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ORIGINAL ARTICLE

Long-term outcomes after intravitreal dexamethasone treatment in steroid responders

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Abstract

Aims Intravitreal steroid implants have emerged as an adjunctive therapy in diabetic macular edema (DME) in patients refractory to anti-vascular endothelial growth factor agents. However, the use of these agents in patients with a prior history of steroid-induced ocular hypertension is limited. The present study aimed to analyze long-term intraocular pressure (IOP) response to the dexamethasone implant in patients with DME and a history of steroid-induced increase in IOP.

Methods In a multicenter retrospective review, 17 eyes with DME and a history of steroid-induced increase in IOP to > 21 mmHg were treated with the dexamethasone implant and followed for 18 months. Patients with a history of vitrectomy of vitreoretinal interface pathology were excluded. The primary outcomes were the change in IOP and use of IOP-lowering agents.

Results Among the study population (17 eyes), there was no significant change in mean IOP from baseline through 18 months (15.9 ± 2.0–14.6 ± 2.8 mmHg; $p = 0.18$). The number of patients requiring IOP-lowering agents rose from 5 at baseline to 14 at 18 months ($p = 0.0049$). None of the study eyes required surgical treatment.

Conclusions Though dexamethasone does predictably lead to an increase in IOP, this adverse effect was effectively managed with topical treatment. The present study suggests that the intravitreal dexamethasone implant may be considered in patients with DME and a history of steroid-induced ocular hypertension who have exhausted first-line treatments.

Keywords Intravitreal dexamethasone · Diabetic macular edema · Optical coherence tomography · Steroid-induced ocular hypertension

Introduction

In recent years, several new pharmacological therapies have emerged for the treatment of diabetic macular edema (DME) [6, 8, 16]. Intravitreal anti-VEGF injections remain the most commonly utilized first-line agents as they have dramatically advanced outcomes in DME. However, not all patients benefit from treatment [2, 13]. After 2 years of monthly injections, residual macular edema measuring > 250 µm central thickness on optical coherence tomography (OCT) persisted in 20–25% of patients [13]. Additionally, approximately 40% of subjects did not achieve best-corrected visual acuity (BCVA) ≥ 20/40 [13].

Steroid therapies offer an additional treatment modality for patients who do not benefit from anti-VEGF treatment. The intravitreal dexamethasone implant (Ozurdex®, Allergan, Irvine, CA) has been shown to improve outcomes in DME [3]. In the randomized trials studying dexamethasone implant therapy (MEAD) for DME, 22.2% of patients had ≥ 15-letter improvement in BCVA from baseline at year 3 or final study visit [3]. Thus, steroid agents provide an additional treatment for patients with suboptimal responses after anti-VEGF therapy [4, 9]. However, the use of steroid agents

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The members of the Dex Implant Study Group was listed in “Appendix” section.

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is associated with risks including increases in intraocular pressure (IOP) [14, 17].

Ocular steroids have long been known to increase IOP. However, the original randomized trials evaluating the dexamethasone implant demonstrated that dexamethasone-induced increases in IOP could be managed effectively in a vast majority of patients [3]. While nearly one-third of subjects in each dexamethasone implant treatment group had a significant increase in IOP requiring treatment, mean IOP returned to baseline 6 months after each implant. Only 3 of the 690 patients that received a dexamethasone implant required trabeculectomy [3]. The SAFODEX study, a retrospective analysis of 421 eyes receiving the dexamethasone implant, examined real-world IOP responses [10]. With 1000 intravitreal injections, ocular hypertension was seen for 28.5% of injected eyes over a mean follow-up duration of 16.8 months. Thirty-one percent of eyes required IOP-lowering medication. Only three eyes with preexisiting glaucoma required filtering surgery to manage post-injection IOP elevation.

Though a majority of patients in the MEAD trials had controlled IOP after treatment with the dexamethasone implant, the exclusion criteria regarding IOP were strict. Patients were excluded if they had a history of glaucoma, history of steroid-induced rise in IOP, ocular hypertension > 23 mmHg without treatment, IOP > 21 mmHg treated with one IOP-lowering agent, or the use of two or more IOP-lowering agents [3]. Therefore, though the MEAD trials demonstrated the benefits of the dexamethasone implant in subjects with DME, the question remains as to whether dexamethasone can safely be used in patients known to have a history of steroid-induced increase in IOP.

