Original article

Intravitreal triamcinolone acetonide use in diffuse persistent diabetic macular edema

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ABSTRACT

Purpose: To determine the efficacy of intravitreal triamcinolone injections (iv TA) for diffuse persistent diabetic macular oedema (DMO) based on the functional parameter of modification in best corrected visual acuity (BCVA) and the anatomic parameter of quantitative changes in central macular thickness, as determined by optical coherence tomography (OCT). The secondary outcome is to analyse the safety of the procedure.

Methods: In this retrospective study, 16 patients (22 eyes) were included over a period of six months. Type and time of evolution of diabetes mellitus, previous treatments, BCVA, lens status, intraocular pressure (IOP) and central macular thickness, were analysed. During the follow-up period were collected: number of injections, changes in BCVA, IOP, central macular thickness, and complications observed.

Results: Improvement in BCVA was recorded in 30.77%, 47.37% and 52.63%, at one, three and six months, respectively (p<0.05 at 3 months). The IOP increased in 57.69% at one month, and 75 and 47.05%, at 3 and 6 months, respectively (p<0.05 at 3 months). Progression of cataracts was found in 22.72%. No cases of endophthalmitis were observed.

Conclusions: Intravitreal TA is a good therapeutic option for patients with persistent DMO, increasing BCVA and decreasing central macular thickness in the short term, with a percentage of clinical resolution of more than 70%. However, due to the transient effect, and potential adverse effects, it should be administered to selected refractory cases with caution.

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Uso de triamcinolona intravitrea en el tratamiento del edema macular diabético difuso persistente

RESUMEN
Propósito: Explorar la eficacia de las inyecciones de triamcinolona intravitrea (TA iv) en el edema macular diabético (EMD) difuso persistente, según el parámetro funcional de la modificación en la mejor agudeza visual corregida (MAVC) y el parámetro anatómico del cambio cuantitativo en el espesor foveal central, determinado por tomografía de coherencia óptica (OCT). El objetivo secundario es analizar la seguridad del procedimiento.

Métodos: En este estudio retrospectivo se incluyeron 16 pacientes (22 ojos), en un periodo de seis meses. Se analizó tipo y tiempo de evolución de la diabetes mellitus, tratamientos previos, MAVC, estado del cristalino, presión intraocular (PIO) y espesor macular central. A lo largo del seguimiento se recogieron datos relativos al número de inyecciones, así como a cambios en MAVC, PIO, grosor foveal, y complicaciones observadas.

Resultados: Se produjo mejora en la MAVC en el 30,77, 47,37 y 52,63%, al mes, 3 y 6 meses, respectivamente ($p < 0,05$ a los 3 meses). Se observó incremento de la PIO en el 57,69% al mes, y en el 75% y 47,05%, a los 3 y 6 meses ($p < 0,05$ a los 3 meses). Se cuantificó una disminución en el grosor foveal al mes, 3 y 6 meses ($p < 0,05$). Se observó progresión de catarata en 22,72%. No se apreció ningún caso de endoftalmitis.

Conclusiones: La TA iv es una buena opción terapéutica para los pacientes con EMD persistente, mejorando la MAVC y reduciendo el grosor macular a corto plazo, con porcentajes de resolución clínica de más del 70%. Sin embargo, su efecto transitorio y sus potenciales efectos adversos hacen que deba administrarse en casos refractarios con precaución.

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Introduction
Persistent diabetic macular edema (DME) is the most frequent cause of visual acuity loss in patients with diabetic retinopathy. It affects 29% of patients having over 20 years of evolution of the disease.1

Focal or grid laser photocoagulation is the accepted standard treatment. However, the response of edemas in these patients is not uniform because diffuse edemas, particularly those exhibiting cystic patterns, are resistant to conventional laser treatment.

Triamcinolone acetonide (TA) is a corticosteroid with a powerful and lasting anti-inflammatory, hormonal and metabolic action which is acquiring increasing importance in the treatment of retinal, vascular and inflammatory disorders.2 It has been experimentally determined that triamcinolone diminishes the vascular patency and stabilizes the hematoreninal barrier (HRB).3

The intravitreal injection of triamcinolone has the advantage of high bioavailability in its action area without the side effects of systemic corticoids. However, its intraocular use involves potential risks and complications, some of which are common to any substance administered through an invasive pathway (vitreous or retinal hemorrhage, retina detachment, iatrogenic cataracts, endophthalmitis) while others are dependent on the nature of the drug such as ocular hypertension, cataract development or pseudoendophthalmitis.2

The main objective of this study is to explore the efficacy of intravitreal TA injections in persisting diffuse DME, according to the functional parameter of change in best corrected visual acuity (BCVA) and the anatomic parameter of changes in the central foveal thickness determined with optic coherence tomography (OCT). A secondary aim is to determine the safety of the procedure by assessing the applications encountered in a series of patients.

