Widening use of dexamethasone implant for the treatment of macular edema

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Abstract: Sustained-release intravitreal 0.7 mg dexamethasone (DEX) implant is approved in Europe for the treatment of macular edema related to diabetic retinopathy, branch retinal vein occlusion, central retinal vein occlusion, and non-infectious uveitis. The implant is formulated in a biodegradable copolymer to release the active ingredient within the vitreous chamber for up to 6 months after an intravitreal injection, allowing a prolonged interval of efficacy between injections with a good safety profile. Various other ocular pathologies with inflammatory etiopathogeneses associated with macular edema have been treated by DEX implant, including neovascular age-related macular degeneration, Irvine–Gass syndrome, vasoproliferative retinal tumors, retinal telangiectasia, Coats’ disease, radiation maculopathy, retinitis pigmentosa, and macular edema secondary to scleral buckling and pars plana vitrectomy. We undertook a review to provide a comprehensive collection of all of the diseases that benefit from the use of the sustained-release DEX implant, alone or in combination with concomitant therapies. A MEDLINE search revealed lack of randomized controlled trials related to these indications. Therefore we included and analyzed all available studies (retrospective and prospective, comparative and non-comparative, randomized and nonrandomized, single center and multicenter, and case report). There are reports in the literature of the use of DEX implant across a range of macular edema-related pathologies, with their clinical experience supporting the use of DEX implant on a case-by-case basis with the aim of improving patient outcomes in many macular pathologies. As many of the reported macular pathologies are difficult to treat, a new treatment option that has a beneficial influence on the clinical course of the disease may be useful in clinical practice.

Keywords: macular edema, dexamethasone, intravitreal, implant, corticosteroids

Introduction

The sustained-release intravitreal (IV) 0.7 mg dexamethasone (DEX) implant (Ozurdex®, Allergan Pharmaceuticals, Irvine, CA, USA) is approved in Europe for the treatment of macular edema related to the following diseases: diabetic retinopathy, branch retinal vein occlusion or central retinal vein occlusion, and non-infectious uveitis.¹

DEX is one of the 3 most commonly used intraocular corticosteroids together with triamcinolone acetonide (TA) and fluocinolone acetonide. However, compared with these, DEX differs in its pharmacokinetics and pharmacodynamics properties due to certain biological effectiveness: different glucocorticoid receptor binding affinity (DEX > fluocinolone > triamcinolone) and different anti-inflammatory activities (DEX = fluocinolone and is 5 times more active than triamcinolone).¹² The advantage of a DEX implant, containing micronized, preservative-free DEX 0.7 mg in a biodegradable copolymer of polylactic-co-glycolic acid (which eventually breaks down...
into carbon dioxide and water), is the release of the active ingredient within the vitreous chamber for up to 6 months after an IV injection. All these aforementioned features allow reduction in the frequency of injections with benefit in terms of hospital and patient resource saving, including diminished complications related to injection procedure (eg, retinal detachment, endophthalmitis, lens iatrogenic injury, etc). However, in real life it has been shown that a shorter-interval re-treatment is required because of the loss of the drug’s effectiveness before 6 months, with a reported range varying from 4 to 5.9 months. Another relevant pharmacological aspect, as demonstrated by experimental studies, is the reduction of IV drugs half-life in vitrectomized eyes compared with non-vitrectomized ones, making their use ineffective. On the contrary, DEX implant has the advantage of maintaining the same half-life and, therefore, the same pharmacological properties in both vitrectomized and non-vitrectomized eyes.

Regarding complications related to the use of DEX implant, pivotal studies and real-life studies have confirmed a good safety profile with only a few complications: cataract progression in the range from 29.8% to 67.9%, closely related to the number of implants received, and an increase of intraocular pressure (IOP) >10 mmHg from baseline reported in a range of 15.4% and 27.7% of cases. There are several reviews collecting literature data about the approved use of sustained-release DEX implants. However, there are various ocular pathologies with inflammatory etiopathogeneses associated with macular edema, such as: neovascular age-related macular degeneration (nAMD); Irvine–Gass syndrome (IGS); vasoproliferative retinal tumors (VPRTs); retinal telangiectasia and Coats’ disease; radiation maculopathy; retinitis pigmentosa; macular edema secondary to scleral buckling and pars plana vitrectomy (PPV), all of which have been treated by DEX implant.

The aim of this review was to provide a systematic collection of all of the diseases that benefit from the use of the sustained-release DEX implant alone or in combination with concomitant therapies in order to provide a valuable therapy option for these diseases in clinical practice.

**Methods**

MEDLINE databases for the period 2009 to September 2016 were searched by using the medical subject heading “Dexamethasone intravitreal implant/Ozurdex” and the keywords “macular edema, age-related macular degeneration, Irvine–Gass, pseudophakic cystoid macular edema, post-operative macular edema, PPV, scleral buckling, retinitis pigmentosa, prostaglandin, radiation macular edema, telangiectasia.” Studies were limited to the English language. Because randomized controlled trials on these topics were lacking, all studies (retrospective and prospective, comparative and non-comparative, randomized and nonrandomized, single center and multicenter, and case reports) were analyzed. Aims, and anatomical and functional outcomes, and complications after DEX implant were analyzed.