The present study, a multicenter retrospective chart review, examined the outcomes of dexamethasone implant therapy in patients with DME who also had a documented history of steroid-induced rise in IOP.

Methods

Study design

The present investigation was a multicenter (seven site) retrospective chart review. The study was performed in concordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Institutional review board approval was obtained at each site.

Study population

Seventeen eyes with DME and a known history of steroid-induced increase in IOP to > 21 mmHg were included. Demographic details, diabetes history, measurements of visual acuity and retinal thickness, and treatment details were collected. All patients were followed for at least 18 months with visits at 1, 3, 6, 12, and 18 months. Inclusion criteria included: (1) documented diagnosis of DME, (2) age ≥ 18 years old, (3) recorded history of steroid-induced increase in IOP to a pressure > 21 mmHg, (4) ≤ 21 mmHg IOP before first dexamethasone implant, and (5) availability of recorded IOP and BCVA data throughout follow-up. Baseline BCVA was measured with refraction. All subjects received a dilated eye examination and OCT before receiving treatment with the dexamethasone implant. Eyes with vitreoretinal interface pathologies including epiretinal membrane, vitreomacular traction, macular hole or history of prior vitrectomy were excluded. Cases with confirmed diagnosis of primary open or angle closure glaucoma, and secondary glaucoma due to neovascularization (neovascular glaucoma), uveitis, and trauma were also excluded. Dexamethasone implant therapy was administered as per standard protocol. No perioperative complications including intraoperative lens injury, retinal detachment, and endophthalmitis occurred. Retreatment was based on clinician judgment informed by change in visual acuity and OCT findings.

Statistical methodology

The upper limit of normal IOP was defined as 21 mmHg. Baseline IOP was recorded at the outset of the study and subsequently at each follow-up visit. All IOP measurements were done using Goldmann applanation tonometer to maintain uniformity in IOP recordings. Mean baseline IOP was compared to mean IOP at each follow-up visit using paired t test. The number of eyes with pressures above normal at each study visit was documented. Eyes requiring medical and surgical management of IOP were recorded, including the type and number of agents used. Fisher's exact test was used to compare the number of eyes requiring IOP-lowering agent at baseline and 18-month follow-up. BCVA was converted from Snellen into LogMAR [7]. Paired t test was used to compare BCVA and central subfield thickness (CST) at baseline and each follow-up visit.

Multivariable regression analysis including age, gender, duration of diabetes, baseline IOP, and number of dexamethasone implants was performed to assess for factors correlating with the number of IOP-lowering agents required at the 18 month follow-up visit. Statistical analysis was completed with Stata (Stata data analysis and statistical software, version 13.0, StataCorp, College Station, TX, USA). A p value of < 0.05 was considered statistically significant.

Results

Seventeen eyes were included in the analysis, 15 from males and 2 from females. Ten subjects (58.8%) were of Indian ethnicity, six (35.3%) were Caucasian, and one (5.9%) was Asian. The mean age of subjects was 68.6 ± 10.9 years. Eleven of the seventeen eyes (64.7%) were pseudophakic at baseline. Seven eyes (41.2%) had lasered proliferative diabetic retinopathy at baseline, five (29.4%) had severe non-proliferative diabetic retinopathy (NPDR), four (23.5%) had moderate NPDR, and one eye (5.9%) had mild NPDR. The mean duration of diabetes among the subjects was 15.2 ± 6.2 years. All eyes had been previously treated for DME. Fourteen of the seventeen (82.4%) had received anti-VEGF agents. Thirteen eyes had received laser (76.5%) and nine (53%) had received triamcinolone injection. At baseline, all eyes had controlled pressures within normal range. The mean baseline IOP was 15.9 ± 2.0 mmHg. The mean baseline BCVA was 0.62 ± 0.38 LogMAR with a mean baseline CST of 599 ± 198 µm. Over the course of 18 months of follow-up, study eyes received a mean of 3.1 ± 1.9 injections.

