Efficacy of intravitreal triamcinolone after or concomitant with laser photocoagulation in nonproliferative diabetic retinopathy with macular edema

ERDINC AYDIN¹, HELIN DENIZ DEMIR¹, HUSEYIN YARDIM², UNAL ERKORKMAZ²

¹Department of Ophthalmology
²Department of Biostatistics, Gaziosmanpasa University Faculty of Medicine, Tokat - Turkey

INTRODUCTION

Diabetic macular edema (DME) is the primary cause of visual deterioration and affects approximately 29% of diabetic patients with more than 20 years duration of disease (1). The Early Treatment Diabetic Retinopathy Study group (ETDRS) reported that focal laser photocoagulation alleviated moderate visual loss in eyes with clinically significant macular edema (CSME) by 50% (2). However, 12% of treated eyes still showed a loss of two or more letters (on the ETDRS chart) at the end of 3 years. Some reports have asserted that diffuse DME is refractory to macular photocoagulation (3). Intravitreal triamcinolone acetonide (IVTA) is reported to generate favorable results in the treatment of diffuse macular edema (4, 5). However, the main limitation of IVTA is the recurrence of DME, which de-
develops after a relatively short duration of action. It has been also reported that the difference between the central macular thickness of IVTA-injected eyes and control eyes were no longer different after 6 months due to the recurrence of macular edema (5). On the other hand, repeated administration of IVTA might be an option but the effectiveness of this approach has been under debate (6).

Although IVTA has been recently familiarized as a novel trend for the treatment of diffuse macular edema refractory to grid photocoagulation, few reports on the effects of macular laser treatment performed following IVTA have been published (7, 8). To our knowledge, comparative reports on efficacy of macular grid laser photocoagulation concomitant with IVTA application in nonproliferative diabetes have not been reported. In this study, we explored whether macular grid laser photocoagulation 3 weeks after IVTA or macular grid laser photocoagulation concomitant with IVTA application might be useful in the improvement of CSME and maintenance of vision.

METHODS

This prospective, interventional, comparative clinical study included 49 eyes of 49 patients with nonproliferative diabetic retinopathy (NPDR) (moderate and severe) and CSME. Eyes with only focal macular leakage, hard exudates, macular ischemia, taut posterior hyaloid, epiretinal membrane, unclear optic media, glaucoma, cataracts (grade 3 and 4), and previous surgery or grid laser photocoagulation were excluded. All patients underwent fluorescein angiography at baseline and during the follow-up. The presence of CSME and the severity of diabetic retinopathy were assessed by two independent retina specialists. Cases of inconvenience in assessing the type of macular edema or severity of the proliferative disease were excluded. The degree of retinopathy met the criteria of moderate and severe NPDR in the ETDRS grading system in all eyes (9). All patients had type 2 diabetes mellitus. Seven patients (14.2%) had a history of systemic hypertension and were taking oral systemic antihypertensive agents. The study was designed and performed in accordance with the ethical standards of the Declaration of Helsinki. All patients provided informed consent after the aim of the study and the possible risks were fully explained.

An intravitreal injection of 4 mg of triamcinolone acetone (TA) (Kenacort-A, Bristol-Myers Squibb, Princeton, NJ) was carried out in the operating room under sterile conditions (in Group 1, 3 weeks before the laser procedure; in Group 2, immediately after macular laser photocoagulation; in Group 3, only IVTA application). A vial of TA was used without any filtration or purification procedure and contained benzyl alcohol, sodium chloride, polysorbate 80, and carboxymethylcellulose. After sterilization of the peripalpebral region and conjunctiva with 5% povidone-iodine solution, proparacaine was instilled into the conjunctival fornix for topical anesthesia. The injections were performed through the pars plana in the inferior temporal quadrant (4 mm post-limbus in phakics; 3.5 mm post-limbus in pseudophakics) using a 27-gauge needle. The injection of TA into the central vitreous cavity was carefully managed, to prevent dispersion of suspended particles in front of the anterior hyaloid or posterior to the lens. Then, one drop of 5% povidone-iodine was applied and the eye was occluded with an antibiotic ointment. A topical antibiotic therapy 5 times a day was continued for the next 5 days following the injection.