**nAMD**

Approved first-line therapy for nAMD is based on the use of anti-vascular endothelial grow factor (VEGF) IV injections such as pegaptanib, ranibizumab, and aflibercept. However, there are patients who have a non-complete response to anti-VEGF injections as well as patients who, after an optimal functional and anatomical response, develop tachyphylaxis. The explanation for this incomplete response lies in the multifactorial pathogenesis of AMD, which involves VEGF, inflammation, and oxidative stress, as seen in histological studies performed on neovascular membranes after their surgical excision. Neovascular membrane growth in the subretinal space is stimulated by activated macrophages (and other inflammatory cells secreting cytokines) and enzymes that can damage the Bruch’s membrane. Therefore, inflammation is another potential target of nAMD treatment that could be counteracted by the use of corticosteroids.

Combination therapy consisting of anti-VEGF therapy and a corticosteroid relies on the use of drugs with different mechanisms of action, and could allow the reduction of anti-VEGF IV injection frequency and therefore, improve long-term efficacy and safety while reducing scarring results. Using combination therapies to treat nAMD dates back to photodynamic therapy (PDT), when it was associated with the IV TA injection. However, side effects due to IV TA, such as cataract progression and increased IOP, sometimes resistant to medical therapy, halted these procedures despite anatomical and functional benefits. Cataract surgery has been reported in around 45.2% of eyes that underwent triamcinolone injection, and ocular hypertension (IOP >21 mmHg) in around 44.6% of eyes, with IOP-lowering surgery required in 0.3% of eyes.

The LuceDex study was the first study using the IV DEX injections (500 mg in 0.05 mL), followed by IV ranibizumab (4 monthly injections of 0.5 mg in 0.05 mL) that was compared with IV ranibizumab monotherapy (Group 2; total...
After 4 consecutive months, in both groups, ranibizumab pro re nata treatment was administered if signs of lesion activity were present. The results of this study showed a clear benefit for combination therapy, with reduction in the dimension of the choroidal neovascular membrane, detected by fluorescein angiography, improvement in visual acuity, and reduced treatment frequency. Central macular thickness (CMT) and volume reductions were also observed, although these changes were not statistically significant.

After the approval of the DEX implant, several authors evaluated its efficacy in nAMD22–25 (Table 1). Compared with ranibizumab monotherapy, studies showed no long-term improvement of best corrected visual acuity (BCVA) and reduction of CMT,22–25 however, DEX implant in some cases allowed a reduced number of anti-VEGF injections.23,24

One study23 reported an incidence of cataract surgery of 9% in ranibizumab-treated eyes and 33% in eyes receiving 2 DEX implants. The incidence of ocular hypertension ranged from 15% to 42%,22–25 all treated with topical hypotonizing therapy.

IGS
The most likely physiopathological hypothesis for IGS is an inflammatory response instigated by the inflammatory mediators released during and after surgical procedures, causing alterations to the blood–retinal barrier. Many risk factors have been identified, such as posterior capsule rupture and vitreous loss, as well as the use of iris retractors, the presence of an epiretinal membrane, a vein occlusion, a history of uveitis or diabetes and the use of prostaglandin eye drops.26

First-line treatment for IGS involves the use of different therapies: topical nonsteroidal anti-inflammatory drugs (NSAIDs), oral acetazolamide, and topical corticosteroids. In patients resistant to such treatments, the following off-label treatment options have been tried:26–32
- IV anti-VEGF
- Subcutaneous interferon α2a injections
- IV infliximab (anti-tumor necrosis factor-α)
- Intra-, retro-, and peribulbar corticosteroids
- PPV

Several authors have evaluated the efficacy of DEX implant for chronic IGS31–45 (Table 2).

Most of the studies had a 6-month follow-up; they showed a significant improvement in BCVA and a significant reduction in CMT with 1 DEX implant. Two prospective studies38,43 of DEX compared with IVTA showed similar functional effects and anatomical effects: one found a lower incidence of ocular hypertension in the DEX group (at 6 months 0% vs 20%, P=0.044).

A retrospective long-term study44 that included 58 cases of IGS in a total of 100 eyes found that efficacy was maintained at 24 months, after a mean number of 1.77 DEX implants in the first year and 1.70 in the second year. At 24 months, an IOP >25 mmHg was found in 6.2% of the patients, all treated with hypotensive eye drops and not requiring filtering surgery.44

VPRTs
Several approaches have been used to treat VPRTs, including cryotherapy, laser photoocoagulation, PDT, IV anti-VEGF, plaque brachytherapy, and PPV.45–47

VPRTs treated by DEX and PDT were reported in 3 cases48 (Table 3). Total involution of the tumor was reported within 2 months and regression of exudates continued for several months, leaving fibrotic scar tissue in the inferior half of the retina.48

Retinal telangiectasia and Coats’ disease
Retinal telangiectasia
Yannuzzi et al49 have recently classified different forms of idiopathic macular telangiectasia: aneurismal telangiectasia, idiopathic perifoveal telangiectasia, and occlusive telangiectasia. Although several approaches have been suggested for the treatment of idiopathic macular telangiectasia (including laser photoocoagulation,50 PDT,51 IV anti-VEGF,52 PPV53), no treatment has yet been shown to provide a consistent effect on visual acuity. Also, corticosteroids have been used to treat these vascular pathologies due to their biological effect44 and DEX implant can be assumed to be an useful therapeutic device.55,56 which can also be administered in pediatric patients57 (Table 4).

