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ORIGINAL PAPER

Dexamethasone implant as an adjuvant therapy to ranibizumab loading dose in persistent diabetic macular edema

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Abstract

Purpose This study evaluates the effectiveness of a single-dose dexamethasone implant (DI) as an auxiliary therapy to continued intravitreal ranibizumab (IVR) treatment in patients with persistent diabetic macular edema (DME).

Methods Twenty-five pseudophakic eyes of 25 patients with DME who underwent a single injection of DI as an adjuvant therapy following an IVR loading dose were examined retrospectively. All patients were treatment naive and had a poor response to a loading dose of three consecutive monthly IVR injections. IVR treatments were continued pro re nata after the DI. The main outcome measures were changes in best-corrected visual acuity (BCVA) and central macular thickness (CMT) at 1, 3, 6 and 8 months post-DI treatment.

Results After the IVR loading dose, the mean BCVA and CMT were 0.9 ± 0.6 LogMAR and 478.2 ± 107.8 µm, respectively. One month after the DI, the mean BCVA and CMT had improved to 0.6 ± 0.4 LogMAR ($p = 0.005$) and 313.8 ± 62.7 µm ($p < 0.001$), respectively. This improvement was maintained with mean 0.8 ± 0.8 IVR injections throughout the follow-up period. The final mean BCVA and CMT were 0.5 ± 0.5 LogMAR and 298.4 ± 71.5 µm. Subgroup analyses revealed that different DME types did not have any effect on CMT or BCVA improvement ($p = 0.188$, $p = 0.136$; respectively).

Conclusion Adding DI results in rapid anatomical and visual improvement in patients who respond poorly to an IVR loading dose. Improvements may be maintained with additional IVR in follow-up.

Keywords Dexamethasone · Diabetic macular edema · Adjuvant therapy

Introduction

Diabetic macular edema (DME) is the most common cause of visual acuity loss in diabetic patients [1]. While the cause of DME is still under investigation, ischemia and inflammation both have key roles in the pathogenesis of DME. Several studies have reported that the increased permeability of macular capillaries in the course of hypoxia causes increased levels of vascular endothelial growth factor (VEGF) and proinflammatory factors, such as interleukin-6 (IL-6), IL-8 and prostaglandins [2, 3]. Due to increased VEGF levels, intravitreal anti-VEGF therapies have proven to be effective treatments for DME [4–6]. Although anti-VEGF therapy is a good option for DME, some

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patients do not respond to intravitreal anti-VEGF therapies. Therefore, other treatment options are needed.

In recent years, corticosteroid treatment has emerged as an alternative treatment for DME, due to its anti-inflammatory, anti-VEGF and anti-proliferative effects [7, 8]. Triamcinolone has been one of the corticosteroid agents used for DME. Although intravitreal triamcinolone has been shown to result in improved anatomical and functional outcomes, its usage decreased in recent years due to undesirable side effects, such as elevated intraocular pressure, cataract progression and potential of retinal toxicity [9, 10]. Additionally, it is off-label, and with the recent addition of the dexamethasone implant (DI), an approved drug with more long-lasting effects, triamcinolone is no longer used. DI (Ozurdex, Allergan Inc., Irvine, CA) is a slow-release dexamethasone delivery system developed for intravitreal administration that has recently been introduced as a therapeutic option in DME [11, 12].

Switching between anti-VEGF agents and corticosteroids is a current topic of study, but there is an ongoing debate regarding the proper time to switch between agents. Analyses of data obtained from two clinical trials—the comparison of Age-Related Macular Degeneration Treatments Trials (CATT) and the Diabetic Retinopathy Clinical Research Network (DRCRnet)—demonstrated that patients with poor initial responses to anti-VEGF treatment who continued using the original agent without switching to another agent eventually achieved comparable visual and anatomical improvements [13]. Similarly, Chatziralli et al. [14] conducted a study based on real-life data to identify the point in time to best define suboptimal response following intravitreal ranibizumab (IVR) for DME, and the study reported that, although visual and anatomical improvement was first seen after the loading dose, maximal response was observed at 12 months.

