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BACKGROUND AND OBJECTIVE: To assess the effect on best-corrected visual acuity (BCVA) and efficacy of the intravitreal sustained-release 0.7 mg dexamethasone implant (Ozurdex; Allergan, Irvine, CA) in patients with recalcitrant diabetic macular edema (DME).

PATIENTS AND METHODS: Meta-analysis utilizing the MOOSE framework and a random effects model. Studies included adults undergoing treatment with Ozurdex for DME. The methodologic quality of each study was assessed using the MINORS and the Cochrane Collaboration Risk of Bias for randomized studies.

RESULTS: A total of 3,859 patients among 15 studies were included in the final analysis. The mean difference in BCVA was a gain of four lines or 20 Early Treatment of Diabetic Retinopathy Study letters with Ozurdex at a mean follow-up period of 6 months.

CONCLUSIONS: Treatment with Ozurdex is associated with significant mean improvement in visual acuity. Clinicians should have a multimodality approach to treating DME and be aware of this treatment option in those who have a suboptimal response to anti-VEGF therapy.


INTRODUCTION

In the 1980s, the Early Treatment of Diabetic Retinopathy Study (ETDRS) established laser photocoagulation as the gold-standard treatment of diabetic macular edema (DME). 1 Although laser photocoagulation significantly reduces the risk of moderate vision loss, large vision gains have been infrequent. More recently, vascular endothelial growth factor (VEGF) inhibition has been established as providing better visual outcomes compared to laser photocoagulation in DME and is regarded as first-line therapy for center-involving DME. 2-6 Depending upon the evidence examined, reported improvements in vision using anti-VEGF therapy have been up to approximately 11 letters to 15 letters; however, up to 40% of patients fail to achieve these gains after 6 months of intensive therapy. 12,13

Corticosteroids serve to dampen the downstream proinflammatory products in DME and downregulate a variety of damaging pathways, including the production of VEGF. 11 Although studies have shown that intraocular corticosteroids resolve DME, 3,13 the extent of this visual improvement in these cases has been variable, particularly when considering cataract progression and its short half-life in the vitreous cavity. 2,3 As such, a biodegradable 0.7 mg dexamethasone intravitreal implant (Ozurdex; Allergan, Irvine, CA) was created to enable a steady release of steroid in the treatment of DME. 28

Ozurdex, in conjunction with or in place of anti-VEGF therapy, has been shown to improve visual outcomes in diabetic macular edema; 13 however, there...
is no evidence-based survey on the effect of Ozurdex in patients refractory to anti-VEGF therapy. Here, we present a meta-analysis on the efficacy of Ozurdex for DME in patients refractory to anti-VEGF blockade. Specifically, we elucidate clinically useful parameters on the efficacy of Ozurdex dosing in patients who may not optimally respond to anti-VEGF therapy.

PATIENTS AND METHODS

Literature Search

We searched MEDLINE from 1946 to present and Embase from 1947 to present (as of September 1, 2015). The search was restricted to English. The search included all the following study types: clinical trials, comparative studies, controlled clinical trials, meta-analyses, multicenter studies, randomized controlled trials, twin studies, and validation studies. The search excluded case reports, case series, and non-English studies. The MOOSE framework was utilized for the meta-analysis (outlined in Table).

Study Selection

We included all studies that assessed adult participants with DME and a history of suboptimal anti-VEGF therapy undergoing treatment with Ozurdex. A reasonable trial of anti-VEGF therapy was defined as three consecutive rounds of treatment. An incomplete response to anti-VEGF treatment was defined as failure of vision to improve due to persistent macular edema on clinical exam or imaging. All studies had to have discontinued anti-VEGF treatment during treatment with Ozurdex and must have published the following variables for its participants: number of patients, age, sex, pre- and posttreatment measures of best-corrected visual acuity (BCVA), and duration of follow-up (with a minimum follow-up of 3 months). Two reviewers (ZK, MK) independently screened the

Figure 1. PRISMA flow diagram for studies selected and reviewed. This demonstrates the flow of studies throughout our review. The 15 studies included three randomized, controlled trials; six retrospective studies; and six prospective observational studies.
citations, including titles and abstracts, and reviewed the full text of citations considered relevant. Studies were excluded if patients had alternative causes of macular edema such as secondary to retinal vein occlusion or noninfectious posterior uveitis.