In these cases, with a longer follow-up, multiple DEX implants were performed, at each time successfully (leading to BCVA improvement and CMT reduction).56–58

Coats’ disease
In Coats’ disease, ablative therapy by laser photoocoagulation and cryotherapy is the gold standard of treatment59 with photoocoagulation preferred over cryotherapy in cases with little or no subretinal fluid.57 IV therapies such as anti-VEGF and steroids could be used to improve anatomic and visual outcomes58,59 in particular, in combination with ablative therapies. IV corticosteroids, including DEX implant60–62
<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>No of eyes</th>
<th>Previous treatment</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Retreatment</th>
<th>BCVA</th>
<th>CMT</th>
<th>Complications</th>
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</thead>
<tbody>
<tr>
<td>Calvo et al²²</td>
<td>Retrospective</td>
<td>7 refractory</td>
<td>3 anti-VEGF</td>
<td>1 DEX + ranibizumab monthly</td>
<td>6 months</td>
<td>2 DEX (28.5%)</td>
<td>From 0.53±0.13 logMAR to 3 months: 0.45±0.3 (P=0.23) 6 months: 0.52±0.2 (P=0.23)</td>
<td>From 273.14±50.94 µm to 3 months: 241.5±36.6 µm (P=0.04) 6 months: 260.71±58.51 µm (P=0.40)</td>
<td>3 ocular hypertension (42.8%) (27–32 mmHg)</td>
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<tr>
<td>Kuppermann et al²³</td>
<td>Prospective multicenter randomized</td>
<td>243 naïve: vs 57 sham + ranibizumab PRN</td>
<td>58 DEX + ranibizumab + ranibizumab PRN</td>
<td>6 months</td>
<td>3.15 DEX + ranibizumab PRN</td>
<td>Naive Change from baseline: DEX: +0.3 to +2.7 L Sham: −0.5 to +2.6 L</td>
<td>Naive Change from baseline: DEX: −12.6±9.4 µm Sham: −34.7±10.6 µm (P&lt;0.05)</td>
<td>18.2% DEX</td>
<td>IOP ≥25 mmHg</td>
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<tr>
<td>Rezar-Dreindl et al²⁴</td>
<td>Prospective randomized</td>
<td>40 ranibizumab</td>
<td>20 ranibizumab</td>
<td>12 months</td>
<td>7.95 ranibizumab (P=0.042)</td>
<td>Change from baseline: 10.8±13.2 L 3.0±10.5 L (P=0.766)</td>
<td>Change from baseline: 31.7±27.3% to 13.3%±27.0% (P=0.236)</td>
<td>9% cataract surgery 0% IOP &gt;30 mmHg</td>
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<tr>
<td>Chaudhary et al²⁵</td>
<td>Prospective multicenter randomized</td>
<td>10 NR</td>
<td>5 ranibizumab</td>
<td>6 months</td>
<td>6.2±2.3</td>
<td>Change from baseline: 10.8±13.2 L 3.0±10.5 L (P=0.766)</td>
<td>1 IOP ≥30 mmHg</td>
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**Abbreviations:** BCVA, best corrected visual acuity; CMT, central macular thickness; DEX, dexamethasone implant; IOP, intraocular pressure; Naïve, previously untreated; NR, not reported; ns, not significant; prev treatment, previously treated; PRN, pro re nata; VEGF, vascular endothelial growth factor.
### Table 2 Published studies on the use of DeX implant for Irvine–Gass syndrome