The purpose of the current study is to evaluate the effect of a single-dose intravitreal injection of DI as an adjuvant therapy to achieve a rapid recovery in patients with a poor initial response to an IVR loading dose.

Methods

Ethics

This retrospective study was conducted in accordance with the Declaration of Helsinki. All necessary authorizations were obtained from the Institutional Ethical Board of Okmeydani Research & Training Hospital in Istanbul, Turkey.

Patients

This study evaluated 25 pseudophakic eyes of 25 patients who underwent a single-dose DI due to persistent DME after a loading dose of IVR treatment at Okmeydani Research & Training Hospital between January 2016 and January 2017. All of the patients were treatment naive, received a loading dose of three consecutive monthly IVR injections (0.5 mg/0.05 ml) and responded poorly to this treatment. Next, the DI was injected at the fourth month, after which IVR treatment continued as needed (pro re nata) after the DI therapy. The total follow-up time was 12 months (IVR plus DI treatment). Persistent DME was defined as macular edema where the central macular thickness (CMT) is greater than 300 μm as measured with spectral domain optical coherence tomography (SD-OCT) after at least three consecutive IVR injections. The IVR retreatment criteria were CMT $>$ 300 μm as detected by SD-OCT or visual loss $\geq$ 1 Snellen line at monthly visits.

DME was classified into three types—diffuse retinal thickening (DRT), cystoid macular edema (CME) and serous retinal detachment (SRD)—in order to perform subgroup analyses to see whether the responses to DI were different. DRT was defined as sponge-like retinal swelling of the macula with reduced intraretinal reflectivity. CME was defined as intraretinal cystoid spaces of low reflectivity and highly reflective septa separating cystoid-like cavities in the macular area. SRD was defined as a shallow elevation of the retina and an optically clear space between the retina and retinal pigment epithelium. DRT was restricted to only pure DRT. If DRT was combined with CME or SRD, the pattern was classified as either CME or SRD, as appropriate, and when DRT, CME and SRD were all present, the type was classified as SRD (Fig. 1).