The eyes with only TA injection served as controls (Group 3). The study eyes (in Groups 1 and 2) underwent macular grid laser photocoagulation (MP) according to ETDRS guidelines sparing the papillomacular bundle (10). Microaneurysms located between 500 and 3000 µm from the center of the macula were treated with focal laser photocoagulation. The grid laser pattern consisted of gray to medium-white laser burns placed over the area of diffuse capillary leakage. The spot size, power, and time settings were 50–200 µm, 100–220 mW, and 0.1–0.15 s. We used a solid-state laser (Zeiss Corp., CA), a green laser at a 532 nm wavelength, for both MP.

Primary outcome measures were best-corrected visual acuity (VA) and the grade of the macular edema. A secondary outcome measure was the rate of complications (intraocular pressure [IOP] increase over 21 mmHg, cataract progression determined by slit-lamp biomicroscopy, endophthalmitis, and vitreous hemorrhage).

The best-corrected distance VA was measured on a Snellen chart at the end of the first, third, and sixth months. The grade of macular edema in fluorescein
angiography was determined as follows: complete resolution where there was no leakage into the macular area; decrease in macular edema where the leakage level was lower than the pretreatment level; and recurrence of macular edema where the leakage was the same as or more than the pretreatment level. Cases with no retinal thickening under biomicroscopic macular evaluation were considered as cases without macular edema, even when fluorescein angiography disclosed persisting leaking sites. Color fundus photographs and fluorescein angiography were obtained using a TCR-50IX fundus camera (Topcon Corp., Japan). Possible complications such as increased IOP, cataract progression, and endophthalmitis were noted.

**Statistical analysis**

For statistical analysis, the mean geometric VAs and standard deviations were calculated by converting Snellen VA measurements to decimal units. Variables were determined to have normal distribution by the Kolmogorov-Smirnov test, and one-way analysis of variance (ANOVA) was used in the comparisons of groups. The comparison of differences within groups was performed by repeated measures ANOVA. For categorical variable (gender), chi-square tests were used to find out differences between groups. A p value of < 0.05 was defined as statistically significant. Statistical analyses were performed using the Statistical Package for Social Sciences software (SPSS version 15, SPSS Inc., Chicago, IL).

**RESULTS**

There were 20 men and 29 women. The mean age of the patients was 59.2±8.7 years (range 42–73 years) in Group 1, 61.8±8.2 years (range 51–75 years) in Group 2, and 61.6±7.1 years (range 51–74 years) in Group 3. The mean duration of diabetes was 12.1±6.7 years (range 1–30 years) in Group 1, 15.0±4.1 years (range 5–20 years) in Group 2, and 13.9±6.3 years (range 2–25 years) in Group 3 (Tab. I).

The mean follow-up time was 6 months in all groups. In the study groups (Groups 1 and 2), the mean VA improved from 0.17±0.09 at baseline to 0.24±0.15, 0.27±0.16, and 0.28±0.15 (F=2.375, p=0.114) and from 0.19±0.08 at baseline to 0.14±0.08, 0.15±0.09, and 0.14±0.08 (F= 2.288, p=0.141) at the first, third, and sixth month of the follow-up interval, respectively (Tab. II, Fig. 1). The macular edema was unchanged in 5 eyes and decreased in 12 eyes in Group 1. In Group 2, macular edema was increased in 3 eyes, unchanged in 6 eyes, and decreased in 4 eyes (Figs. 3 and 4).

**TABLE I - BASELINE CHARACTERISTICS OF THREE GROUPS ENROLLED IN THE STUDY**

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=17)</th>
<th>Group 2 (n=13)</th>
<th>Group 3 (n=19)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y, mean ± SD</td>
<td>59.2±8.7</td>
<td>61.8±8.2</td>
<td>61.6±7.1</td>
<td>0.589</td>
</tr>
<tr>
<td>Male/female</td>
<td>8/9</td>
<td>5/8</td>
<td>7/12</td>
<td>0.807</td>
</tr>
<tr>
<td>Duration of diabetes mellitus, mo, mean ± SD</td>
<td>12.1±6.7</td>
<td>15.0±4.1</td>
<td>13.9±6.3</td>
<td>0.428</td>
</tr>
<tr>
<td>Fasting glucose level</td>
<td>179.1±30.4</td>
<td>181.3±31.4</td>
<td>164.1±26.3</td>
<td>0.184</td>
</tr>
<tr>
<td>Macular edema, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Decreased</td>
<td>12 (70.5)</td>
<td>4 (30.7)</td>
<td>13 (68.4)</td>
<td></td>
</tr>
<tr>
<td>Unchanged</td>
<td>5 (29.4)</td>
<td>6 (46.1)</td>
<td>6 (31.5)</td>
<td></td>
</tr>
<tr>
<td>Increased</td>
<td>—</td>
<td>3 (23.0)</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Complications, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cataract</td>
<td>1 (5.8)</td>
<td>2 (15.3)</td>
<td>1 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
<tr>
<td>Increase of IOP (&gt;21 mmHg)</td>
<td>1 (5.8)</td>
<td>1 (7.6)</td>
<td>1 (5.2)</td>
<td></td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>