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<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>No of eyes</th>
<th>Previous treatment</th>
<th>Treatment</th>
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<th>CMT</th>
<th>Complications</th>
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</thead>
<tbody>
<tr>
<td>Williams et al&lt;sup&gt;33&lt;/sup&gt;</td>
<td>Prospective multicenter randomized</td>
<td>41 uveitis + IGS (27)</td>
<td>Laser Medical therapy</td>
<td>DEX 0.7 mg or DEX 0.35 mg observation</td>
<td>6 months</td>
<td>NR</td>
<td>53.8% improvement ≥ 10 L after 3 months (P=0.029) 41.7% improvement ≥ 10 L after 3 months (P=0.117) 14.3% improvement ≥ 10 L after 3 months (P=0.009)</td>
<td>NR</td>
<td>31% IOP &gt;25 mmHg (0.7 mg)</td>
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<tr>
<td>Meyer and Schönfeld&lt;sup&gt;24&lt;/sup&gt;</td>
<td>Case report</td>
<td>1</td>
<td>3 IVT 0.4 mg dexamethasone</td>
<td>I DEX</td>
<td>4 months</td>
<td>NR</td>
<td>From 0.30 to 0.8 (for at least 3 months) From 0.62±0.15 logMAR to 1 month: 0.47±0.21 (P=0.008) 3 months: 0.37±0.24 (P=0.001) 6 months: 0.37±0.26 (P=0.002)</td>
<td>From 393 µm to 212 µm after 3 months (P=0.031)</td>
<td>NR</td>
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<tr>
<td>Dutra Medeiros et al&lt;sup&gt;35&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>9</td>
<td>CAIs Topical NSAIDs Corticosteroids IVT anti-VEGF IVT TA</td>
<td>I DEX</td>
<td>6 months</td>
<td>NR</td>
<td>From 0.62±0.15 logMAR to 1 month: 0.47±0.21 (P=0.008) 3 months: 0.37±0.24 (P=0.001) 6 months: 0.37±0.26 (P=0.002)</td>
<td>From 542.22±134.78 µm to 350.88±98.71 µm after 3 months (P=0.001) 3 months: 319.22±60.96 µm (P=0.002) 6 months: 398.33±127.89 µm (P=0.001)</td>
<td>NR</td>
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<td>Brynskov et al&lt;sup&gt;36&lt;/sup&gt;</td>
<td>Case report</td>
<td>1</td>
<td>TA Sub-Tenon’s 5 Ranibizumab IVT</td>
<td>DEX</td>
<td>12 Second DEX (187 days later)</td>
<td>First DEX: from 78 ETDRS letters to 76 (P&lt;0.001) Second DEX: from 76 ETDRS letters to 85 (P=0.002)</td>
<td>Re: from 20/70 to 20 days 20/20</td>
<td>NR</td>
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<tr>
<td>Fenicia et al&lt;sup&gt;37&lt;/sup&gt;</td>
<td>Case report</td>
<td>1 patient (2 eyes)</td>
<td>RE: topical NSAIDs Oral indomethacin 3 peribulbar methylprednisolone LE: topical NSAIDs Oral indomethacin Ranibizumab IVT</td>
<td>RE: DEX + Ranibizumab IVT (84 days later)</td>
<td>NR</td>
<td>LE: DEX</td>
<td>1 month: VA 44% (P=0.625 vs TA) 2 months: VA 39% (P=0.941 vs TA) 3 months: VA 39% (P=0.553 vs TA) 6 months: VA 33% (P=0.856 vs TA)</td>
<td>1 month: −175 µm (mean change), P=0.783 vs TA 2 months: −145 µm (mean change), P=0.044 vs TA 3 months: −126 µm (mean change), P=0.049 vs TA</td>
<td>1 month: 6% IOP &gt;21 mmHg 2 months: 6% IOP &gt;21 mmHg 3 months: 6% IOP &gt;21 mmHg 6 months: 0% IOP &gt;21 mmHg (P=0.044)</td>
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<td>Dang et al&lt;sup&gt;38&lt;/sup&gt;</td>
<td>Prospective, nonrandomized, comparative</td>
<td>18</td>
<td>Topical steroids Topical NSAIDs</td>
<td>DEX</td>
<td>6 months</td>
<td>NR</td>
<td>1 month: VA 44% (mean change), P=0.625 vs TA 2 months: VA 39% (mean change), P=0.941 vs TA 3 months: VA 39% (mean change), P=0.553 vs TA 6 months: VA 33% (mean change), P=0.856 vs TA</td>
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<td>Bonfiglio et al</td>
<td>Retrospective</td>
<td>25</td>
<td>TA</td>
<td>15 1 IVT TA</td>
<td>1 month: VAI 52% (mean change)</td>
<td>6 months: −125 µm (mean change), P=0.812 vs TA</td>
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<td>9 2 IVT TA</td>
<td>2 months: VAI 40% (mean change)</td>
<td>1 month: −193 µm (mean change)</td>
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<td>1 3 IVT TA</td>
<td>3 months: VAI 48% (mean change)</td>
<td>2 months: −95 µm (mean change)</td>
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<td>6 months: VAI 36% (mean change)</td>
<td>3 months: −173 µm (mean change)</td>
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<td>6 months: −140 µm (mean change)</td>
<td>6 months: VAI</td>
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<td>Furino et al</td>
<td>Retrospective</td>
<td>11</td>
<td>NR</td>
<td>1 DEX</td>
<td>From 20/40 to 20/22 (P&lt;0.0001)</td>
<td>From 462±100 µm to 276±8 µm (P&lt;0.0001)</td>
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<td>Al Zamil</td>
<td>Retrospective</td>
<td>11</td>
<td>Oral CAIs</td>
<td>1 DEX</td>
<td>From 0.58±0.17 logMAR to 1 month: 0.37±0.16 logMAR (P=0.008)</td>
<td>From 513.8±134.9 µm to 1 month: 371.6±91.9 µm (P=0.001)</td>
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<td>Topical NSAIDs</td>
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<td>3 months: 0.20±0.13 logMAR (P=0.001)</td>
<td>3 months: 302.6±50.9 µm (P=0.002)</td>
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<td>Corticosteroids</td>
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<td>6 months: 0.21±0.15 logMAR (P=0.002)</td>
<td>6 months: 308.0±54.5 µm (P=0.031)</td>
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<td>IVT anti-VEGF</td>
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<tr>
<td>Khurana et al</td>
<td>Prospective case series</td>
<td>6</td>
<td>Topical NSAIDs</td>
<td>1 DEX</td>
<td>From 0.3 to 1 month: 0.575 logMAR (mean)</td>
<td>1 month: −100 µm (mean change) (P&lt;0.01)</td>
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<td>3 months: 0.575 logMAR (mean)</td>
<td>6 months: −72 µm (mean change) (P=0.004)</td>
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<tr>
<td>Ortega-Evangelico and Diago Sempere</td>
<td>Retrospective</td>
<td>4</td>
<td>NR</td>
<td>1 DEX</td>
<td>From 0.3 to 1 month: 0.575 logMAR (mean)</td>
<td>From 414 µm to 1 month: 330.25 µm (mean change)</td>
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<td>3 months: 0.575 logMAR (mean)</td>
<td>3 months: 346.75 µm (mean change)</td>
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<tr>
<td>Study</td>
<td>Design</td>
<td>Patients</td>
<td>Baseline</td>
<td>Treatment</td>
<td>Follow-up</td>
<td>Results</td>
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<tr>
<td>Mylonas et al.</td>
<td>Prospective randomized</td>
<td>29</td>
<td>NR</td>
<td>14 IVTA</td>
<td>6</td>
<td>From 63±13 L to 1 month: 73±11 L (P=0.001) 3 months: 73±11 L (P=0.001) 6 months: 71±13 L (P=0.001)</td>
<td>From 51±121 µm to 1 month: 355±59 µm (P=0.003) 3 months: 389±89 µm (P=0.001) 6 months: 365±74 µm (P=0.002)</td>
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<td>EPISODIC 2</td>
<td>Retrospective</td>
<td>58 IGS of 100 overall</td>
<td>Baseline mean</td>
<td>1 DEX</td>
<td>24 months</td>
<td>Baseline 518.13±117.2 µm 18 months: 346.7±115.7 µm (P&lt;0.001) 24 months: 340.2±116 µm (P=0.05)</td>
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<tr>
<td>Sacchi et al.</td>
<td>Case report</td>
<td>1</td>
<td>Sub Tenon's betamethasone</td>
<td>1 DEX</td>
<td>6 months</td>
<td>From 20/40 to 1 month: NR IOP &gt;21 mmHg</td>
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</tbody>
</table>