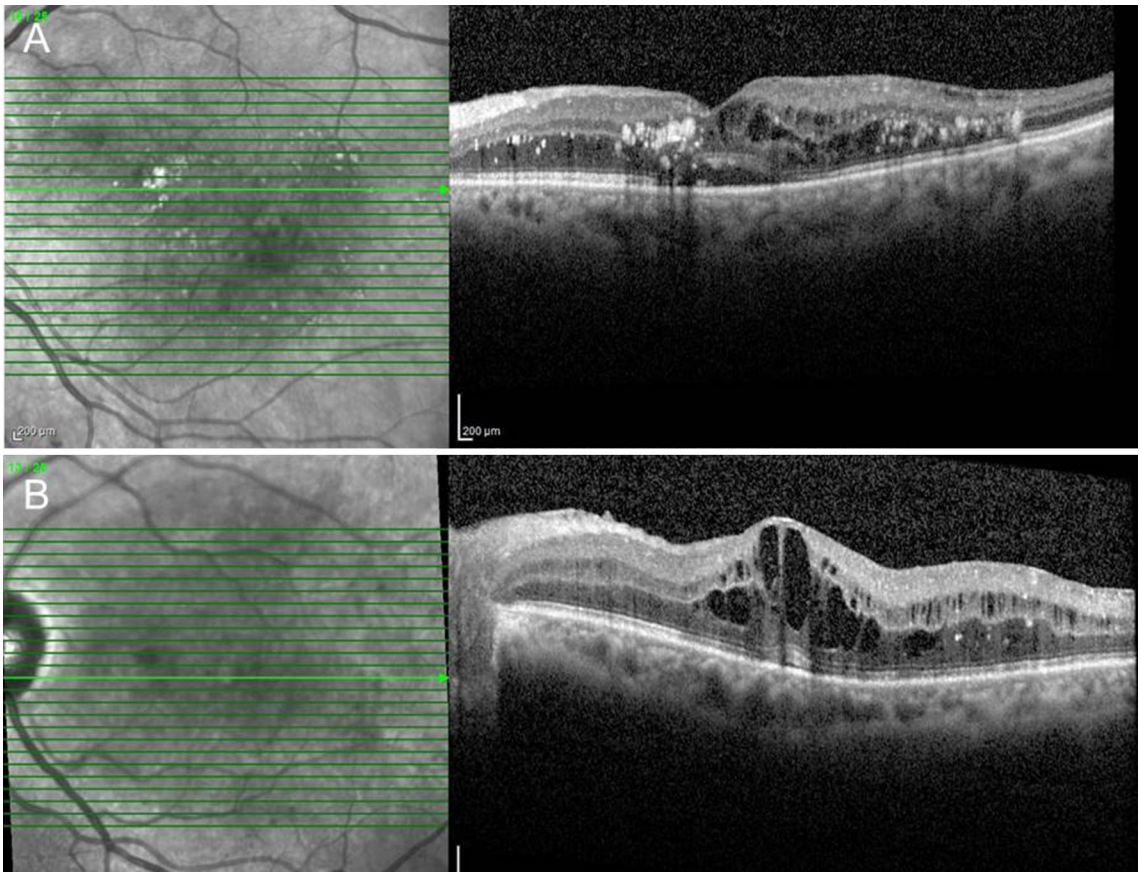

Fig. 1 Reference sample figure for serous retinal detachment (SRD) (**a**) and cystoid macular edema (CME) (**b**)

Patients with phakic eyes, a history of glaucoma, any vitreomacular interface pathologies detected by SD-OCT, a history of vitrectomy, other vitreoretinal diseases and retinopathies, laser photocoagulation throughout the follow-up period or anti-VEGF injections other than IVR were excluded.

The CMT, best-corrected visual acuity (BCVA) and number of IVR injections after DI and during the follow-up period were reviewed. These parameters were evaluated at baseline, prior to DI, and at 1, 3, 6 and 8 months after DI treatment. The necessity of anti-glaucomatous treatment, insulin usage, final CMT and BCVA, number of additional IVR injections, HbA1c levels and status of laser photocoagulation were also recorded.

For each agent, the injections were performed with the use of topical anesthetic in the operating room. Informed consent was obtained from all patients prior to injection. Under sterile conditions, a sterile lid speculum was used, and povidone-iodine was applied to the injection site, after which 0.5 mg ranibizumab (Lucentis, Genentech) and dexamethasone 700 µg (Ozurdex, Allergan) were injected at 3.5 mm posterior to the corneoscleral limbus. A topical antibiotic (moxifloxacin) was used four times daily for 72 h.

Ophthalmic examinations

All of the patients underwent standard ophthalmic examinations prior to treatment and at 1, 3, 6 and 8 months post-DI. The examinations included slit-lamp biomicroscopy, BCVA, tonometry, SD-OCT and fundoscopy. The BCVA was measured with a Snellen chart, and the decimal visual acuity was converted to logarithm of the minimal angle of resolution (LogMAR) units for statistical analyses. Fundus fluorescein angiography (FFA) was performed in all cases prior to treatment. Retinal ischemia was defined as a non-perfusion area of 1 optic disk diameter or greater.

SD-OCT measurement

The OCT acquisition was performed on the SD-OCT (Cirrus HD-OCT, Carl Zeiss Meditec). The morphologic features of macular edema, CMT and the presence of subretinal fluid were assessed and analyzed with SD-OCT by two experienced ophthalmologists. The average value was considered for statistical analyses.

Sample size calculation

G*Power 3.1.9.2 (Universitat Düsseldorf) was used to calculate sample size, and it determined that the study had to recruit 23 individuals to have 95% power with a 5% type 1 error level. The effect size was computed automatically by the program with the mean and standard deviations of the sample as the data input.

Statistical analyses

Statistical analyses were performed using SPSS (version 15). Descriptive analyses were presented using means and standard deviations for normally distributed variables. The change in CMT and BCVA over time was investigated using repeated measures of analysis of variance (ANOVA). The effect of the type of macular edema was also evaluated with this test. The Greenhouse–Geisser correction was used when the sphericity assumption was violated. In the subgroup analysis, the Kruskal–Wallis test was conducted to compare nonparametric parameters among the groups, and a one-way ANOVA test was used to compare parameters among the groups. A p value of less than 0.05 was considered to show a statistically significant result.