The mean IOP at 18 months (14.6 ± 2.8 mmHg) was not significantly different from baseline (15.9 ± 2.0 mmHg, $p = 0.18$). Additionally, there was no significant difference between the mean baseline IOP and the mean IOP at each subsequent study visit (Fig. 1).Throughout the follow-up period, seven eyes (41.2%) had at least one recorded pressure above 21 mmHg (range of 22–45 mmHg). Only two eyes (11.8%) had pressures above 21 mmHg at two separate visits. At the 3-month visit, four eyes (23.5%) had elevated pressures (range of 22–45 mmHg) (Fig. 2). This number fell to three eyes (17.6%) at the 6-month follow-up (range

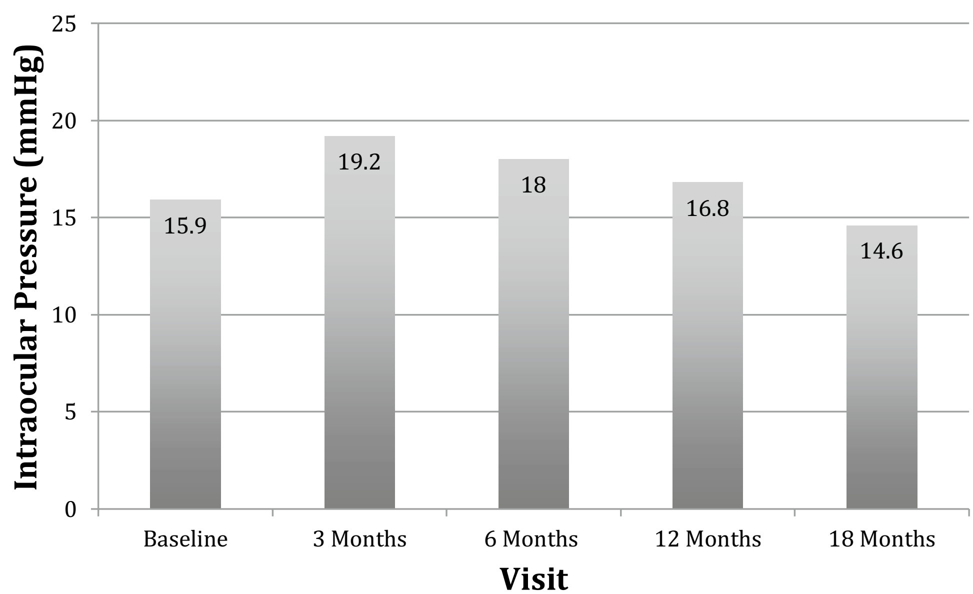

Fig. 1 Change in intraocular pressure from baseline to final 18-month visit

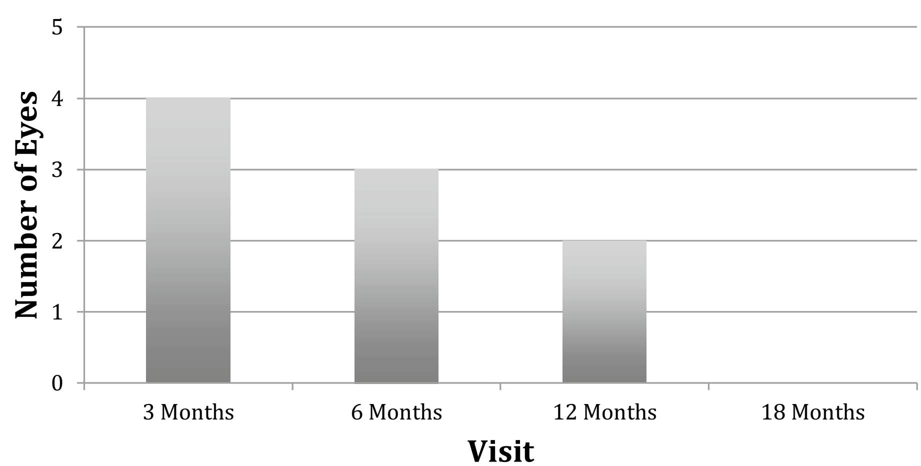

Fig. 2 Number of eyes with elevated intraocular pressure (> 21 mmHg) at each follow-up visit

of 23–30 mmHg) and two eyes (11.8%) at 12 months (range of 22–32 mmHg). None of the study eyes had pressures > 21 mmHg at the final study visit at 18 months.