**Abbreviations:** BCVA, best corrected visual acuity; CAIs, carbonic anhydrase inhibitors; CMT, central macular thickness; DEX, dexamethasone implant; ETDRS, Early Treatment Diabetic Retinopathy Study; IGS, Irvine-Gass syndrome; IOP, intraocular pressure; IVT, intravitreal; IVTA, intravitreal triamcinolone acetonide; L, ETDRS letters; LE, left eye; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; RE, right eye; TA, triamcinolone acetonide; VAI, visual acuity improvement >10 L; VEGF, vascular endothelial growth factor.
have been used to reduce intraocular inflammation, tighten capillary walls, and suppress cell proliferation, also having anti-VEGF properties.\textsuperscript{58} (Table 5).

In one case, DEX implant led to a resolution of the exudative retinal detachment allowing laser photoagulation of telangiectatic vessels.\textsuperscript{53} In other cases, final BCVA was influenced by subfoveal fibrosis, present at the time of the treatment\textsuperscript{59} or existing over a long-term.\textsuperscript{60}

## Radiation maculopathy

Several treatments have been proposed for radiation maculopathy, including laser photoagulation, PDT, pericoroidal injection of TA, IV anti-VEGF and, most recently, DEX implant (Table 6).\textsuperscript{62-66} All of these studies demonstrated a significant anatomical benefit with DEX implant in cases of recalcitrant radiation macular edema, with significant changes in visual acuity in most of the cases. Two comparative studies\textsuperscript{65,67} comparing DEX implant with anti-VEGF therapy, found no difference in outcomes, and a reduction in the number of injections in DEX-treated eyes.\textsuperscript{65}

IOP increased in some eyes,\textsuperscript{63,64,66} all successfully treated by topical hypotonizing therapy. Cataract development in these cases\textsuperscript{64-66} could be caused by DEX or the radiation therapy.

### Retinitis pigmentosa

The exact pathogenesis of macular edema, whether it is related to chronic and low-grade inflammatory process\textsuperscript{69} or to autoimmune process as antiretinal antibodies\textsuperscript{70} or to the failure of the retinal pigment epithelium pumping mechanism, is unknown as yet.\textsuperscript{71} Treatments attempted include topical and systemic administration of CAI,\textsuperscript{71} NSAIDs, retinal laser photocoagulation, vitrectomy surgery,\textsuperscript{72} and IV anti-VEGF.\textsuperscript{73} Also, IV corticosteroids injections have been performed as these drugs may modulate the inflammatory mediators and the autoimmune process.\textsuperscript{74-76}

The studies reporting on the use of DEX in macular edema related to retinitis pigmentosa consist of case report studies, which include only a few eyes (Table 7).\textsuperscript{77-80} Nevertheless, an anatomical and functional improvement has been shown, but a relapse of macular edema occurred before 6 months from the implant\textsuperscript{77} and an additional DEX was required in some cases;\textsuperscript{77,78} DEX implant proved to be safe with an IOP rise >21 mmHg recorded in only one eye.\textsuperscript{78}

## Table 3 DEX in vasoproliferative retinal tumors

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>No of eyes</th>
<th>Previous treatment</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Retreatment</th>
<th>BCVA</th>
<th>CMT</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cebeci et al\textsuperscript{49}</td>
<td>Case report</td>
<td>3</td>
<td>IVT BEV</td>
<td>DEX</td>
<td>12 months</td>
<td>1 DEX + PDT (1 week after)</td>
<td>From 20/25 to 20/40</td>
<td>NR</td>
<td>I subcapsular cataract</td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best corrected visual acuity; BEV, bevacizumab; CMT, central macular thickness; DEX, dexamethasone implant; IVT, intravitreal; NR, not reported; PDT, photodynamic therapy.