Subjects, material and methods
A retrospective, longitudinal study carried out in patients diagnosed with persistent diffuse macular edema in our hospital, secondary to diabetic retinopathy and treated with 4 mg/0.05 ml injections of intravitreal TA (TA iv) (Trigon Depot® Bristol-Myers Squibb, New York).

The design of the study was accepted by the Ethics Committee of the hospital, and all the patients signed an informed consent. The methodology of the study was designed in accordance with the guidelines of the Helsinki Declaration. The inclusion criteria were: patients over 18 years of age with diffuse diabetic ME with foveal center compromise (Fig. 1), absence of ocular hypertension or glaucoma, absence of ocular surgical interventions or treatments in the past 6 months and having received single or multiple iv TA injections due to their ME.

The injections were administered after being prepared in the lab with centrifugation at 3000rpm during 5 min, withdrawal of solvents and subsequent reconstitution with BSS.

All the patients underwent a complete ophthalmological exploration, including BCVA assessment with Snellen optotypes, biomicroscopic exploration of the anterior and posterior segment,planation tonometry, angiofluoresceigraph (AFG) (Imageet, Topcon, Tokio) and OCT. The OCT studies were carried out under midriasis, either with the
temporal domain system (Stratus III OCT, Carl Zeiss Meditec, Germany) or the spectral system (Cirrus HD-OCT, Carl Zeiss Meditec, Germany). Scans of 3 and/or 6 mm were made in the horizontal and vertical meridians, and the foveal thicknesses were measured utilizing the equipment software. All the measures made on the same patient were obtained utilizing the same system, either Cirrus or Stratus.

The classification was made on the basis of the presence of specific patterns: cystic macular edema, diffuse foveal thickening or presence of subretinal liquid.

- The cystic macular edema (CME) was defined as the presence of intraretinal hyporeflective cystic spaces.
- The diffuse retinal thickening (or spongelike pattern) was defined as an increased foveal thickness (>200 μm) with low intraretinal reflectiveness and areas of low reflectiveness in external retina layers.
- The presence of subretinal liquid or serous detachment was defined as the presence of a subretinal low reflectiveness area surrounded by a hyporeflective “hunchback” elevation corresponding to a detached retina.

The patients were included in a database which collected the following variables: Age, sex, diabetes mellitus type and evolution time, previous treatments, BCVA, condition of the lens, ophthalmoscopic findings, intraocular pressure (IOP) and central macular thickness. Throughout the follow-up, the data on the number of administered injections, local complications, BCVA and foveal thickness changes were recorded, as well as IOP values and lends condition in accordance with the Lens Opacity Classification System (LOCS).

The statistical study was made with the SPSS software (version 15.0, SPSS Inc., Chicago, IL), utilizing the range non-parametric test with Wilcoxon sign. In all cases, statistical significance was taken as the presence of an error probability equal to 5% or below.

### Results

The study included 22 eyes of 16 patients with persistent diffuse DME, with a follow-up period of 6 months. The baseline characteristics of the patients are detailed in Table 1.

Overall, 28 iv injections of TA 4 mg/0.05 ml were administered. Seven of the 16 patients received bilateral injections. The mean number of injections in each eye was 1.41. Eight eyes received more than one injection due to recurring macular edema.

The mean BCVA at the beginning of the study was of 0.18 (SD: 0.13), increasing to 0.23 (SD: 0.16), 0.25 (SD: 0.17) and 0.25 (SD: 0.17), respectively, at month 1, 3 and 6 of the treatment.

The treatment produced BCVA improvements of 30.77%, 47.37% and 52.63% at month 1, 3 and 6, respectively. These differences were statistically significant at month 3 of the injection, with a p = 0.022 (p < 0.05) but not statistically significant at month 1 (p = 0.055) and month 6 (p = 0.126) (p > 0.05) (Fig. 2).

