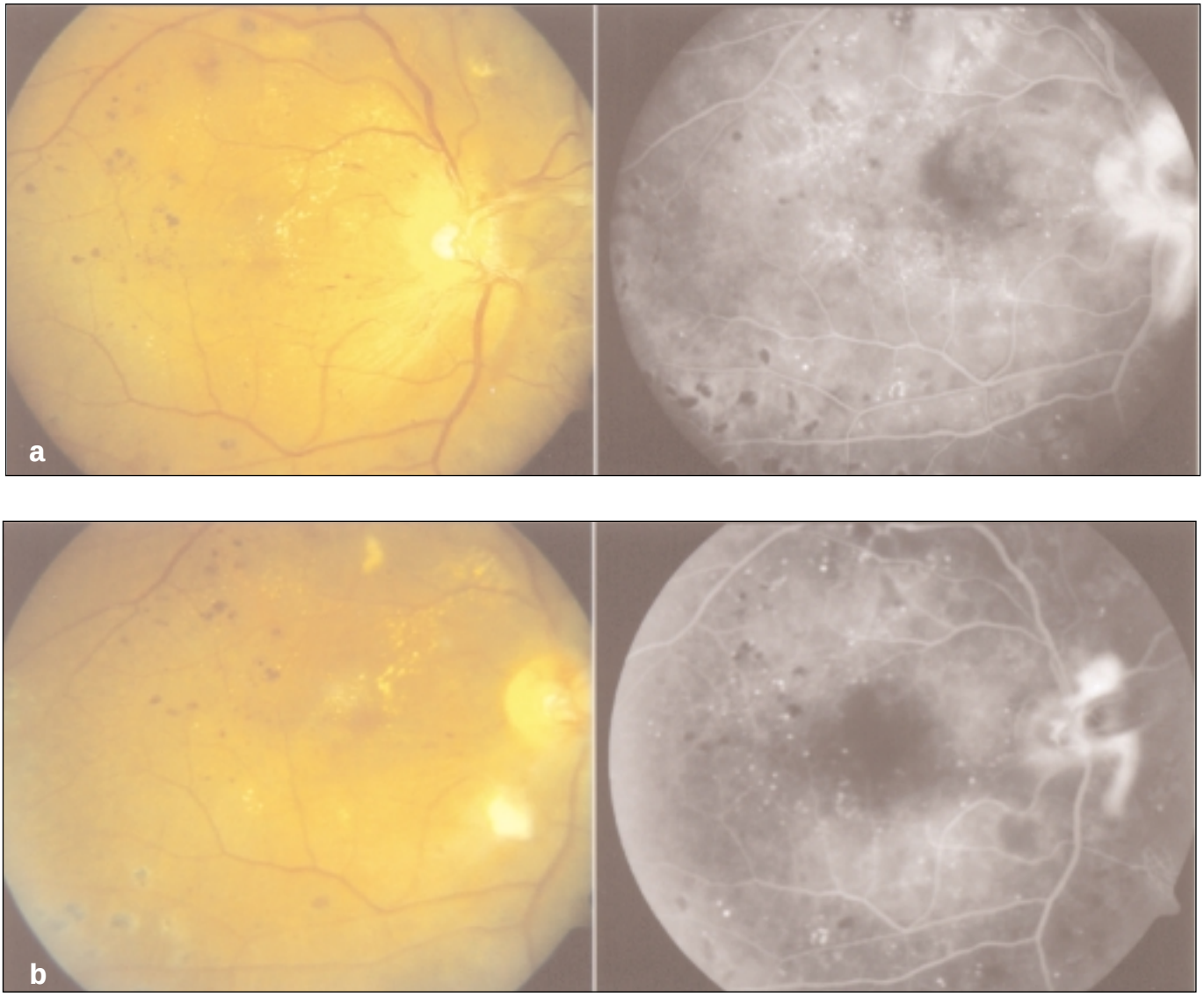

Fig. 1 - *Color fundus photograph and late phase of fundus fluorescein angiography of a patient.* **a)** *Before injection;* **b)** *Three months after intravitreal triamcinolone injection. Note the decrease in fluorescein leakage after treatment.*

Corticosteroids have been used to reduce the breakdown of the inner blood-retinal barrier and extravasation from leaking blood vessels. They inhibit the release of arachidonic acid from cell membranes, the precursor of prostaglandins, which are well-known mediators of vascular permeability (28). So, corticosteroids contribute to the integrity of the inner blood-retinal barrier, reduce extravasation from leaking blood vessels, and have beneficial effect in the prevention and treatment of macular edema (29). The safety of corticosteroids has been confirmed by previous animal studies and human trials (11, 30). Triamcinolone acetonide is a long-acting corticosteroid with no known toxicity when injected intravitreally in vitrectomized and nonvitrectomized eyes (11, 12). IVT injection has recently been reported to be effective in macular edema of various etiologies (14-22).

