A cost-effectiveness study of dexamethasone implants in macular edema

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Abstract

Objective: To analyse the cost-effectiveness and benefits of a dexamethasone intravitreal implant (Ozurdex®, Allergan, Irvine, CA, USA) in its clinically relevant applications.

Materials and methods: A total of 88 eyes of 86 patients with macular edema of >300 μm measured by optical coherence tomography (Cirrus Zeiss, Dublin, CA, USA) were included in this 2-year retrospective study, with a minimum of 6 months follow-up. The patients were divided into three groups: group 1 with macular edema in retinal vein occlusion, group 2 with non-infectious posterior uveitis, and group 3 with diabetic macular edema. The treatment was off-label but supported by the literature. Before implantation, and on days 1, 30, 60, 90 and 180, corrected visual acuity (Snellen), central retinal thickness, intraocular pressure and biomicroscopy were evaluated. The cost-benefit analysis was tabulated by line of visual acuity gained, comparing the main therapeutic alternatives and assessment of the safety profile of the dexamethasone intravitreal implant (Ozurdex®, Allergan, Irvine, CA, USA).

Results: The results of this study did not differ from the published studies, in terms of visual acuity improvement in 63.3% of cases, and with central macular thickness improvement in 97% of cases. There were relapses, which occurred after 120 days on average, and the need for retreatment was 40.9%. Increased intraocular pressure >23 mmHg was among the side effects in 29.54%, and was controlled with topical treatment, except in 1.13% requiring surgical treatment. The development of cataract was 44.7%, and 10.6% required surgery. Treatment results showed less frequent use of Ozurdex® than other treatments for disease control, being a cost saving option.

Discussion: Cost-effectiveness analyses are clinically relevant when applying treatment strategies in patients with macular edema. Dexamethasone intravitreal implant appears to be a safe and efficient therapy.

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Resultados coste-efectividad del implante de dexametasona en edema macular

RESUMEN

Objetivo: Analizar el beneficio coste-efectividad del implante intravítreo de dexametasona (Ozurdex®, Allergan, Irvine, CA, EE.UU.) en sus aplicaciones clínicamente relevantes.

Material y métodos: Un total de 88 ojos de 86 pacientes con edema macular de > 300 µm medido mediante tomografía de coherencia óptica (Zeiss Cirrus, Dublin, CA, EE. UU.) fueron incluidos en este trabajo retrospectivo de 2 años, con un seguimiento mínimo de 6 meses. Se incluyeron 3 grupos de pacientes: el grupo 1 con edema macular en oclusión venosa retiniana, el grupo 2 con uveítis posterior no infecciosa y el grupo 3 con edema macular diabético, estando este fuera de indicación pero avalado por la literatura médica. Antes del implante y los días 1, 30, 60, 90 y 180 se evaluó la agudeza visual corregida (Snellen), espesor retiniano central, presión intraocular y biomicroscopia. Los análisis de coste-beneficio se tabularon por línea de visión ganada, comparando las principales alternativas terapéuticas, y se valoró el perfil de seguridad del implante intravítreo de dexametasona (Ozurdex®; Allergan, Irvine, CA, EE. UU.).

Resultados: Los resultados de este estudio no difirieron de los publicados por otros, en términos de mejoría de la agudeza visual en el 63,3% y del espesor macular central en el 97%. En los casos de recidiva, se produjo a los 120 días de media; la necesidad de retratamiento fue del 40,9%. Entre los efectos secundarios, el incremento de presión intraocular > 23 mmHg se produjo en el 29,54%, controlándose con tratamiento tópico, excepto un 1,13% de los casos que requirieron tratamiento quirúrgico. El desarrollo de catarata fue del 44,7%, requiriendo cirugía un 10,6%. Los resultados del tratamiento mostraron una menor necesidad en la frecuencia del uso de Ozurdex® frente a otros tratamientos para el control de la enfermedad, convirtiéndose en una opción que permite el ahorro de costes.

Discusión: Los análisis coste-efectividad son clínicamente relevantes cuando se aplican estrategias terapéuticas en pacientes con edema macular. El implante de dexametasona intravítreo es una opción terapéutica segura y eficiente.

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Introduction

Macular edema (MO) is a frequent outcome in several vascular retinal conditions such as retinal vein occlusions (RVO), uveitis and diabetic retinopathy, causing decreased visual acuity (VA). Several studies have shown the beneficial effects of corticoids in the treatment of MO. The sustained-release dexamethasone intravitreal implant (Ozurdex®, Allergan, Irvine, CA, USA) is detected in the retina and vitreous humor for up to 6 months after administration, showing a peak concentration after 2 months. This implant has proved to be effective for the treatment of MO related to RVO [1] and non-infectious posterior uveitis [1] and a phase III trial is being conducted so that it may be approved by the FDA for use in diabetic macular edema (DMO). In vitrectomised eyes, the pharmacokinetic and pharmacodynamic characteristics are altered, with increased drug clearance in the vitreous humor, thus reducing its half-life; despite these circumstances, treatment with dexamethasone intravitreal implant has proved to be effective.