Nine patients had a steroid response after intravitreal triamcinolone acetonide injection whereas another eight patients had steroid response after administration of topical steroids (prednisolone acetate). At baseline, 12 of the 17 eyes (70.6%) did not require any topical IOP-lowering agents (Fig. 3). The remaining five eyes (29.4%) were all using a single agent. Sixteen of the seventeen eyes (94.1%) required topical IOP-lowering agents at any point throughout the follow-up period. None of the eyes required incisional treatment for elevated pressures. By the 18-month visit, 14 of 17 eyes (82.4%) were requiring at least one IOP-lowering agent ($p = 0.0049$ compared to baseline). Five eyes (29.4%) were using one agent, eight (47.1%) were using two agents, and one (5.9%) required three agents. Thirteen eyes (76.5%) received beta-blocker-based therapy, ten (58.8%) received alpha agonist-based therapy, and eight (47.1%) had carbonic anhydrase-based treatment. Multivariable regression analysis including age, gender, duration of diabetes, baseline IOP, and number of dexamethasone implants received did not show any significant correlation with the number of agents required at 18 months.

There was a significant improvement in BCVA from baseline (0.62 ± 0.38 LogMAR) to 3 months (0.47 ± 0.37 LogMAR, $p = 0.0049$) (Fig. 4). However, by 6 months there was no longer any significant difference in BCVA compared to baseline (0.53 ± 0.44 LogMAR, $p = 0.0718$). No significant change in mean BCVA was observed after the 3-month visit throughout the 18 months of follow-up (0.67 ± 0.47 LogMAR at 18 months, $p = 0.63$). Eight of the seventeen eyes (47.1%) demonstrated improvements in LogMAR of − 0.1 or better, the equivalent of five or more Early Treatment

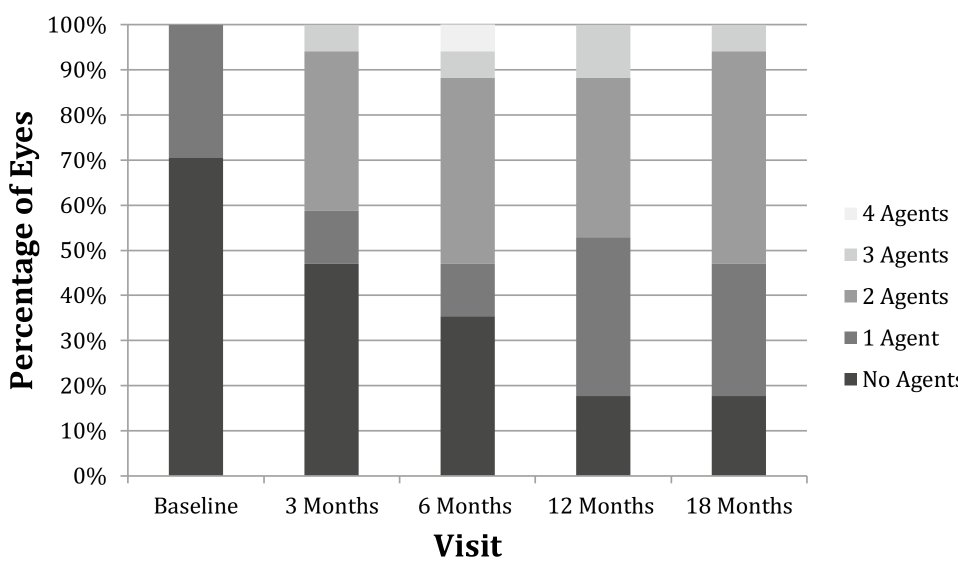

Fig. 3 Intraocular pressure-lowering agents required from baseline through 18 months