Results

Baseline characteristics

Of the 25 pseudophakic eyes included in this study, eight (32%) had CME, nine (36%) had DRT and the remaining eight (32%) had SRD. All of the patients underwent a single intravitreal injection of DI. The DME subgroups were similar in terms of demographic and ocular characteristics. HbA1c levels were all comparable between subgroups ($p = 0.541$). Table 1 shows the baseline and final clinical characteristics of the patients.

Anatomical and functional outcomes

Initially, the mean CMT of the full group was 449.4 ± 129.4 μm before the IVR loading dose, and this increased to 478.2 ± 107.8 μm after three consecutive monthly IVR injections ($p = 0.374$). A single intravitreal DI resulted in a statistically significant decrease in CMT at 1 and 3 months (313.8 ± 62.7 μm and 275.8 ± 66.6 μm, respectively; $p < 0.001$). The effect of the DI in the whole study group diminished from the third month to the sixth month (351.4 ± 102.4 μm), and additional IVR injections induced a reduction in the mean CMT at the final visit (298.4 ± 71.5 μm; $p = 0.011$). The change in CMT over time was depicted in Fig. 2.

At baseline, the mean BCVA of the total group was 0.6 ± 0.4 LogMAR, which decreased to 0.9 ± 0.6 after the IVR loading dose ($p = 0.109$). A single intravitreal DI resulted in a statistically significant improvement in BCVA within the first, third and sixth months after DI (0.6 ± 0.4, 0.5 ± 0.4 and 0.5 ± 0.5, respectively; $p = 0.002$). After the first month, BCVA was preserved during the follow-up period. Additional IVR injections did not result in a significant improvement in BCVA (0.5 ± 0.5 LogMAR; $p = 0.479$). The change in BCVA over time is illustrated in Fig. 3.

Subgroup analysis of CMT and BCVA according to types of macular edema

At baseline, all of the groups had similar CMT (423.5 ± 194.7 μm in the CME group, 481.6 ± 88.9 μm in the DRT group and 439.1 ± 91.0 μm in the SRD group; $p = 0.648$). Subsequently, all of them showed an improvement in CMT over the entire observation period ($p < 0.001$). There was no statistically significant difference between the groups in terms of CMT improvement ($p = 0.188$). This trend in CMT is depicted in Fig. 4.

At baseline, all of the groups had similar BCVA LogMAR (0.4 ± 0.1 in the CME group, 0.8 ± 0.5 in the DRT group and 0.7 ± 0.5 in the SRD group; $p = 0.180$). After DI, all of them showed an improvement in BCVA over the entire observation period ($p = 0.002$). There was no statistically significant difference between the groups in terms of BCVA

Table 1 Demographic characteristics of the patients

	Total	CME group	DRT group	SRD group	*p*
Number (eyes %)	25 (100%)	8 (32%)	9 (36%)	8 (32%)	
Age (years ± SD)	63.9 ± 9.3	69.1 ± 7.8	61.6 ± 10.6	61.3 ± 7.9	0.156
Gender (men/women)	16/9	7/1	5/4	4/4	0.251
Follow-up period after DI (months)	7.8 ± 1.4	7.8 ± 2.2	7.7 ± 0.9	8.0 ± 1.0	0.955
HbA1c levels	7.7 ± 1.2	7.7 ± 1.0	7.4 ± 1.0	8.0 ± 1.5	0.541
Anti-glaucomatous therapy (*n*[%])	6 (24%)	2 (8%)	2 (8%)	2 (8%)	0.988
Proliferative DR (*n*[%])	11 (44%)	3 (12%)	4 (16%)	4 (16%)	0.885
Insulin usage (*n*[%])	12 (48%)	3 (12%)	4 (16%)	5 (20%)	0.598
Ischemia in FFA (*n*[%])	21 (84%)	6 (24%)	8 (32%)	7 (28%)	0.709
PRP status (*n*[%])	13 (52%)	4 (16%)	5 (20%)	4 (16%)	0.966
No. of additional IVR after DI	0.8 ± 0.8	0.7 ± 1.0	0.7 ± 0.6	1.0 ± 0.7	0.802
CMT prior to DI (μm)	478.2 ± 107.8	410.2 ± 98.6	481.4 ± 90.8	542.7 ± 103.1	0.041
Final CMT (μm)	298.4 ± 71.5	310.8 ± 71.20	281.3 ± 57.5	305.1 ± 90.1	0.681
BCVA LogMAR prior to DI	0.9 ± 0.6	1.2 ± 0.7	0.8 ± 0.5	0.6 ± 0.6	0.434
Final BCVA	0.5 ± .5	0.5 ± 0.3	0.4 ± 0.6	0.6 ± 0.6	0.726