Assessment of Study Methodologic Quality
The methodologic quality of each included study was assessed. The Methodological Index for Non-Randomized Studies (MINORS) was used to assess nonrandomized studies. The 12 items are scored as 0 (not reported), 1 (reported but inadequate), or 2 (reported and adequate). The global ideal score on this scale was 6 for noncomparative studies and 24 for comparative studies. To determine the quality of randomized studies, the Cochrane Collaboration Risk of Bias was used to grade the risk of bias as high, low, or unclear.

Outcome Measures
The primary outcome measure was mean change in BCVA after treatment with Ozurdex. Forest plots, funnel plots, and heterogeneity was carried out to summarize results. Efficacy of Ozurdex was assessed with respect to timing after anti-VEGF therapy.

Statistical Analysis
The meta-analysis was conducted using a random effects model with all variables decided a priori. All calculations were carried out using Comprehensive Meta-Analysis Software (Biostat, Englewood, NJ). Finally, heterogeneity was tested for using the I-squared (I²) statistic.

RESULTS
We identified 236 studies from our literature search strategy, from which 15 studies were included in our final analysis. All 236 articles underwent title and abstract screening, with 21 studies being excluded due to foreign language and 115 articles were excluded due to inapplicable content. Finally, 100 articles underwent full review. Among
these, 85 had no reported measures of prior treatment regimen, lacked detailed BCVA measurement, or failed to report complete follow-up duration. Figure 1 illustrates our PRISMA Flow Diagram. The total number of patients studied was 3,859. The 15 studies included three randomized control trials, six retrospective studies, and six prospective observational studies. The 12 nonrandomized studies had an average score of 22 out of 24 on the MINORS scale. All randomized clinical trials had a low risk of bias as ascertained with the Cochrane Collaboration Risk of Bias. Using the random effects model, patients treated with the Ozurdex for DME refractory to anti-VEGF therapy gained a mean of four lines (20 ETDRS letters). The mean follow-up period of patients in studies was 6 months (range: 3 months to 36 months). A test of heterogeneity found an I² value of 90.4. All patients were treated for recalcitrant diabetic macular edema with at least six prior treatments of intravitreal anti-VEGF therapy. Control groups in the randomized control trials were maintained on anti-VEGF therapy. The funnel plot (Figure 2) outlines five outlier studies; two of the five were marked as borderline studies and the remaining three were clear outliers indicating a degree of publication bias in the meta-analysis. The forest plot (Figure 3) plots the mean improvement in BCVA in all studies. The BCVA is plotted in logMAR and demonstrates an improvement in all 15 studies. Overall, the mean improvement in vision is 0.471 logMAR (range: 0.305 logMAR to 0.637 logMAR). This gain in vision is equivalent to approximately four lines (or 20 ETDRS letters) of visual acuity. The funnel plot (Figure 3) plots the mean improvement in BCVA in all studies. The BCVA is plotted in logMAR and demonstrates an improvement in all 15 studies. Overall, when all studies are considered, the mean improvement in vision is 0.471 logMAR (range: 0.305 logMAR to 0.637 logMAR).

**DISCUSSION**

The current meta-analysis demonstrates effectiveness of Ozurdex in the treatment of recalcitrant DME. To date, the treatment of anti-VEGF refractory DME poses a significant clinical challenge to ophthalmologists; however, our analysis shows that treatment with Ozurdex is associated with a significant mean improvement in visual acuity of four lines. Although patients received multiple anti-VEGF treatments, there was still a significant improvement in BCVA after switching to Ozurdex. Although at least six rounds of intravitreal anti-VEGF treatment were given and DME was deemed to be recalcitrant, it is possible that it was undertreated or the efficacy of this therapy can be slow to appear. With new evidence pointing to early consideration of corticosteroid therapy in DME, this study highlights...
# MOOSE Checklist