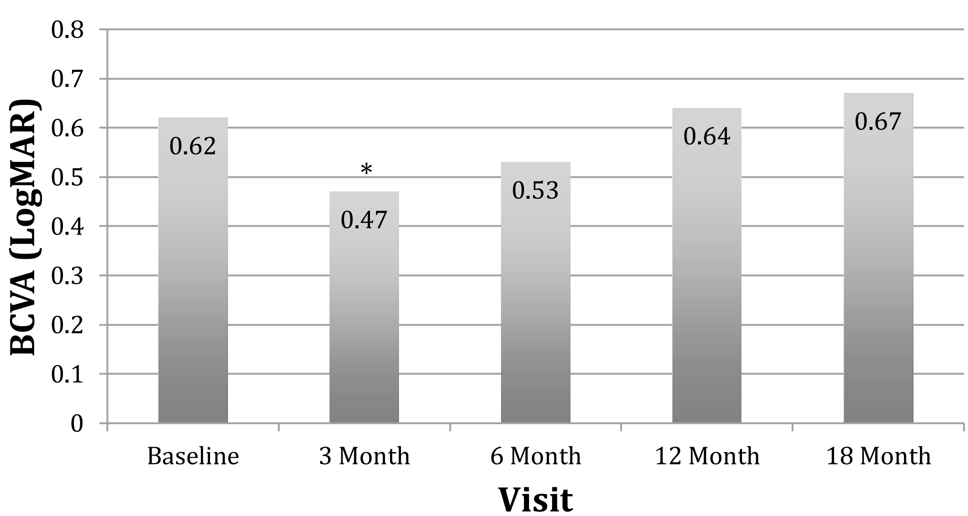

Fig. 4 Change in best-corrected visual acuity (BCVA) from baseline through 18 months. *$p = 0.0049$

Diabetic Retinopathy Study (ETDRS) letter gains. Mean CST significantly decreased from 599 ± 198 µm at baseline to 423 ± 123 µm at 18 months ($p = 0.02$) (Fig. 5). Six of the seventeen eyes (35.3%) were phakic at baseline. Four of these eyes (66.6%) underwent cataract surgery during the 18-month follow-up period.

Discussion

The benefits of dexamethasone implant therapy in DME, including in eyes failing prior treatment with anti-VEGF therapy, are well documented [1, 3]. However, because of the association of ocular steroid use and increases in IOP, the landmark studies that established the benefits of the dexamethasone implant excluded patients with a history of elevated IOP after steroid therapy [3, 5]. These same studies of dexamethasone also demonstrated that for a majority of subjects that did go on to develop elevated IOP, most were well controlled with topical therapy and the need for incisional treatment was rare [12]. Thus, the question remains as to whether steroid therapy may be safely used in patients with DME and a history of steroid-induced increases in IOP, particularly when they have exhausted other treatment options.

The present study in eyes with DME and a documented history of steroid-induced increases in IOP suggests that IOP increases may be controlled with topical therapy even in these high-risk patients. Though a vast majority of study eyes expectedly experienced increases in IOP after treatment, the elevations were controlled with topical IOP-lowering agents alone. After 18 months of follow-up, there was no significant change in mean IOP from baseline. Additionally, with the use of combination agents the patients' burden of treatment was not excessive as a majority (82.4%) did not require more than one drop at once during follow-up.

Initially, the mean BCVA significantly improved from baseline to the 3-month visit. However, by 6 months, there was no longer any significant improvement in BCVA. The lack of overall improvement in visual acuity in this study set is not unexpected given the recalcitrant nature of disease in these eyes. All eyes had previously been treated for DME without adequate improvement in BCVA and/or edema. Nevertheless, there was sustained, statistically significant improvement in macular edema over the course of 18 months, from 599 µm at baseline to 423 µm at 18 months on OCT. An improvement in CST without a significant improvement in BCVA was also seen in the DRCR Protocol U results, which compared combination dexamethasone and ranibizumab therapy to ranibizumab monotherapy [11]. The lack of improvement in BCVA in the setting of macular drying may be due to delayed time to the transition of therapy, when retinal structural damage may have already occurred. Larger studies including SD-OCT analysis will help to resolve this question.

The main limitations of this study are its small sample size and retrospective nature. Given the hesitation of clinicians to use steroid treatments in patients with documented histories of steroid-induced IOP response, it is difficult to gather large patient numbers in a study. Treatment criteria were also less stringent than in a prospective study. The definition of steroid response was intentionally broad as the data available in the medical records was not robust for all patients.

