Original article

Intravitreal triamcinolone combined with grid laser photocoagulation for patients with cystoid macular edema and advanced diabetic retinopathy: Pilot study

J.F. Arévalo a,b,* , C.F. Fernández c , A.J. Mendoza c , R.A. García c , F.A. Arévalo c

a División de Retina, Wilmer Eye Institute, Escuela de Medicina de la Universidad de Johns Hopkins, Baltimore, MD, USA
b King Khaled Eye Specialist Hospital, Riad, Saudi Arabia
c Servicio de Retina y Vitreo, Clínica Oftalmológica Centro Caracas, Caracas, Venezuela

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ABSTRACT

Background: To determine if primary intravitreal injection of triamcinolone acetonide (TA) plus grid laser photocoagulation (GLP) is effective in treating cystoid diabetic macular edema (DME).

Methods: Prospective comparative non-randomized clinical trial. Fourteen eyes (14 patients) diagnosed with cystoid DME were treated with GLP according to the Early Treatment Diabetic Retinopathy Study (ETDRS) guidelines, plus an intravitreal injection of 4 mg of TA. A matched control group (16 eyes [16 patients]) treated with GLP was selected retrospectively from our medical records. Best-corrected visual acuity (BCVA), and quantitative change in optical coherence tomography (OCT) macular thickness were assessed.

Results: Mean follow up was 14.9 months (12 to 19 months). In 3 (21.4%) eyes BCVA increased >2 ETDRS lines, in 5 (35.7%) eyes BCVA remained the same, and BCVA decreased >2 ETDRS lines in 6 (42.8%) eyes. Central macular thickness, as measured by OCT, decreased a mean of 106.2 μm (30.2%). The difference with the control group was not statistically significant (p = 0.2). Four (28.5%) eyes developed an increase in intraocular pressure in our study group.

Conclusions: Although all of our patients showed an improvement of cystoid DME by means of OCT and fluorescein angiography, 42.8% (6 eyes) lost 2 or more lines in BCVA with primary intravitreal injection of TA plus GLP. Primary intravitreal injection of TA plus GLP may not be effective for cystoid DME at 12 months.

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* Corresponding author.
E-mail address: arevaloj@jhu.edu (J.F. Arévalo).

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Triamcinolona intravitrea combinada con fotocoagulación láser en rejilla en pacientes con edema macular quístico y retinopatía diabética avanzada: estudio piloto

Palabras clave:
Edema macular diabético quístico
Fotocoagulación láser en rejilla
Retinopatía diabética
Terapia combinada
Triamcinolona intravitrea

R E S U M E N

Objetivo: Determinar si el tratamiento inicial de inyección intravitrea de triamcinolona (TA) asociada a la fotocoagulación con láser en rejilla (FLR) es más efectivo que el tratamiento láser aislado en el edema macular diabético (EMD) quístico.

Métodos: Estudio clínico prospectivo no aleatorizado. Catorce ojos (14 pacientes) con diagnóstico de EMD quístico fueron tratados con FLR, según el protocolo del Estudio de Tratamiento Precoz de la Retinopatía Diabética (ETDRS), asociando una inyección de 4 mg de TA. Se seleccionó de forma retrospectiva un grupo control (16 ojos [16 pacientes]) tratado únicamente con FLR. Las principales medidas a analizar fueron los cambios en la agudeza visual (AV) y en el grosor del edema macular medido por tomografía de coherencia óptica (OCT).

Resultados: En el grupo tratado, la media de seguimiento fue de 14,9 meses (rango 12 a 19). La AV en tres ojos (21,4%) se incrementó > 2 líneas ETDRS, en cinco ojos (35,7%) permaneció sin cambios y en 6 ojos (42,8%) disminuyó >2 líneas ETDRS. El grosor macular central disminuyó de media 106,2 μm (30,2%). No hubo diferencias estadísticamente significativas con el grupo control, en los cambios de la AV ni en la disminución del espesor macular (p = 0,2). En 4 ojos (28,5%) hubo incremento patológico de la presión intraocular.

Conclusions: Aunque todos nuestros pacientes mejoraron anatómicamente el EMD quístico en relación con los parámetros de OCT y angiografía fluoresceínica, el 42,8% perdieron dos o más líneas de AV con el tratamiento asociado de inyección intravitrea de TA y FLR. Añadir la inyección intravitrea de TA a la FLR no resultó efectiva a los 12 meses de seguimiento para el manejo del EMD quístico.