## Table 4 Published studies on the use of DEX implant for retinal telangiectasia

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>No of eyes</th>
<th>Previous treatment</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Retreatment</th>
<th>BCVA</th>
<th>CMT</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sandali et al\textsuperscript{53}</td>
<td>Case report</td>
<td>1</td>
<td>3 BEV IVT</td>
<td>DEX</td>
<td>15 months</td>
<td>2 DEX</td>
<td>From 20/32 to 1 month: 20/20</td>
<td>From 398 (\mu) m to 1 month: 250 (\mu) m</td>
<td></td>
</tr>
<tr>
<td>Loutfi et al\textsuperscript{54}</td>
<td>Case report</td>
<td>1</td>
<td>3 BEV IVT</td>
<td>DEX</td>
<td>NR</td>
<td>3 DEX</td>
<td>From 0.3 to 0.59 logMAR: 6 weeks after 1st DEX; from 0.3 to 0.64 logMAR: 6 weeks after 2nd DEX; from 0.3 to 0.78 logMAR: 2 weeks after 3rd DEX</td>
<td>From 397 (\mu) m to 286 (\mu) m: 1° DEX; 6 weeks after 2° DEX; 279 (\mu) m; 2 weeks after 3° DEX</td>
<td></td>
</tr>
<tr>
<td>Lei and Lam\textsuperscript{62}</td>
<td>Retrospective</td>
<td>1</td>
<td>8 ranibizumab</td>
<td>DEX</td>
<td>17 months</td>
<td>4 DEX</td>
<td>From 1 to 52 weeks: 0.5 logMAR</td>
<td>From 607 (\mu) m to 52 weeks: 346 (\mu) m</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best corrected visual acuity; BEV, bevacizumab; CMT, central macular thickness; DEX, dexamethasone implant; IVT, intravitreal; IVTA, intravitreal triamcinolone acetonide; NR, not reported.
### Table 5: DEX implant in Coats’ disease

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>No of eyes</th>
<th>Previous treatment</th>
<th>Primary treatment</th>
<th>Follow-up</th>
<th>Retreatment</th>
<th>BCVA</th>
<th>CMT</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Saatci et al&lt;sup&gt;60&lt;/sup&gt;</td>
<td>Case report</td>
<td>2</td>
<td>5 ranibizumab IVT + laser photocoagulation in 1 eye</td>
<td>DEX in one patient DEX + laser photocoagulation in the other patient</td>
<td>12 months 6 months</td>
<td>NR</td>
<td>Unchanged</td>
<td>NR</td>
<td>IOP rise &gt;25 mmHg in both eyes</td>
</tr>
<tr>
<td>Martínez-Castillo et al&lt;sup&gt;61&lt;/sup&gt;</td>
<td>Case report</td>
<td>1</td>
<td>None</td>
<td>DEX + laser photocoagulation</td>
<td>12 months</td>
<td>NR</td>
<td>From 20/200 to 20/25</td>
<td>NR</td>
<td>None</td>
</tr>
<tr>
<td>Lei and Lam&lt;sup&gt;62&lt;/sup&gt;</td>
<td>Retrospective chart review</td>
<td>1</td>
<td>3 BEV IVT + laser photocoagulation</td>
<td>DEX</td>
<td>16 months</td>
<td>3 DEX</td>
<td>From 1.3 to 52 weeks: 1.8 logMAR</td>
<td>From 821 µm to 52 weeks: 589 µm</td>
<td>None</td>
</tr>
</tbody>
</table>

**Abbreviations:** BCVA, best corrected visual acuity; BEV, bevacizumab; CMT, central macular thickness; DEX, dexamethasone implant; IOP, intraocular pressure; IVT, intravitreal; NR, not reported.

### Table 6: Published studies on the use of DEX implant for radiation maculopathy

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>No of eyes</th>
<th>Previous treatment</th>
<th>Primary treatment</th>
<th>Follow-up</th>
<th>Retreatment</th>
<th>BCVA</th>
<th>CMT</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baillif et al&lt;sup&gt;63&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>5</td>
<td>None</td>
<td>DEX</td>
<td>6.4 months</td>
<td>3 eyes: 1 DEX 2 eyes: 2 DEX</td>
<td>From 41 L to 2 months: 47 L</td>
<td>From 487.1 µm to 2 months: 331.2 µm</td>
<td>I eye IOP rise &gt;25 mmHg</td>
</tr>
<tr>
<td>Caminal et al&lt;sup&gt;64&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>12</td>
<td>2 laser 2 VEGF IVT 5 laser + anti-VEGF IVT</td>
<td>DEX</td>
<td>8.2±7.8 months</td>
<td>1 eye: 2 DEX</td>
<td>From 1±0.58 to 0.8±1.58 logMAR (P=0.091)</td>
<td>From 416±263 to 254±170 µm (P=0.016)</td>
<td>I eye cataract</td>
</tr>
<tr>
<td>Russo et al&lt;sup&gt;65&lt;/sup&gt;</td>
<td>Retrospective comparative</td>
<td>16</td>
<td>NR</td>
<td>8 DEX 8 ranibizumab IVT</td>
<td>Range 7–52 months 2.4±0.9 DEX (24 months) (P=0.018 vs ranibizumab) 6±1.8 ranibizumab (24 months)</td>
<td>DEX: from 0.45±0.18 to last follow-up: 0.27±0.15 logMAR (P=0.011) Ranibizumab: from 0.49±0.14 to last follow-up: 0.34±0.13 logMAR (P=0.012)</td>
<td>From 437±71 µm to last follow-up: 254±44 µm (P=0.012)</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