**SD = standard deviation; IOP = intraocular pressure.**
line to 17.46±1.71, 16.69±1.70, and 16.23±1.73 (F=30.217, p<0.001) at the first, third, and sixth month, respectively, in Groups 1 and 2 (Tab. II, Fig. 2).

IOP exceeded 21 mmHg in 3 eyes (6.1 %) between the first and third months after the injection, which was then controlled by topical medication. Cataract progression was detected in 4 eyes (8.1%). Endophthalmitis, pseudo-endophthalmitis, or other injection-related complications were not viewed in any of the eyes (Tab. I).

In the control group (Group 3), the mean VA improved from 15.68±1.49 at the baseline to 17.05±1.87, 16.73±1.28, and 16.31±1.20 (F=4.467, p=0.018) at the first, third, and sixth month, respectively (Tab. II, Figs. 1 and 2). The macular edema remained unchanged in 6 eyes and decreased in 13 eyes in Group 3 (Fig. 5). We did not re-treat the previously treated areas of focal or diffuse leakage in
Fig. 3 - (A) Pretreatment late phase of the right eye of a 58-year-old man with diffuse clinically significant macular edema and severe nonproliferative diabetic retinopathy. Angiogram revealed diffuse vascular leakage and microaneurysms. (B) At 6th month, macular laser photocoagulation 3 weeks after intravitreal triamcinolone acetonide demonstrated reduction in macular edema and increase in visual acuity from 0.10 to 0.20.

Fig. 4 - (A) Pretreatment late phase of the right eye of a 59-year-old woman with diffuse clinically significant macular edema and severe nonproliferative diabetic retinopathy. Angiogram showed diffuse vascular leakage, microaneurysms, and few focal laser spots in posterior pole. (B) At 6th month, although macular laser photocoagulation concomitant with intravitreal triamcinolone acetonide was applied, macular edema remained persistent and visual acuity was unchanged.

Fig. 5 - Fluorescein angiography of a 75-year-old woman with diffuse macular edema before and 20 weeks after intravitreal triamcinolone acetonide. Decreased leakage and increased visual acuity from 0.10 to 0.30 are shown.
any of the eyes. At the sixth month of follow-up, 3 eyes had persistent macular edema. The persistent macular edema disappeared in 2 eyes following supplemental laser photocoagulation, but one eye developed cystoid macular edema within a month after the additional laser treatment (Tab. I).

DISCUSSION

Diabetic macular edema is characterized by intraretinal and subretinal accumulation of fluid, resulting principally from retinal vascular leakage (11). Fluorescein angiography shows microvascular obstruction and ischemia-induced disarrangements in the integrity of the inner blood–retinal barrier. Conversely, outer blood–retinal barrier damage at the level of the retinal pigment epithelium has also been speculated as a mechanism to explain the development of diffuse edema (12-14).

Previous studies have demonstrated that direct argon laser photocoagulation applied to focally leaking microaneurysms and/or a grid treatment applied to areas of diffuse macular edema results in a substantial reduction of the risk of visual loss in eyes with DME (2, 3, 15). Although the exact mechanism underlying grid photocoagulation remains a subject of debate, it may be attributable to the effects on both endothelial cells of the retinal blood vessels and the retinal pigment epithelial cells. Some authors have suggested that grid photocoagulation increases the debridement of disordered retinal pigment epithelial cells and leads to their replacement by a healthy population of cells (14). Laser-induced changes in the retinal pigment epithelium may also stimulate the repair of endothelial cells in the inner blood–retinal barrier with subsequent resolution of the macular edema (16). Grid laser photocoagulation may also work simply by destroying a certain population of photoreceptors, as eliminating high oxygen consumers may result in an increase in the level of inner retinal oxygen and a reduction in tissue vascular endothelial growth factor, which has been implicated in the development of DME (17). In diffuse DME, profound foveal thickening, retinal opacification, and fluid accumulation, predominantly in the retinal outer layers, interfere with the transmission of laser energy into the retinal pigment epithelium. Jonas et al (3) demonstrated that visual acuity decreased by 3 lines or more in 24.6% of eyes after grid-pattern laser photocoagulation for diffuse DME. In our study, we applied grid laser photocoagulation concomitant with IVTA for DME. Our results show that this type of combination therapy is not beneficial to efficiently reduce diffuse DME and improve VA.