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Introduction

Diabetic macular edema (DME) is one of the main causes of visual acuity (VA) loss in retinopathy patients. Even though the Early Treatment Diabetic Retinopathy Study (ETDRS) demonstrated moderate visual acuity loss in 50% of cases with focal macular photocoagulation, 12% of treated eyes exhibit significant vision loss of 15 or more ETDRS letters during 3 years follow-up. In addition, 24% of cases exhibited chronic macular edema in what concerns macular thickness refractory to laser photocoagulation.

Machemer and other researchers studied the possibility of injecting corticoids directly into the vitreous cavity in animal as well as human studies in specific clinical situations. Various studies have demonstrated that a single intravitreal injection of triamcinolone (TA) can be an efficient co-adjuvant treatment for exudative age-related macular degeneration, neovascular glaucoma, neovascularization of proliferative diabetic retinopathy, DME and DME secondary to venous occlusions, severe uveitis and in cases of ocular hypotony pre- ptisis bulbi.

The objective of this study is to determine whether intravitreal TA injections, combined with grid laser photocoagulation (GLP) of the macula is more efficient than isolated typical laser treatment for cystic DME.

Patients, material and methods

Authorization was obtained of the Ethics Committee as well as the signature of a specific informed consent for this prospective, nonrandomized and comparative clinical study. The study was carried out between January 2002 and March 2003 in the Retina and Vitreous Service.

Fourteen eyes (14 patients) diagnosed with cystic DME were prospectively treated initially with GLP (Green argon) in accordance with the ETDRS protocols, associating a 4 mg intravitreal injection of TA (Kenacort, Squibb & Sons, Caracas, Venezuela) immediately after applying the laser. The inclusion criteria was the presence of cystic DME defined as evidence of retinal thickening or hard exudates (without ring-shaped circular pattern) involving the center of the fovea (clinically significant DME as defined by ETDRS with biomicroscopic examination) and diffuse or cystic fluorescein leak involving the center of the macula with fluorescein angiography (FA) with at least 33% leak associated to microaneurysms. In addition, optic coherence tomography (OCT) had to demonstrate significant reflectivity reduction (cysts) in the outer retinal layers or the presence of subretinal fluid aggregation.

The exclusion criteria comprised other conditions which are known to cause macular edema such as venous branch occlusion, central retinal vein occlusion, age-related macular degeneration or previous radiation. In addition, patients (eyes) with cystic DME previously treated with intravitreal...
Table 1 - Pre-treatment clinical characteristics of the study group (14 eyes).

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Eye</th>
<th>Age (years)</th>
<th>Lens</th>
<th>Retinopathy</th>
<th>Dx of DM</th>
<th>HbA1C (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Right</td>
<td>59</td>
<td>Pseudophakic</td>
<td>PDR</td>
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<td>7.8</td>
</tr>
<tr>
<td>2</td>
<td>Left</td>
<td>63</td>
<td>Pseudophakic</td>
<td>PDR</td>
<td>5</td>
<td>8.2</td>
</tr>
<tr>
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<td>68</td>
<td>Phakic</td>
<td>NPDR</td>
<td>24</td>
<td>8.2</td>
</tr>
<tr>
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<td>Left</td>
<td>70</td>
<td>Phakic</td>
<td>PDR</td>
<td>20</td>
<td>7.7</td>
</tr>
<tr>
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<td>48</td>
<td>Phakic</td>
<td>PDR</td>
<td>12</td>
<td>8.3</td>
</tr>
<tr>
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<td>Right</td>
<td>34</td>
<td>Phakic</td>
<td>PDR</td>
<td>30</td>
<td>8.3</td>
</tr>
<tr>
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<td>Phakic</td>
<td>PDR</td>
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</tr>
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<td>PDR</td>
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</tr>
<tr>
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<td>Phakic</td>
<td>PDR</td>
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<td>8.8</td>
</tr>
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<td>65</td>
<td>Phakic</td>
<td>PDR</td>
<td>29</td>
<td>12.1</td>
</tr>
<tr>
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<td>Left</td>
<td>60</td>
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<td>NPDR</td>
<td>12</td>
<td>6.9</td>
</tr>
<tr>
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<td>Right</td>
<td>70</td>
<td>Phakic</td>
<td>NPDR</td>
<td>16</td>
<td>6.7</td>
</tr>
<tr>
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<td>Right</td>
<td>47</td>
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<td>PDR</td>
<td>20</td>
<td>11.7</td>
</tr>
<tr>
<td>14</td>
<td>Left</td>
<td>51</td>
<td>Phakic</td>
<td>PDR</td>
<td>20</td>
<td>11</td>
</tr>
</tbody>
</table>

Dx of DM: years of diabetes evolution; HbA1C: glycosylated hemoglobin; Nr.: number; NPDR: nonproliferative diabetic retinopathy; PDR: proliferative diabetic retinopathy.