Table 1 – Baseline patient characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean ± SD (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age</td>
<td>69.75 (61–86)</td>
</tr>
<tr>
<td>Females</td>
<td>7/16 (43.75%)</td>
</tr>
<tr>
<td>Males</td>
<td>9/16 (56.25%)</td>
</tr>
<tr>
<td>DM type 1</td>
<td>2/16 (12.5%)</td>
</tr>
<tr>
<td>DM type 2</td>
<td>14/16 (87.5%)</td>
</tr>
<tr>
<td>Mean DM evolution time (years)</td>
<td>15.22 (3–36)</td>
</tr>
<tr>
<td>Phakic</td>
<td>13/22 (59.09%)</td>
</tr>
<tr>
<td>Transparent</td>
<td>1/13 (7.69%)</td>
</tr>
<tr>
<td>Sclerosis</td>
<td>3/13 (23.07%)</td>
</tr>
<tr>
<td>Cortical-nuclear cataracts</td>
<td>6/13 (46.15%)</td>
</tr>
<tr>
<td>Posterior subcapsular cataracts</td>
<td>3/13 (23.07%)</td>
</tr>
<tr>
<td>Pseudophakic</td>
<td>9/22 (40.90%)a</td>
</tr>
<tr>
<td>OCT patterns</td>
<td></td>
</tr>
<tr>
<td>Cystic macular edema</td>
<td>18/22 (81.81%)</td>
</tr>
<tr>
<td>Sponge-like pattern</td>
<td>4/22 (18.18%)</td>
</tr>
<tr>
<td>Subretinal liquid pattern</td>
<td>0/22 (0%)</td>
</tr>
<tr>
<td>Previous treatments</td>
<td></td>
</tr>
<tr>
<td>Laser photoacogulation</td>
<td>12/22 (54.54%)</td>
</tr>
<tr>
<td>Antiangiogenicsb</td>
<td>4/22 (18.18%)</td>
</tr>
<tr>
<td>Vitrectomized</td>
<td>1/22 (45.45%)</td>
</tr>
<tr>
<td>ERM</td>
<td>7/22 (31.81%)</td>
</tr>
</tbody>
</table>

ERM: epiretinal membrane; OCT: optic coherence tomography.

a Thirteen patients intervened during follow-up.
b All patients treated with bevacizumab (Avastin®).
In what concerns foveal thickness a reduction was observed at month 1 and month 3, with a new increase at month 6 which did not reach baseline levels. The restoration of the foveal profile was verified after 23 of the 28 injections, representing 82.14% of cases.

The mean was of 631.37 (SD: 170.10) μm at the beginning of the study, and 343.50 (SD: 235.10) μm, 307.33 (SD: 180.77) μm and 334.79 (SD: 194.45) μm at month 1, 3 and 6, respectively. These differences were statistically significant with a p = 0.005. p = 0.007 and p = 0.003 (p < 0.05) at month 1, 3 and 6, respectively (Fig. 3).

As regards IOP, the mean value at the beginning of the follow-up was of 15.04 (SD: 4.30) mmHg and 17.25 (SD: 3.85) mmHg, 19.29 (SD: 7.51) mmHg, and 17.75 (SD: 4.17) mmHg, at month 1, 3 and 6, respectively (Fig. 4).

IOP increased against baseline levels in 57.69% patients at month 1 and in 75% and 47.05%, at month 3 and 6. The mean increase was of 4.4 mmHg, 4.72 mmHg and 7 mmHg, at month 1, 3 and 6, respectively. These differences were statistically significant at month 3 after the injection (p = 0.022) but not significant at month 1 (p = 0.055) and month 6 (p = 0.126) (p > 0.05).

Values above 21 mmHg, in one case at month 1 and in 2 cases at month 3 and month 6. In all of these, IOP returned to normal values with topical anti-glaucoma treatment.

No statistically significant differences were observed vis-à-vis BCVA, IOP and foveal thickness between the patients with and without other previous treatments (laser photocoagulation or antiangiogenics) (p > 0.05).

Lens opacity appeared or increased in 5 eyes of 5 patients who required phacoemulsification surgery with IOL implant in 3 of them.

Epiretinal membrane (ERM) developed in 2 eyes of 2 patients (9.09%) at month 2 post injection.

None of the patients developed endophthalmitis, retinal detachment or tear or any other type of complication.

Discussion

DME arises due an accumulation of fluid between the retina layers at the macular level as the result of microvascular changes and alterations in the blood-retina barrier. Even though standard treatment is laser photocoagulation, a substantial number of patients do not respond to it. In recent years, new discoveries about the pathogeny of macular edema, combined with new imaging techniques such as OCT, have facilitated the identification of various edema patterns that

Fig. 2 – Box diagram representing the best corrected visual acuity (BCVA) ranges before the injection of intravitreal triamcinolone acetonide (TA) and at month 1, 3 and 6 post-injection.

Fig. 3 – Box diagram representing the foveal thickness (FT) ranges at the macular level before the injection of intravitreal triamcinolone acetonide (TA) and at month 1, 3 and 6 post-injection.