These new treatments entail a cost that must be considered based on the patient’s benefit. In this study, we assess the results obtained with Ozurdex® in the treatment of MO related to RVO, uveitis [4] and DMO [5] the last group being off label but supported by the published medical literature. The overall cost of treatment is tabulated by line of visual acuity gained. We try to promote a critical assessment of the different treatments that are available for MO, not only from the point of view of the visual benefit and product safety, but also based on the financial considerations of our clinical practice.

Subjects, materials and methods

This retrospective study includes 88 eyes of 86 Caucasian patients, 49 male and 37 female, with a mean age of 63 years and a minimum 6-month (180 days) follow-up for MO related to RVO, non-infectious posterior uveitis and DMO (Table 1). Patients with MO > 300 µm were treated with a dexamethasone intravitreal implant (Ozurdex®; Allergan, Irvine, CA, USA). Group 1 included 42 eyes of 42 patients with short-term MO (<3 months), 28 related to branch retinal vein occlusion (BRVO) and 14 related to central retinal vein occlusion (CRVO). Group 2 included eight eyes from eight patients with long-term MO (>3 months) and little response to treatment for non-infectious posterior uveitis. Group 3 included 38 eyes of 36 patients with long-term DMO (>3 months) and little response to treatment. Out of them, five patients were vitrectomised in group 1, four patients in group 2 and nine patients in group 3.

The treatment and follow-up protocol was based on pivotal studies applied to our clinical practice. Before implantation
Table 1 – Demographic characteristics of study subjects.

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Gender</th>
<th>Mean age</th>
<th>Pathology</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Male</td>
<td>% Female</td>
<td>% CRVO</td>
</tr>
<tr>
<td>86</td>
<td>56.9</td>
<td>43</td>
<td>16.3</td>
</tr>
<tr>
<td></td>
<td>n = 14</td>
<td>n = 28</td>
<td>n = 36</td>
</tr>
</tbody>
</table>

and on days 1, 30, 60, 90 and 180 after implantation, corrected VA (Snellen), central retinal thickness measured by optical coherence tomography (Zeiss Cirrus, Dublin, CA, USA), intraocular pressure, biomicroscopy and funduscopy were evaluated. A fluorescein angiography was performed in 91.8% of the patients (79/86 patients). Measured VA was estimated in lines of visual acuity, dividing the number of letters obtained by 5. The line of VA gained was used to compare the results of different forms of treatment of MO in a year.

Patients with MO who showed no previous response to corticoids, a history of corticoid-induced ocular hypertension, advanced or neovascular glaucoma and uncontrolled systemic disease were not treated with the dexamethasone implant. Retreatment criteria comprised decreased VA of more than three lines of visual acuity or increased central retinal thickness higher than 200 μm.

To calculate the cost per treatment with the dexamethasone intravitreal implant (Ozurdex®; Allergan, Irvine, CA, USA) the drug cost together with the direct costs associated with each administration have been considered. Indirect costs, derived, among others, from adverse effects, such as antiglaucomatous therapy and cataract surgery, were not included in this study. Treatment has been compared to the rest of the surgical and therapeutic alternatives for one year of treatment. Statistical analysis: Data were analyzed by IBM® SPSS® Statistics (version 20).

Results

The results showed that after 180 days of treatment, the mean VA improvement was of 1.4 lines (SD ± 1.12; p < 0.03); in group 1, it was of 1.98 lines (SD ± 1.53; p < 0.01); in group 2, it was of 0.75 lines (SD ± 0.57; p < 0.03); and in group 3, it was of 1.6 (SD ± 1.32; p < 0.05). Mean decrease in central macular thickness was of 110.95 μm (range of 57–741 μm; p < 0.05). In group 1, it was of 158.85 μm (range of 31–741 μm; p > 0.05); in group 2, it was of 84.75 μm (range of 37–181 μm; p > 0.05); and in group 3, it was of 98.31 μm (range of 5–548 μm; p < 0.04).

After 180 days of follow-up, there was a VA gain in 32.9% of cases (29/88), while the rest of the cases, 67% (59/88), did not show any VA gain. In most cases, a VA improvement was observed as from the first month of follow-up, reaching the maximum treatment effect in terms of VA improvement and decreased central retinal thickness between days 60 and 90 following implantation (Figs. 1 and 2). This trend was similar in all patients, regardless of the edema etiology (Figs. 3 and 4). A greater VA gain was observed on day 180 in patients with higher central retinal thickness, a shorter-term MO and a higher baseline VA (Figs. 5–7).