Despite these obstacles, the present study is of clinical significance in beginning to address the use of dexamethasone implant therapy in a population that is often not considered for steroid therapy nor included in randomized

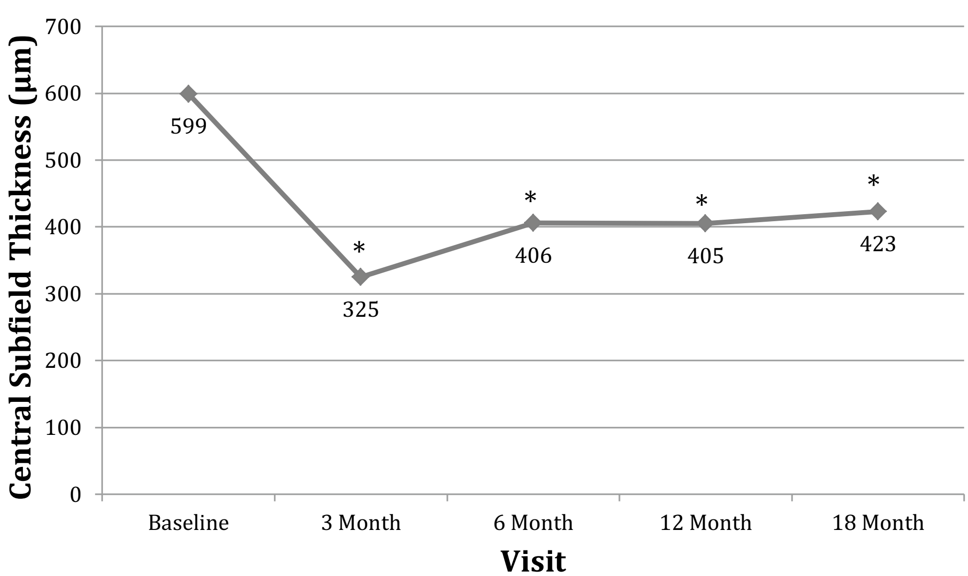

Fig. 5 Change in central subfield thickness from baseline through 18 months. *$p < 0.05$

controlled trials but may yet benefit from treatment. Similar results were found in a recent study examining patients with glaucoma who received the dexamethasone implant [15]. These patients exhibited increases in IOP that were well managed with topical therapy alone.

Ultimately, the present study suggests that for DME patients with a history of steroid-induced rise in IOP dexamethasone may be a safe treatment option when they have exhausted other treatment modalities. Though dexamethasone does predictably lead to an increase in IOP this adverse effect can be managed with topical treatment. Furthermore, these patients demonstrate significant macular drying after treatment. Thus, clinicians should not exclude the use of the dexamethasone implant in patients with DME solely because they have a documented history of steroid-induced increases in IOP. Earlier administration of the dexamethasone implant, before retinal structural damage occurs, may benefit these patients who are recalcitrant to other treatments such as intravitreal anti-VEGF injections.

Compliance with ethical standards

Conflict of interest (A) Funding/support: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. (B) Financial disclosures: Hasenin Al-khersan, MD has no financial disclosures. Seenu M. Hariprasad, MD is a consultant or on the speaker's bureau for Alcon, Allergan, Bayer, OD-OS, Clearside Biomedical, Ocular Therapeutix, Alimera Sciences, Leica, Spark Therapeutics, and Regeneron. Sumit Randhir Singh, MD has no financial disclosures. Jay Chabblani, MD is on the speaker's bureau for Allergan, Novartis, and OD-OS. (C) No acknowledgments are to be made. Rest authors declare that they have no conflict of interest.

Ethical approval The present investigation was a multicenter (seven site) retrospective chart review. The study was performed in concordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Institutional review board approval was obtained at each site.

Informed consent Institutional review board (IRB) approval was obtained at all sites. The study was performed in concordance with the Declaration of Helsinki and the Health Insurance Portability and Accountability Act. Given the retrospective nature of the study, informed consent waiver was approved by the respective IRBs.

Appendix

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