Fig. 4 – Box diagram representing the intraocular pressure (IOP) ranges before the injection of intravitreal triamcinolone acetonide (TA) and at month 1, 3 and 6 post-injection. It can be seen how one patient exhibited IOP > 30 mmHg at month 6.
can respond in a differentiated manner to a range of therapeutic approaches. For this reason, there is a growing interest in the pharmacological approach to DME treatment. The Diabetic Retinopathy Clinical Research Network (DRCR.net)4 carried out a study in 840 eyes of 693 subjects to assess the effectiveness of iv TA (1 mg and 4 mg) compared with argon laser photocoagulation (focal/grid). The study found that even though iv TA produced an initial benefit in a dose of 4 mg vis-à-vis the 1 mg dose and photocoagulation, in anatomical and BCVA terms this effect diminished at month 4 to the point that after 2 years BCVA was better in the group of patients treated with laser than in those treated with TA. In addition, the study found a high prevalence of increased IOP as well as cataracts.

The results of this study reaffirm the usefulness of laser but it does not allow to conclude that steroid treatment is not useful. Questions such as dosage, optimum formulation or release method are yet to be answered. On the other hand a precise study of other factors such as patient age, glyceremia control, previous treatments and edema patterns could help to define indications in a more individualized manner.

Our study found a positive visual effects of iv TA over DME with significant BCVA with a maximum effect at month 3 post-injection. An improvement thereof was observed in 30.77%, 47.37% and 52.63% of cases, at month 1, 3 and 6, respectively.

Jonas et al.5 found BCVA improvements in 68% of their patients, with a mean improvement of 2 Snellen lines. However in regular checkups BCVA remained without changes during 4 months and diminished up to the end of the follow-up period. It is important to take into account that the iv TA dose was of 25 mg, and besides the control group was made up by patients who had been treated with laser and this could influence results. Ciardella et al.6 and Martidis et al.7 also found BCVA improvements, in the latter case of 2.4, 2.4 and 1.3 lines at month 1, 3 and 6 post-injection. Our study produced smaller improvements of 1.1, 1.6 and 1.6 Snellen lines at month 1, 3 and 6.

From the anatomic point of view, edema improvements were observed as central macular thickness reductions which were significant at month 1 and 3, increasing at month 6 but without reaching the baseline levels.

Martidis et al.7 observed in their study foveal thickness reduction of 55%, 57.5% and 38% at month 1, 3 and 6, respectively, while Ciardella et al.6 also found diminished foveal thickness at month 1 and 3 with increased at month 6 without reaching baseline levels, exactly like in our study.

In what concerns IOP increases, we found elevation percentages of 57.69% 75% and 47.05% at month 1, 3 and 6, respectively. IOP values of ≥21 mmHg were found only in 3.5% at month 1 and 7.2% at month 3 and 6 and resolved with topical anti-glaucomatous treatment. Other authors such as Bashshur et al.8 and Ciardella et al.6 obtained percentages of 26.10% and 40%, respectively, for IOP values above 21 mmHg.

In what concerns the progression of cataracts in our series of cases, we found percentages of 38.46% (of these, 50% correspond to posterior subcapsular cataract), with 40% of these patients requiring surgery. Gillies et al.9 carried out a randomized study in 69 patients (34 treated/35 placebo) with 54% of treated patients requiring cataract surgery against 0% of nontreated patients.

A complication with a much lower prevalence is endophthalmitis. Moshfegui et al.10 presented a study of 8 cases of post-surgical acute infectious endophthalmitis after iv TA injection in various retinal disorders, with a prevalence of 0.87%. Baath et al.,11 Bhavsar et al.12 and Angulo Bocco et al.13 obtained percentages of 0.3%, 0.05% and 0.1%, respectively. Other complications such as tears, retina detachment and vitreous hemorrhage described in isolation in the literature1 were also absent in our study.

To conclude, intravitreal triamcinolone treatment provides a good therapeutic option for patients with persistent disk fused diabetic macular edema, giving rise to BCVA improvement (peaking at about 3 months), diminished macular thickness and height clinic resolution percentages exceeding 70% of cases.

However, the temporary nature of the beneficial effects and the fact that the treatment is not free of complications (of which IOP increase and cataract progression are the more frequent ones) signifies that this treatment should be administered with precaution.

The limitations in our study are inherent to its retrospective nature and to the limited number of patients as well as the absence of a control group.

New therapeutic alternatives are being explored and large multicenter studies are attempting to elucidate the role of these pharmacological therapies, on their own or combined with laser, to address this severe and complex disease.

Conflict of interests

The authors have no conflict of interests to declare.

REFERENCES