Previous reports have demonstrated improvements in visual acuity and alleviation of diffuse macular edema after IVTA. The mechanism of action of corticosteroids in the treatment of macular edema has been well-defined. Their action may depend on their ability to inhibit the arachidonic acid pathway and down-regulate the production of vascular endothelial growth factor (14). These phenomena result in the reduction of overall vascular permeability (18, 19). Although IVTA has been reserved for DME refractory to laser photocoagulation, in some studies IVTA as a primary treatment for diffuse DME has recently been advocated due to its favorable results (5, 20-22). On the other hand, the clinical effect of intravitreal TA was found to be most prominent 1–3 months after the injection (5, 23), with the recurrence of macular edema necessitating repeated injections in a proportion of eyes (24). On the other hand, repeated IVTA may potentiate toxicity due to intraocular corticosteroids, characterized as IOP increase (25), cataract formation (26), injection-related endophthalmitis (27), and toxicity to ocular structures, including photoreceptors and retinal pigment epithelial cells (12, 28). Chan et al (6) also reported that best-corrected visual acuity (BCVA) improved after repeat injections of the more conventional dose of 4 mg of IVTA, but BCVAs were significantly worse than at the initial injection at all time points. For these reasons, we used IVTA with MP as combination therapy to prevent exacerbation of macular edema.

An interval of 3 weeks for the separation of macular grid laser treatment from IVTA was chosen empirically because this is when the therapeutic effects of IVTA were found to reach maximum level in most previous studies (4, 5). We also performed IVTA 3 weeks prior to macular grid laser treatment, and this method showed superiority to IVTA application in terms of early visual recovery.

Although the exact mechanism underlying the maintenance of improved vision and decreased diffuse DME due to grid laser treatment after IVTA was not pre-
IVTA after or concomitant with photocoagulation for macular edema

cisely identified, we consider that improvements are due to several factors. First, decreased foveal thickness after IVTA may improve the effects of grid laser photocoagulation on the photoreceptors and retinal pigment epithelia. Second, steroids might act favorably in the process of mature laser scar formation. It has been established that 2 or 3 weeks should pass for the formation of a mature laser scar, and laser treatment itself frequently induces the aggravation of macular edema or inflammation during this period (29). The presence of intravitreal steroids might exert certain protective effects against the initial deleterious events that follow grid laser treatment, and might also modulate retinal pigment epithelial remodeling after grid laser treatment. In the treatment of exudative age-related maculopathy, IVTA conducted on the same day as photodynamic therapy exerted a synergistic effect (30). For that reason, we applied macular grid photocoagulation concomitant with IVTA as an alternative treatment.

In our study, the elevation of IOP and the development of lens opacity constituted the major complications occurring in all groups. The incidence of complications among Groups 1, 2, and 3 were similar, and the rates were in accordance with those reported in previous IVTA studies (4, 26). Thus, it appeared that all complications that were attributable to intraocular triamcinolone and macular laser treatment did not cause any significant additional complications. There were some limitations to this study. Visual acuity was measured on a Snellen chart and converted to decimal unit, as opposed to the more standardized chart utilized in the ETDRS, which can affect visual comparisons. Another limitation might be that IVTA increased cataractogenesis, so the vision of patients may have been affected in the follow-up period.

In conclusion, laser treatment for macular edema should be only considered in particularly type 2 diabetes following IVTA application. In the present study, macular grid laser photocoagulation after IVTA improved visual acuity and allowed rapid resolution of macular edema and may also reduce the risk of recurrent macular edema compared with MP concomitant with IVTA or only IVTA application. IVTA can be an adjunctive therapy before macular laser photocoagulation in order to be gained early visual recovery in diabetic patients. Further trials with a longer follow-up period and larger number of patients are needed.

None of the authors has financial or proprietary interest in any method or material mentioned.

Reprint requests to:
Erdinc Aydin, MD
Department of Ophthalmology
Gaziosmanpasa University Hospital
60100 Tokat, Turkey
erdincaydin@yahoo.com

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