Results

The pre-treatment characteristics of our study group are described in Table 1. The treatment results are described in Table 2. Panretinophotocoagulation (PRP) in 11 of the 14 eyes of the study group (78.5%) (five eyes [45.4%] before GLP + TA, six eyes [54.5%] after); and in 6 of the 16 eyes of the control group (37.5%) (four eyes [66.6%] before GLP, and in two eyes [33.3%] after). When the PRP was performed prior to laser macular treatment or intravitreal injection, a minimum period of 6 months was allowed to elapse before treating cystic DME.

The mean follow-up period in the study group was of 14.9 months (12 to 19 months). The change variability of BCVA in the study group was −0.5 lines ETDRS (range: −6 to +5 lines). In 3 eyes (21.4%) BCVA increased >2 ETDRS lines, in 5 (35.7%) it remained without changes and in 6 (42.8%) it diminished >2 ETDRS lines (Table 2).

The change variability of BCVA in the control group was of 0.5 ETDRS lines (range: −8 to +10 lines). In 4 eyes (25%) BCVA improved, in 11 (68.7%) it remained without changes and in one (6.2%) it diminished. The difference was not statistically significant (p = 0.2) between the study and the control groups. Similarly, a statistically significant difference was not found between the eyes treated with PRP before or after the macular treatment.

The mean initial central macular thickness measured by OCT in the study group was of 350.2 μm (range: 232–505 μm). All the eyes had diffuse macular edema with cystoid changes evident in OCT. All the eyes exhibited important macular thickness reductions, with a mean value of 244 μm (range: 178–315 μm) (reduction of 30.2%) (Figs. 1 and 2).

The mean initial central macular thickness measured by OCT in the control group was of 375 μm (range: 250–552 μm). All the eyes exhibited significant macular thickness reductions, with a mean of 253 μm (range: 198–333 μm) (reduction of 32.5%). The difference was not statistically significant (p = 0.2) between the study and the control group. In addition, a significant reduction in the angiographic diffusion was documented in the study group as well as in the control group after the treatment (Figs. 1 and 2).

steroids or with the presence of macular ischemia, intraocular inflammation, uncontrolled intraocular pressure (IOP), cataract surgery in the past 6 months or previous history of vitreoretinal surgery were excluded.

GLP was applied with the following parameters: laser impacts with a spot size between 50 and 100 μm were applied at a minimum of 500 μm from the center of the fovea and the external edge of the papilla. TA was slowly injected through pars plana at a dose of 4 mg (0.1 ml). The injection was in the external inferior quadrant at 3.5/2.5 mm of the limbus, depending on the eye being phakic or pseudophakic, using a 27 or 30 G needle. The adequate intravitreal location of the suspension and the profusion of the optic papilla were checked by means of indirect ophthalmoscopy.

The main measures to assess the efficacy of the treatment were changes in best corrected visual acuity (BCVA) of ≥2 ETDRS lines and in macular thickness measured by OCT (Stratus OCT, Carl Zeiss, Dublin, CA, USA). The patients were examined at post-surgery day one, week one, months 1, 3, 6 and 12 after the treatment, monitoring the appearance of possible complications including IOP increase, cataract progression, retina detachment, vitreous hemorrhage and endophthalmitis. Systemic risk factors involved in diabetic retinopathy and macular edema severity, i.e., glycemia control and arterial hypertension were also checked.

The control group (16 eyes [16 patients]) was retrospectively selected from our medical files between January 2001 and January 2002, obtaining all the data of patients who, during initial examination, fulfilled the inclusion criteria for the study group. In order to avoid bias, all the retina examinations and macular treatments were carried out by the same surgeon (JFA) and with the same criteria and guidelines applied to the study group.

No concomitant additional treatments for cystic DME were applied in either group.

The statistical analysis was carried out applying the Mann–Whitney, t for student and Chi square tests by means of the SAS Institute computer application, (Carey, NC, USA). A value of p < 0.05 was taken as statistically significant.
Table 2 – Results of intravitreal injection of triamcinolone plus grid laser photocoagulation (14 eyes).