DI dexamethasone implant, *DR* diabetic retinopathy, *FFA* fundus fluorescein angiography, *PRP* panretinal laser photocoagulation, *IVR* intravitreal ranibizumab, *CMT* central macular thickness, *BCVA* best-corrected visual acuity

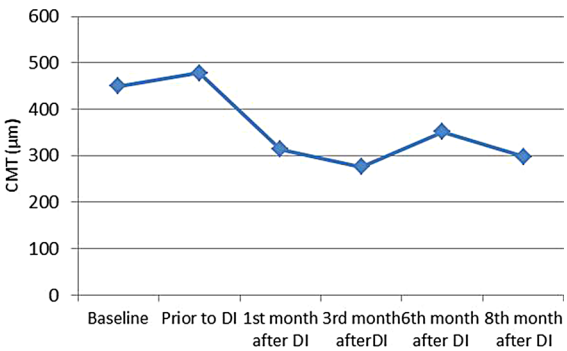

Fig. 2 Longitudinal changes in central macular thickness (CMT) after dexamethasone implantation (DI). A single intravitreal DI resulted in a statistically significant improvement in CMT

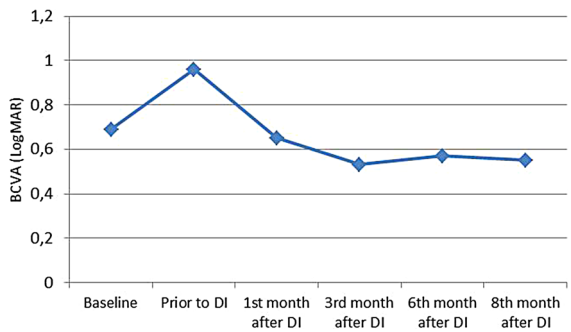

Fig. 3 Longitudinal changes in best-corrected visual acuity (BCVA) after dexamethasone implantation. A single intravitreal DI resulted in a statistically significant improvement in BCVA at the first month

improvement ($p = 0.136$). This trend in BCVA is shown in Fig. 5.

Safety

No serious systemic complications associated with intravitreal DI were observed in any of the eyes during the study period. No endophthalmitis was experienced. Six (24%) of the patients had elevated intraocular pressure (≥ 25 mmHg) that was controlled with anti-glaucomatous medications.

Discussion

In this retrospective study, the addition of a DI treatment following a poor response to an IVR loading dose resulted in a rapid improvement in BCVA and CMT in a group of DME patients. This gain was maintained with ongoing IVR treatment throughout the 8-month follow-up period. A recently published DRCRnet phase 2 randomized clinical trial revealed that, although the addition of intravitreal dexamethasone to an ongoing IVR therapy reduces retinal

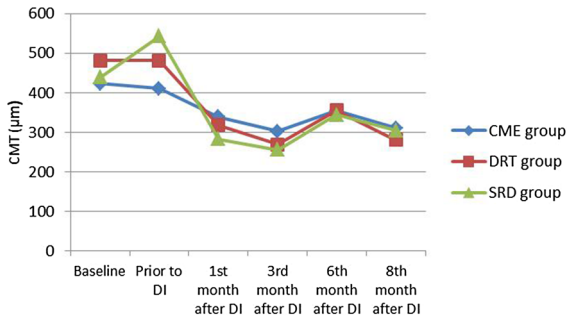

Fig. 4 Subgroup analyses of central macular thickness (CMT) according to macular edema types [diffuse retinal thickening (DRT), cystoid macular edema (CME) and serous retinal detachment (SRD)]. The trend was similar in all groups