In the subgroup analysis, when the vein occlusion type is compared, there exists a higher gain in VA in patients with BRVO, with 2.46 lines of VA (p < 0.04) vs 0.79 lines of VA (p < 0.02), despite the fact that the central retinal thickness shows a higher reduction in the CRVO, with a 242-μm decrease (p < 0.01) vs a 75.7-μm decrease (p < 0.02), which does not correspond to the VA improvement. Moreover, it has been observed that the BRVO is more frequent than the CRVO.

The VA improvement after 180 days was higher in patients with a higher baseline VA; on the other hand, in patients with a baseline VA ≤ one line, 26% lost VA, 55% maintained their VA and the rest showed a gain. In patients with a baseline VA of 1–3 lines, 50% showed a VA gain and only 15% lost VA, while the rest maintained their VA. In patients with a baseline VA
Fig. 3 – Mean gain in VA throughout the study according to etiology.

Fig. 4 – Mean decrease in central retinal thickness measured by OCT throughout the study according to etiology.

Fig. 5 – Increased central retinal thickness is more likely to show higher VA gain.

Fig. 6 – Shorter MO duration is more likely to show higher VA gain.

> 3 lines, 71% showed a VA gain and only 11% lost VA, while the rest maintained their VA (Figs. 8 and 9).

MO was refractory in 55.6% (49/88) of patients, 31.8% of them having received prior treatment with bevacizumab (Avastin®, Genentech/Roche, San Francisco, CA, USA); in 18 cases of MO related to RVO and in 10 cases of DMO. Moreover, 5.6% of patients received prior treatment with ranibizumab (Lucentis®, Genentech, San Francisco, CA, USA); in three cases of MO related to RVO and in two cases of DMO. Other treatments used were laser therapy (43.1%) in 19 cases of DMO and in 19 cases of MO related to RVO (Fig. 10). Systemic and topical corticoids (eight cases of uveitis) and intravitreal corticoids (21 cases of MO related RVO, 16 cases of DMO and four cases of MO related to uveitis) were also used. In five patients with uveitis, MO persisted despite the fact that patients were under treatment with immunosuppressant drugs. Combination therapies may entail an improvement compared to monotherapy, with both anti-VEGF drugs and laser therapy, since they may have a synergistic effect and reduce the need for treatment.

Fig. 7 – Increased baseline VA is more likely to show higher VA gain.
Patients experienced recurrent MO in 76.1% (67/88) of cases, after a mean period of 120 days (±44). By groups, relapse in group 1 was observed after 160 days (±43), in group 2 after 120 days (±0) and in group 3 after 90 days (±45). Vitrectomised patients showed recurrent MO in 83.3% (15/18) of cases; in group 1 it occurred after a mean period of 120 days (±0), in group 2 after a mean period of 90 days (±0) and in group 3 after a mean period of 90 days (±45) (Fig. 11). During the observational period, 40.9% (36/88) of patients received retreatment with dexamethasone implant. In group 1, relapse was of 50% (15 cases required a second dose, three cases required a third dose); in group 2 it was of 5.55% (two cases required a second dose) and in group 3 it was of 44.4% (16 cases required a second dose) (Fig. 12). In the subgroup comprised of vitrectomised patients, the improvement in MO is also associated with the removal of vitreous humor, which facilitates molecular transport and retinal oxygenation.9

With respect to the assessment of adverse effects, the IOP was within normal ranges in all patients before treatment start. A >23 mmHg increase in IOP was detected in 29.54% of cases (26/88), in parallel to the 12-month pivotal study that showed a ≥10 mmHg increase in IOP in 32.8% of patients with respect to re-treatment cases.10 The IOP was controlled with topical anti-hypertensive treatment in 23.86% of cases (21/88), anti-glaucoma surgery was required in one case (1.13%) and panphotocoagulation was required in four (4.5%) cases of neovascular glaucoma; thus IOP was eventually controlled in all study patients. The percentage of cataracts among phakic patients was 44.7% (21/47), with surgery required in one case (2.12%) of non-infectious posterior uveitis and in four cases (8.5%) of DMO; cataract removal was at the ophthalmologist’s discretion. In the case of diabetic patients, the criterion for cataract removal was not only a decreased VA but also the difficulty of performing laser therapy (Table 2).
The remaining adverse effects were not significant and most of them were related to a local reaction at the injection site, such as conjunctival hemorrhage, eye pain and an inflammatory reaction in the anterior chamber. No further severe adverse effects, such as vitreous hemorrhage, retinal detachment or endophthalmitis, were seen.