(Continued)
Table 6 (Continued)

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>No of eyes</th>
<th>Primary treatment</th>
<th>Follow-up</th>
<th>Retreatment</th>
<th>BCVA</th>
<th>CMT</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bui et al&lt;sup&gt;66&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>2</td>
<td>16 BEV IVT +4 IVTA</td>
<td>DEX</td>
<td>NR</td>
<td>2 DEX</td>
<td>From 20/60 Snellen to 3 months: unchanged</td>
<td>From 456 to 238 µm after first DEX, 277 µm after second DEX</td>
</tr>
<tr>
<td>Seibel et al&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Retrospective comparative</td>
<td>5 DEX</td>
<td>None</td>
<td>BEV</td>
<td>1–2 DEX</td>
<td>IVTA (range 1–10)</td>
<td>From 440 µm to 4 weeks 265 µm (P=0.049)</td>
<td>2 IOP rise</td>
</tr>
<tr>
<td>Tarmann et al&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>4</td>
<td>BEV IVT in 3 eyes BEV IVT + panretinal laser photocoagulation and IVTA in 1 eye</td>
<td>DEX</td>
<td>NR</td>
<td>NR</td>
<td>From 20/100 Snellen to 2–4 weeks 20/50 to 10 weeks 20/80 Snellen to 14–17 weeks: 20/100 Snellen</td>
<td>1 eye IOP</td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best corrected visual acuity; BEV, bevacizumab; CMT, central macular thickness; DEX, dexamethasone implant; IOP, intraocular pressure; IVT, intravitreal; IVTA, intravitreal triamcinolone acetonide; NR, not reported; VEGF, vascular endothelial growth factor.

Table 7 DEX implant in retinitis pigmentosa

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>No of eyes</th>
<th>Previous treatment</th>
<th>Treatment</th>
<th>Follow-up</th>
<th>Retreatment</th>
<th>BCVA</th>
<th>CMT</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Srour et al&lt;sup&gt;67&lt;/sup&gt;</td>
<td>Retrospective</td>
<td>4</td>
<td>CAIs in all cases subtenon TA 1 case NSAIDs in 2 cases</td>
<td>DEX</td>
<td>6 months</td>
<td>2 DEX in 2 eyes after 3 months</td>
<td>From 20/160 to 6 months: 20/125 after 1 DEX</td>
<td>From 443±185 µm to 6 months: 30±24 µm after 1 DEX</td>
<td>None</td>
</tr>
<tr>
<td>Ahn et al&lt;sup&gt;68&lt;/sup&gt;</td>
<td>Case report</td>
<td>2 eyes of one patient</td>
<td>CAIs Anti-VEGF IVT</td>
<td>DEX</td>
<td>12 months</td>
<td>2 DEX in 1 eye 6 months after DEX</td>
<td>From 20/100 to 12 months: 20/60 RE from 20/150 to 12 months: 20/100 LE from 2/10 to 1 week: 4/10 both eyes</td>
<td>From 43±185 µm to 6 months: 30±24 µm after 1 DEX</td>
<td>IOP rise</td>
</tr>
<tr>
<td>Saatci et al&lt;sup&gt;69&lt;/sup&gt;</td>
<td>Case report</td>
<td>2 eyes of one patient</td>
<td>Topical CAIs</td>
<td>I DEX</td>
<td>7 months</td>
<td>NR</td>
<td>From 2/10 to 1 week: 4/10 both eyes 3 months: 2/10 both eyes</td>
<td>From 616 µm to 2–4 weeks 399 µm to 10 weeks 393 µm to 14–17 weeks: 568 µm Snellen</td>
<td>NR</td>
</tr>
<tr>
<td>Patil and Lottery&lt;sup&gt;70&lt;/sup&gt;</td>
<td>Case report</td>
<td>1</td>
<td>Topical CAIs Depo-Medrone Parabulbar Anti-VEGF IVT</td>
<td>I DEX</td>
<td>10 months</td>
<td>NR</td>
<td>From 1.01 logMAR to 6 weeks: 0.89 logMAR</td>
<td>From 559 µm to 6 weeks: 271 µm</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best corrected visual acuity; CAIs, carbonic anhydrase inhibitors; CMT, central macular thickness; DEX, dexamethasone implant; IOP, intraocular pressure; IVT, intravitreal; IVTA, intravitreal triamcinolone acetonide; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; RE, right eye; TA, triamcinolone acetonide; VEGF, vascular endothelial growth factor.
Table 8 Published studies on the use of DEX implant for other conditions