Results of our study suggest that IVT injection appears to be effective in the primary treatment of DME. In our study, 41 eyes showed a significant improve-

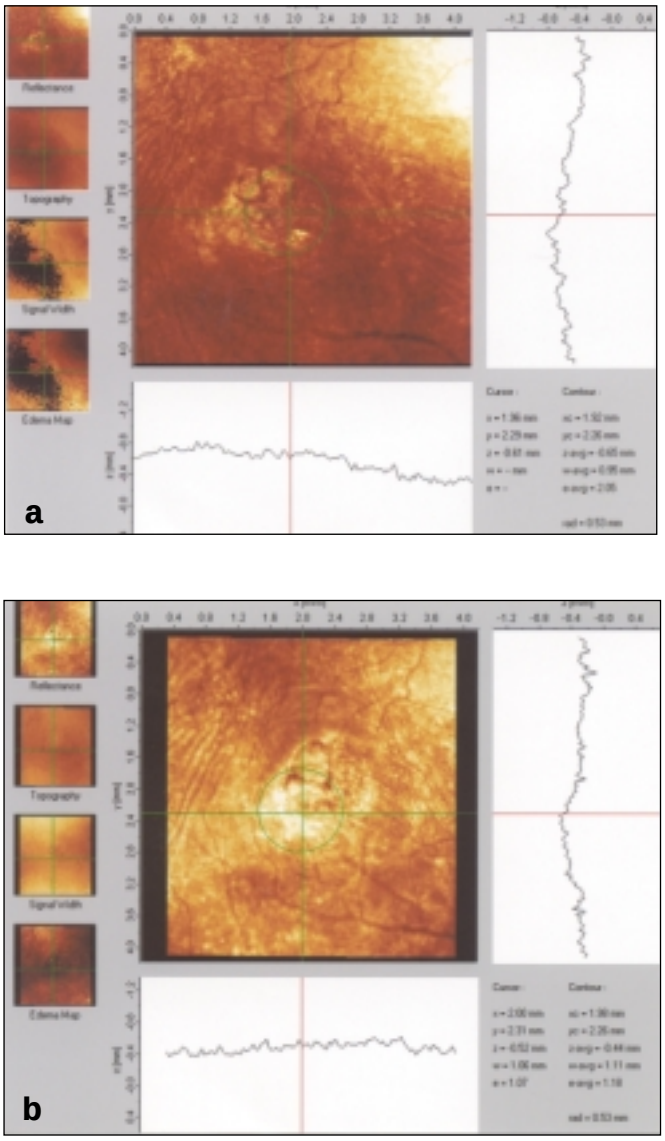

Fig. 2 - *Note the decrease in edema map values.* **a)** *Before treatment;* **b)** *Three months after intravitreal triamcinolone injection.*

ment in visual acuity with a decrease in fluorescein leakage on fundus fluorescein angiography (Fig. 1A, 1B). Edema map values of HRT II showed a reduction in all patients (Fig. 2A, 2B). The results of our study confirm previous reports showing the beneficial effect of IVT in the treatment of DME. In a recent study with an intravitreal injection of 4 mg triamcinolone, Martidis et al (21) found an improvement in visual acuity of 2.4, 2.4, and 1.3 Snellen lines at the 1-, 3-, and 6-month follow-up intervals in patients with DME that fails to respond laser treatment. Mean reduction in central macular thickness was 55%, 57.5%, and 38%, respectively, during these same intervals. Jonas et al (22) reported that visual acuity of the patients was found to improve from 0.12±0.08 at baseline of the study to a maximum of 0.19±0.14 during the follow-up time after intravitreal injection of 25 mg of triamcinolone. In the present study, visual acuity increased with a mean of 3.1, 4.2, and 4.1 Snellen lines at the 1-, 3-, and 6-month follow-up intervals, respectively. This high success in our study may be explained by performing IVT injection as the primary treatment of DME or a short duration of DME in our patients or using of 8 mg of triamcinolone.

After this procedure, injection-related complications such as endophthalmitis, vitreous hemorrhage, and retinal detachment may occur. In our study, one eye exhibited cataract progression and one eye developed a picture simulating endophthalmitis (pseudoendophthalmitis), which completely resolved in 2 weeks after topical and systemic applications of antibiotics and corticosteroids. Pseudoendophthalmitis was characterized by anterior chamber and vitreous reaction without red eye or pain. Vitreous tap showed no evidence of an endophthalmitis; cultures were negative for any organisms. This may be explained by an acute toxic reaction to the vehicle of triamcinolone, or dispersion of triamcinolone particles throughout the vitreous. Such endophthalmitis-like reaction after IVT was reported by Sutter and Gillies (31) in four eyes, by Nelson et al (32) in seven eyes, and by Roth et al (33) in seven eyes, which resolved without specific treatment. IOP elevation usually returns to normal levels with antiglaucomatous treatment as shown in our study. Similar IOP elevations were observed by Martidis et al (21) using 4 mg of triamcinolone acetonide and Jonas et al (22) using 25 mg of triamcinolone acetonide.

The present study has some differences from previous studies. First, the dosage of IVT injected as the primary treatment of macular edema. Martidis et al (21) used 4 mg triamcinolone acetonide in the treatment of DME that fails to respond to at least two previous sessions of laser photocoagulation. Jonas et al (22) used 25 mg of triamcinolone for treatment of diffuse DME. Second, macular edema was evaluated by HRT II before and after IVT injection, and reduction in edema map values was demonstrated as the ef-

fectiveness of IVT application. The present study has several limitations. First, the follow-up time was relatively short, but 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 edema map values of the same patients were compared. Third, visual acuity was measured on a Snellen chart, as opposed to the more standardized and accepted ETDRS chart. However, all eyes were tested with the same correction throughout the follow-up period.

In conclusion, this clinical study demonstrated that IVT application is an effective approach with promising results for the primary treatment of DME. IVT provides rapid resolution of macular edema and improvement in visual acuity. However, further studies are needed to obtain the long-term results of such application.

ACKNOWLEDGEMENTS

The authors thank Öznur Köse, Buket Yancar, and Yaşar Özsoy for their technical assistance.

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