<table>
<thead>
<tr>
<th>Case no.</th>
<th>Visual Acuity</th>
<th>Visual Acuity (log MAR)</th>
<th>OCT</th>
<th>IOP (mmHg)</th>
<th>Follow-up (months)</th>
<th>VA change (lines)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
<td>Final</td>
<td>Initial</td>
<td>Final</td>
</tr>
<tr>
<td>1</td>
<td>20/200</td>
<td>20/320</td>
<td>1.0</td>
<td>1.2</td>
<td>388</td>
<td>197</td>
</tr>
<tr>
<td>2</td>
<td>20/100</td>
<td>20/100</td>
<td>0.7</td>
<td>0.7</td>
<td>500</td>
<td>296</td>
</tr>
<tr>
<td>3</td>
<td>20/80</td>
<td>20/320</td>
<td>0.6</td>
<td>1.2</td>
<td>380</td>
<td>303</td>
</tr>
<tr>
<td>4</td>
<td>20/320</td>
<td>FC</td>
<td>1.2</td>
<td>1.4</td>
<td>253</td>
<td>212</td>
</tr>
<tr>
<td>5</td>
<td>20/200</td>
<td>20/80</td>
<td>1.0</td>
<td>0.6</td>
<td>356</td>
<td>285</td>
</tr>
<tr>
<td>6</td>
<td>20/25</td>
<td>20/50</td>
<td>0.1</td>
<td>0.4</td>
<td>292</td>
<td>282</td>
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<tr>
<td>7</td>
<td>20/25</td>
<td>20/32</td>
<td>0.1</td>
<td>0.2</td>
<td>279</td>
<td>264</td>
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<tr>
<td>8</td>
<td>FC</td>
<td>FC</td>
<td>1.4</td>
<td>1.4</td>
<td>232</td>
<td>182</td>
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<tr>
<td>9</td>
<td>20/50</td>
<td>20/63</td>
<td>0.4</td>
<td>0.5</td>
<td>315</td>
<td>272</td>
</tr>
<tr>
<td>10</td>
<td>20/40</td>
<td>20/32</td>
<td>0.3</td>
<td>0.2</td>
<td>254</td>
<td>238</td>
</tr>
<tr>
<td>11</td>
<td>20/32</td>
<td>20/63</td>
<td>0.2</td>
<td>0.5</td>
<td>387</td>
<td>178</td>
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<tr>
<td>12</td>
<td>20/200</td>
<td>20/63</td>
<td>1.0</td>
<td>0.5</td>
<td>492</td>
<td>192</td>
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<tr>
<td>13</td>
<td>20/320</td>
<td>FC</td>
<td>1.2</td>
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<td>505</td>
<td>315</td>
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<tr>
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<td>20/80</td>
<td>20/40</td>
<td>0.6</td>
<td>0.3</td>
<td>270</td>
<td>200</td>
</tr>
</tbody>
</table>

VA: visual acuity; FC: finger counting; Nr.: number; OCT: optic coherence tomography; IOP: intraocular pressure; MAR: minimum angle of resolution.

Fig. 1 – Patient (#12) with diabetic retinopathy and cystic diabetic macular edema, BEFORE treatment with intravitreal triamcinolone combined with grid laser photocoagulation. (A) Ocular fundus photography. (B) Fluorescein angiography. (C) Optic coherence tomography with macular edema and foveal thickening of 492 μm. Visual acuity 20/200.

Four (28.5%) eyes of the study group developed pathological IOP increases which were controlled with topical treatment in all cases. No progression of development of cataracts or other complications related to intravitreal injection were observed.

Discussion

The fact that GLP, despite being considered the standard universal treatment for diffuse diabetic macular edema (DDME), has very limited efficiency and that the beneficial effect of intravitreal TA injections has been published was the main driver for developing this pilot study, associating as initial treatment for DDME an intravitreal TA injection at GLP. Even though the results of this pilot study cannot be generalized, they suggested that an intravitreal injection of TA associated to GLP is anatomically efficient. The quantitative measurement of macular thickness by means of OCT demonstrated a mean reduction of 106.2 μm (30.2%). However, the functional
response was different. The average BCVA variability in the study group was of −0.5 ETDRS lines and BCVA diminished >2 ETDRS lines in 42.8% of eyes. This variability was not statistically different to the control group, i.e., the group treated only with macular laser photocoagulation without associating intravitreal injections.