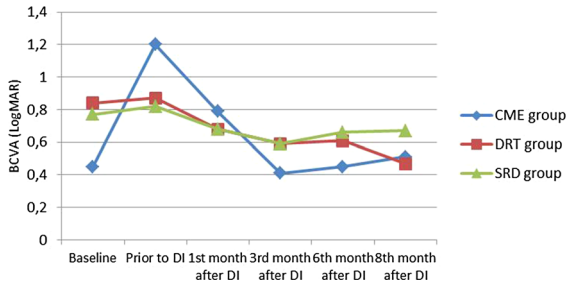

Fig. 5 Subgroup analyses of best-corrected visual acuity (BCVA) according to macular edema types [diffuse retinal thickening (DRT), cystoid macular edema (CME) and serous retinal detachment (SRD)]. The trend was similar in all groups

thickness, it does not improve visual acuity at 24 weeks [15]. However, in the subgroup analyses of that study, the results showed that, while the adjusted mean difference in visual acuity in pseudophakic eyes was +3.1 letters, it was -3.0 letters for phakic eyes [15]. This finding was likely related to the side effects of corticosteroids on cataract formation. The current study included only pseudophakic eyes in order to eliminate the effect of this complication on visual outcome, leading to a superior visual gain in the study patients compared to the DRCRnet trial results.

The treatment response to anti-VEGF differs among patients. Some patients do not respond rapidly to treatment. In the current study, after achieving a good response to one DI, switching to DI would probably have been a treatment option, but it was not a preferred choice. This study is not a switch study; rather, it is a modified anti-VEGF treatment regimen that may be called a 'sandwich regimen' (anti-VEGF–dexamethasone–anti-VEGF). Currently, there are no consistent switching rules in the literature to define the best time to switch or the exact definition of a suboptimal response. Ferris et al. [13] conducted a study with the data from both the CATT and DRCRnet studies [16, 17] investigating the clinical course of eyes that met typical criteria for switching treatments but did not have a change in treatment, and there were observed improvements in visual acuity and retinal thickness at the end of the first year [13]. However, chronic macular edema may induce long-term, irreversible damage to vital segments in the retinal tissue, such as photoreceptors or Müller cells; thus, a rapid recovery may be preferred in most cases. In this respect, the current study sought to discover whether it is possible to achieve a rapid recovery without switching.

Recently, Cicinelli et al. [18] reported that visual and anatomical responses after an IVR loading dose are significant predictors of both short-term and long-term visual acuity improvement after switching to corticosteroids in patients with DME unresponsive to anti-VEGF. Similarly, the current study added DI following an IVR loading dose in poor and nonresponsive cases. The pathogenesis of DME includes variable mediators, such as VEGF, IL-6, IL-8 and prostaglandins [2, 3]. In certain patients, some of these inflammatory mediators may have a more distinctive role than other ischemia-induced mediators in the course of the disease. It is possible that DI and IVR together have a synergetic effect on DME. DI may even facilitate the effects of IVR by reducing persistent retinal thickening and improving the penetration of ranibizumab into the retinal tissue.

In the current study, the subgroup analyses found that different DME types did not have any effect on CMT or BCVA improvement. Since the sample size was so small, this finding must be interpreted cautiously.

The main limitation of this study is that it is not a prospective, randomized, controlled study. Previous studies have shown that patients who meet switching criteria but maintained treatment with the original agent eventually showed improvements in visual acuity and retinal thickness [13, 14]. Furthermore, anti-VEGF therapy is prolonged in DME patients; for example, for aflibercept, the loading phase is five monthly injections compared to three for neovascular age-related macular degeneration. Therefore, the results would be stronger if there was a control group treated only with IVR for entire study period. On the

other hand, the principal strength of the current study arises from intentionally selecting pseudophakic eyes.

In summary, adding DI following a poor response to an IVR loading phase in a pseudophakic eye receiving ongoing IVR injections resulted in an improvement in the mean visual acuity and CMT. This improvement was maintained with additional IVR throughout the follow-up period.

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Compliance with ethical standards

Conflict of interest None of the authors has any financial/conflicting interests to disclose.

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