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study design</th>
<th>No of eyes</th>
<th>Previous treatment</th>
<th>Primary treatment</th>
<th>Follow-up</th>
<th>Retreatment</th>
<th>BCVA</th>
<th>CMT</th>
<th>Complications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furino et al</td>
<td>Retrospective</td>
<td>8 PPV + ILM peeling + cataract surgery</td>
<td>Diclofenac sodium and betamethasone drops</td>
<td>DEX</td>
<td>6.75±0.71 month</td>
<td>NR</td>
<td>From 20/50 to 20/23</td>
<td>From 438±45 µm to 296±49 µm</td>
<td>P&lt;0.00001</td>
</tr>
<tr>
<td>Taney et al</td>
<td>Retrospective</td>
<td>5 PPV with ERM peeling</td>
<td>Topical prednisolone 1% Topical NSAIDs Subtenon TA IVTA in 1 eye Anti-VEGF IVT in 3 eyes Anti-VEGF IVT 1 eye</td>
<td>DEX</td>
<td>NR</td>
<td>1 DEX in 3 eyes 9 DEX in 1 eye 7 DEX in 1 eye</td>
<td>3 Snellen lines improvement in 3 eyes at 4–6 weeks after DEX</td>
<td>Mean CMT decrease of 106 µm (range 56–155 µm) in 4 eyes at 4–6 weeks after DEX</td>
<td>1 eye IOP &gt;25 mmHg Cataract in 1 out of the 2 phakic eyes</td>
</tr>
<tr>
<td>Merkoudis and Granstam</td>
<td>Case report</td>
<td>1 PPV + ILM peeling and C3F8 tamponade + cataract surgery</td>
<td>IVTA Topical NSAIDs Oral CAI Anti-VEGF IVT</td>
<td>I DEX</td>
<td>10 months</td>
<td>NR</td>
<td>From 20/200 to 2 months: 20/40</td>
<td>Reduction of CMT 2 months after DEX</td>
<td>None</td>
</tr>
<tr>
<td>Georgalas et al</td>
<td>Case report</td>
<td>1 PPV + ILM peeling cataract surgery</td>
<td>Topical steroids Subtenon steroids Intravitreal steroids</td>
<td>I DEX</td>
<td>6 months</td>
<td>NR</td>
<td>From counting fingers to 1 week: 6/36</td>
<td>From 640 µm to 1 week: 383 µm</td>
<td>None</td>
</tr>
<tr>
<td>Bonfiglio et al</td>
<td>Case report</td>
<td>1 scleral buckling + cryopexy</td>
<td>Oral prednisolone Oral CAI Topical prednisolone Topical NSAIDs TA Subtenon</td>
<td>I DEX</td>
<td>6 months</td>
<td>NR</td>
<td>From 0.70 to 6 months: 0.20 logMAR</td>
<td>From 510 µm to 6 months: 290 µm</td>
<td>None</td>
</tr>
</tbody>
</table>

Abbreviations: BCVA, best corrected visual acuity; CAI, carbonic anhydrase inhibitor; CMT, central macular thickness; DEX, dexamethasone implant; ERM, epiretinal membrane; ILM, inner limiting membrane; IOP, intraocular pressure; IVT, intravitreal; IVTA, intravitreal triamcinolone; NR, not reported; NSAIDs, nonsteroidal anti-inflammatory drugs; PPV, pars plana vitrectomy; TA, triamcinolone acetonide; VEGF, vascular endothelial growth factor.
DEX implant in macular edema after retinal surgery
DEX implant was used also in case of macular edema secondary to PPV for epiretinal membrane or macular hole or scleral buckling (Table 8). In all cases, an anatomical and functional improvement was shown, even though in 2 cases, multiple DEX implants were performed because of recurrent macular edema. Additionally, the use of DEX allowed resolution of severe choroidal inflammation detected in 1 case following scleral buckle surgery.

Conclusion
The use of DEX implant for all of the aforementioned macular pathologies merits consideration, and the results reported can support the use of DEX implant on a case-by-case basis with the aim of improving patient outcomes in many macular pathologies.

In many of these cases, DEX implant allowed a reduction of CMT with an improvement of BCVA, even if, at long term, many eyes required retreatment because DEX implant started to lose its efficacy, sometimes at 3 months after the injection.

Many of these cases were refractory to previous treatments, and DEX implant was administered as the last treatment option. Consequently, the functional results provided may be influenced by the lateness of DEX implant use. Therefore, considering that many of the reported macular pathologies may be difficult to treat and that some of them are not especially uncommon, having an awareness of a new treatment option and its influence on the clinical course of the disease may represent a great assistance in clinical practice. Furthermore, the use of DEX remains the only solution in treating macular edema in vitrectomized eyes where the efficacy of other IV drug injections, such as anti-VEGF, is lost due to their pharmacokinetic properties.

DEX implant-related adverse events in this expanding-use scenario are consistent with those previously documented for the DEX treatment of diabetic macular edema, uveitis, and retinal vein occlusion. In the cases that we analyzed, cataract was reported in up to 33% of the eyes after 2 DEX implants, and the occurrence of ocular hypertension (IOP ≥25 mmHg) from 6% to 31%, all treated with topical therapy.

In conclusion, DEX implant may allow less frequent anti-VEGF treatment and therefore, the advantages for the patient are clear: the need to undergo stressful treatment is removed while ocular and systemic adverse effects are reduced.

Acknowledgments
We thank Ray Hill, an independent medical writer, who provided English-language editing and journal styling before submission on behalf of Health Publishing & Services Srl. Technical editing and publication fees for this manuscript were supported by Allergan.

Author contributions
All authors contributed to developing the concepts, design, and/or analysis and interpretation of data in this review, writing/revising the manuscript, and approved the final version before submission and agreed to be accountable for all aspects of the work.

Disclosure
The authors report no conflicts of interest in this work.

References