Martidis et al.13 assessed the safety and effectiveness of 4 mg TA intravitreal injections in refractory DME in at least 2 previous laser photocoagulation sessions, finding a mean VA improvement of 2.4 and 1.3 Snellen lines at follow-up months 1 and 6, with central macular thickness reduction measured by OCT of 55% and 38%, respectively. In addition, Jonas et al.14 have published statistically significant VA improvement with an intravitreal 25 mg TA injection.

The safety of intravitreal corticoid injections is sufficiently endorsed in the literature with previous studies in humans.5–8 The main complications can be attributed to the procedure of the injection (retina detachment, vitreous hemorrhage and endophthalmitis),15 which did not occur in any case in this study, or due to the corticoid per se (cataract or glaucoma). Similarly to other publications,13,16 28.5% of the cases of this study experienced IOP increases above 21 mm Hg after the intravitreal TA injection, which was controlled in all cases with topical ocular antihypertensive therapy to recover normal values.

The results of this study are surprising because both modes of treatment, intravitreal TA and GLP, have demonstrated vision improvements in DDME when administered separately. Therefore, why did the combination of these treatments worsen visual results? The authors are unable to precisely determine the reasons for these results. However, they should be interpreted in the context of the peculiar characteristics of the studied population. All the eyes had diffuse macular edema with advanced cystic changes, most of them associating proliferative diabetic retinopathy. Previous studies have demonstrated the complexity of therapeutic management of these cases.2,4 A possible factor could be the needed to carry out PRP in a significant number of patients due to the severity of the retinopathy, even though we did not find statistically significant differences between carrying out the PRP before or after the macular treatment.

The authors believe that the limitations of this study have been the small number of cases, the need of associating PRP in an important number of patients in both groups, the advanced stage of edema with cystoid changes in all the eyes and the absence of a randomized and prospective control group. Said limitations reduce the significance of visual comparisons, even though the quantitative improvement anatomic data are objectively assessed with OCT.

It is also interesting to note that the recent review of the literature demonstrated that, despite it being a highly reduction of central macular thickness measured with OCT in eyes which have been pre-treated with intravitreal steroids, this is not consistently associated with VA improvements. The authors conclude that the literature does not provide sufficient evidence to recommend steroid injection before macular photocoagulation in EMD.17,18

Another significant point to take into account is that, at the time of carrying out the study and preparing this article, antiangiogenes were not available and their usefulness in the treatment of DME had not been published. Since then, several studies have been published demonstrating the efficacy of intravitreal bevacizumab (Avastin®, Genentech Inc., San Francisco, CA, USA) as initial treatment.
for EMD\textsuperscript{19,20} with follow-up periods of up to 24 months. Soheilian et al.\textsuperscript{21} published a study comparing bevacizumab combined with intravitreal TA against macular laser, with bevacizumab+TA demonstrating better visual results than laser photoocoagulation. Although macular laser continues to be an option for treating DME, it is possible that sequential treatment of TA or intravitreal antiangiogenics inducing a partial or full DME resolution prior to macular laser treatment could be more efficient, and obviously this line of combined sequential treatment should be researched further. In fact, recently the Diabetic Retinopathy Clinical Research Network (DRCNET) published its results on the combined treatment of ranibizumab (Lucentis, Genentech Inc., San Francisco, CA, USA) or TA+early or deferred laser for treating EMD.\textsuperscript{22} DRCNET found that intravitreal ranibizumab+early or deferred laser is more effective with at least one-year follow-up than only early laser for DME management involving the center of the macula, adding that, in pseudophakic eyes, intravitreal TA plus early laser seems more effective than only early laser but which is frequently associated to IOP increases. However, with a follow-up period of 3 years, the same group (DRCNET) reported that the results suggest that treatment with macular laser (focal/grid) at the beginning of intravitreal ranibizumab injections are not better and possibly worse in what concerns the visual results than deferring laser treatment for 24 weeks or more in eyes with DME involving the center of the fovea.\textsuperscript{23}

In summary, even though all the patients of this study exhibited anatomical improvement of cystic DMA, nearly half experienced significant VA loss (2 or more lines) with the initial treatment of TA and macular grid laser. The poor visual efficacy of this combined technique as a simultaneous initial treatment seems to suggest it would be better to reserve intravitreal TA only for cases refractory to an initial treatment of macular grid laser on its own, or combining intravitreal TA with laser in a subsequent session (deferred according to DRCNET) when the fovea has recovered a more normal anatomic shape, particularly in pseudophakic eyes.

**Conflict of interests**

No conflict of interests has been declared by the authors.

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