<table>
<thead>
<tr>
<th>Criteria</th>
<th>Brief Description of How the Criteria Were Handled in the Meta-Analysis</th>
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<tbody>
<tr>
<td><strong>Reporting of Background Should Include</strong></td>
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<tr>
<td>✔️ Problem definition</td>
<td>Quantify the mean change in BCVA after treatment with ozurdex</td>
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<tr>
<td>✔️ Hypothesis statement</td>
<td></td>
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<tr>
<td>✔️ Description of study outcomes</td>
<td>See attached</td>
</tr>
<tr>
<td>✔️ Type of exposure or intervention used</td>
<td>The intervention studied will be ozurdex treatment</td>
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<tr>
<td>✔️ Type of study designs used</td>
<td>Randomized trials and observational studies</td>
</tr>
<tr>
<td>✔️ Study population</td>
<td>– Human studies only&lt;br&gt;– Participants with diabetic macular edema</td>
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<tr>
<td><strong>Reporting of Search Strategy Should Include</strong></td>
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<tr>
<td>✔️ Qualifications of searchers</td>
<td>– 1 x Librarian at Bracken Health Sciences&lt;br&gt;– 1 x Masters of Librarian and Information Studies (candidate / student)&lt;br&gt;– 1 x Ophthalmology trainee</td>
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<tr>
<td>✔️ Search strategy, including time period included in the synthesis and keywords</td>
<td>See attached search strategy</td>
</tr>
<tr>
<td>✔️ Databases and registries searched</td>
<td>EMBASE; Medline; Medline in-process and other non-indexed citations; Cochrane database of systematic reviews – eye vision group</td>
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<td>✔️ Search software used, name and version, including special features</td>
<td>OVID</td>
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<tr>
<td>✔️ Use of hand searching</td>
<td>N/A</td>
</tr>
<tr>
<td>✔️ List of citations located and those excluded, including justifications</td>
<td>Citations included – see attached search strategies. Excluded with justifications</td>
</tr>
<tr>
<td>✔️ Method of addressing articles published in languages other than English</td>
<td>These articles will be excluded</td>
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<tr>
<td>✔️ Method of handling abstracts and unpublished studies</td>
<td>These are included in the initial search strategy (September 1, 2015). The search is repeated 3 months after initial search to include any further published and unpublished studies (December 1, 2015).</td>
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<tr>
<td>✔️ Description of any contact with authors</td>
<td>All contact with authors, if necessary, will be via email</td>
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<td><strong>Reporting of Methods Should Include</strong></td>
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<td>✔️ Description of relevance or appropriateness of studies assembled for assessing the hypothesis to be tested</td>
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<td>✔️ Rationale for the selection and coding of data</td>
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<td>✔️ Assessment of confounding</td>
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<td>✔️ Assessment of study quality, including blinding of quality assessors; stratification or regression on possible predictors of study results</td>
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<td>✔️ Assessment of heterogeneity</td>
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<td>✔️ Description of statistical methods in sufficient detail to be replicated</td>
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<tr>
<td>✔️ Provision of appropriate tables and graphics</td>
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that clinicians should have a multimodal approach to treating DME.

Ozurdex has recently been approved for treatment of DME, and with its approval and coverage, several clinical studies of various designs have shown positive results. Nonetheless, a comprehensive synthesis of the existing data examining this question has not been published. To our knowledge, this is the first meta-analysis that exclusively examines the effectiveness of Ozurdex in treating DME that is specifically refractory to anti-VEGF. This is timely to augment the ability to treat difficult cases of DME.

The mean follow-up in included studies was 6 months, with a minimum follow-up of 3 months, which we feel provides an adequate time window in assessing the efficacy of Ozurdex in refractory DME. However, it must be noted that the beneficial effect of Ozurdex on visual acuity will subside over time, and repeated injections may be necessary to maintain visual improvement. Longer follow-up times in ongoing studies is needed to help determine whether repeated injections will yield similarly promising effects.

Although objective measures of the frequency of adverse effects were not obtained, the following adverse effects of Ozurdex use were identified: increased intraocular pressure (IOP), cataract progression, retinal hemorrhage, vitreous hemorrhage, pain, retinal tear, retinal detachment, vitreous loss, endophthalmitis, hypotony, and subconjunctival hemorrhage. Some of these adverse events, such as vitreous loss or subconjunctival hemorrhage, were seen in only one study eye. Additionally, rise in IOP is a known side effect after intravitreal corticosteroids injections. Although our study did not specifically look at the IOP effect of patients included in the studies, there were no reports in any of the included studies of IOP elevations requiring surgical intervention.

Our study was limited by an $I^2$ value, suggesting a relatively high heterogeneity within the chosen studies. Nonetheless, until a greater number of studies are available to examine this question, heterogeneity is inevitable due to the varying study designs and follow-up periods of individual studies. Future directions for this review include an analysis of only randomized control trials as well as evaluating whether repeated injections will produce similar results with limited side effects.

In conclusion, treatment with Ozurdex is associated with a significant mean improvement in visual acuity of four lines (20 ETDRS letters) in cases of DME refractory to anti-VEGF therapy. Clinicians should be aware of patients who are responding inferiorly to anti-VEGF and consider corticosteroid
therapy to improve visual acuity outcomes. The modern era of DME therapy requires astute clinicians able to embrace multiple modalities to treat cases of diabetic macular edema.

REFERENCES