The direct cost derived from the patient assessment and the dexamethasone implant administration (Ozurdex®; Allergan, Irvine, CA, USA) was estimated at €1413 (Table 3). Based on an annual treatment cost assessment, it is estimated at €3280 per patient. When we assess the cost versus the visual benefit obtained, comparing the results from the various treatment modalities of MO, we see that the lowest cost per AV line gained in DMO is obtained with bevacizumab (€1668), followed by the dexamethasone implant (Ozurdex®, Allergan, Irvine, CA, USA) in our group (€2050) and the highest cost per VA line gained is obtained with ranibizumab (€8827). In RVO, the highest cost per VA line is still obtained with ranibizumab (€9687 in BRVO and €5653 in CRVO) versus treatment with dexamethasone implant in our group (€1428 in BRVO and €2050 in CRVO) (Table 4).

**Table 2 – Adverse effects of dexamethasone implant: increased IOP and cataract development and percentage of patients that required surgical treatment.**

<table>
<thead>
<tr>
<th></th>
<th>Increase in IOP</th>
<th>Cataract development</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of eyes</td>
<td>29.54% (26/88)</td>
<td>44.7% (21/47)</td>
</tr>
<tr>
<td>No. of eyes requiring surgery</td>
<td>1.13% (1/88) trabeculectomy</td>
<td>2.12% (1/47) uveitis</td>
</tr>
<tr>
<td></td>
<td>4.5% (4/88) panphotocoagulation</td>
<td>8.5% (4/47) diabetes</td>
</tr>
</tbody>
</table>

**Table 3 – Direct costs related to Ozurdex® administration.**

<table>
<thead>
<tr>
<th>Costs of Ozurdex® treatment and assessment process</th>
<th>€</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ophthalmic exam</td>
<td>55.00</td>
</tr>
<tr>
<td>Fluorescein angiography</td>
<td>190.00</td>
</tr>
<tr>
<td>OCT</td>
<td>35.00</td>
</tr>
<tr>
<td>Intravitreal injection procedure</td>
<td>145.00</td>
</tr>
<tr>
<td>Ozurdex®</td>
<td>988.00</td>
</tr>
<tr>
<td>Total</td>
<td>1413.00</td>
</tr>
</tbody>
</table>

**Discussion**

The results from this series of MO cases related to RVO, non-infectious posterior uveitis and DMO, where the application of dexamethasone implant is indicated in our clinical practice, show the favorable response of MO to Ozurdex® after a follow-up period of at least 180 days, in parallel to the published literature. Even though cases of chronic ocular inflammation may require repeated injections, the need for re-treatment in our study was decided based on MO relapse determined by decreased VA and/or increased central retinal thickness in the OCT.

It was observed that the cases that achieve better VA at 6 months post-implant were those with a higher baseline VA, whereas cases with very low baseline VA had little VA

![Fig. 12 – Mean change in VA after baseline treatment and re-treatment.](image-url)
improvement despite the MO improvement in the OCT. In the latter cases, the anatomical improvement was not consistent with a functional improvement. Therefore, long-term studies are required to assess whether only patients with a good response after the first injection should be retreated.

Besides, corticosteroids such as dexamethasone not only have an anti-inflammatory effect but also interfere in the synthesis of the vascular endothelial growth factor (VEGF) and other cytokines. Anti-VEGF drugs such as ranibizumab and bevacizumab have a beneficial effect on the visual function and in the reduction of the central macular thickness in MO. Nevertheless, their short half-life requires multiple injections to maintain their therapeutic effect. In the case of Ozurdex®, as re-treatment is less frequently needed, the overall cost of treatment and the risk of adverse effects are also reduced. Ozurdex® is known to have a satisfactory safety profile, in addition to being a biodegradable implant with an easy-to-apply device that may be administered both in the operating theatre and in a clean area in the office, which makes the procedure easier and reduces costs. Besides, treatment with Ozurdex® involves a reduction in the number of visits and diagnostic tests, and in the costs of technical and pharmaceutical material and personnel.

In general, important treatment decisions in ophthalmology are made regardless of costs, but the high prevalence of MO and the wide differences of up to 15 times in costs among the various treatments make cost assessment unavoidable in this case. Clinicians should be aware of these dilemmas and assess the fact that the VA differences described in recent studies on MO treatment may be statistically significant but their magnitude may not be so beneficial.

We recognize the study limitations such as the sample size, the VA measurement with the Snellen scale, which is not as consistent as the one in the Early Treatment Diabetic Retinopathy Study, and that a longer follow-up period is needed to document the benefit of long-term treatment and to assess its safety, mainly in relation to glaucoma development and cataract progress.

### Conflicts of interest

The authors declare that they do not have any conflicts of interest.

### References