

Original research

# Efficacy of intravitreal dexamethasone implant in persistent diabetic macular edema after primary treatment with intravitreal ranibizumab

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## Abstract

**Purpose:** To evaluate the efficiency and possible complications of intravitreal dexamethasone (IVD) implant in diabetic macular edema (DME) resistant to treatment of three consecutive intravitreal ranibizumab (IVR) injections.

**Methods:** Fifty eyes of 38 patients were considered in this study. The best corrected visual acuity (BCVA), central macular thickness (CMT), and values of intraocular pressure (IOP) were examined preoperatively and postoperatively in the 1st, 2nd, 4th, and 6th months of IVD implantation.

**Results:** Twenty of the patients were women, and 18 of the patients were men. Mean age was  $64.63 \pm 7.15$  (52–83) years. Mean number of IVR injection before IVD implantation was  $3.4 \pm 0.38$ . Mean BCVA (logMAR) was 0.874  $\pm$  0.398 before IVD implantation, 0.598  $\pm$  0.306 at the 1st month, 0.602  $\pm$  0.340 at the 2nd month, 0.708  $\pm$  0.359 at 4th month, and 0.800  $\pm$  0.370 at 6th month. Mean of CMT was 519.700  $\pm$  155.802  $\mu$ m before IVD implantation, 274.000  $\pm$  73.112  $\mu$ m at the 1st month, 307.98  $\pm$  87.869  $\mu$ m at the 2nd month, 387.82  $\pm$  110.503  $\mu$ m at 4th month, and 478.54  $\pm$  163.743  $\mu$ m at 6th month. Improvements in BCVA and CMT were statistically significant ( $P < 0.05$ ) at 1st, 2nd, and 4th months; however, these values were not statistically significant at 6 months. At 1st day, 1st and 2nd months, the values of IOP were increased significantly after IVD. Cataract progression was observed in just 1 of the 22 phakic patients.

**Conclusions:** In DME resistant to treatment of consecutive IVR, IVD implantation has been observed to be effective in increasing BCVA and decreasing CMT in the first 3 months. IVD implantation can be considered an alternative method in the treatment of resistant DME.

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**Keywords:** Diabetes; Intravitreal dexamethasone; Intravitreal ranibizumab; Macular edema

## Introduction

Diabetic retinopathy (DRP) is one of the major causes of vision loss in adults, and the pathology largely responsible for this is the diabetic maculopathy.<sup>1</sup>

The endothelial dysfunction and chronic low-level inflammation play a role in the formation of diabetic macular edema (DME), and the deterioration of the blood-retinal barrier and extracellular lipid and protein accumulation in the macula

occur as a result of increase in inflammatory cytokines, such as interleukin 6 and 8, prostaglandins, and vascular endothelial growth factor (VEGF) in ocular fluids.<sup>2–4</sup>

In the treatment of DME today, the most commonly used and proven treatments include laser photocoagulation (LPC), locally administered corticosteroids, and intravitreal anti-VEGF agents.<sup>5</sup> VEGF, which causes increased vascular permeability and neovascularization development in DRP, is also a chemoattractant for macrophages and monocytes. Anti-VEGF agents are currently used as a standard for the treatment of DME. Anti-VEGF drugs such as ranibizumab and bevacizumab only inhibit VEGF release. In some patients, DME may be persistent and non-responsive to anti-VEGF drugs requiring alternative approaches. Corticosteroids are also effective on angiogenesis and vascular permeability as they

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reduce the production of VEGF in addition to their anti-inflammatory effect through inhibition of the arachidonic acid pathway which leads to prostaglandin and leukotriene formation.<sup>6</sup> For these reasons, since corticosteroids are effective on many mechanisms, they are a good option in the treatment of resistant DME.

The anti-inflammatory effect of dexamethasone, a potent steroid that is water-soluble and used in the treatment of DME, is approximately six times higher than prednisolone and triamcinolone and 25 times higher than hydrocortisone.<sup>7</sup> Low toxicity and high concentration is achieved with the injection of dexamethasone into the vitreous. However, the short duration of the intravitreal half-life of the dexamethasone (approximately 3 h) was a problem for the long-term effect.<sup>8,9</sup>

Ozurdex (Allergan, Inc., Irvine, CA), an intravitreal dexamethasone (IVD) implant developed for long-term effect, is a slow-release and biodegradable agent.<sup>10</sup> It is designed to release dexamethasone from the implant for up to 6 months, while the polymer structure of the slow release formulation is broken down into glycolic and lactic acid and then transformed into water and carbon dioxide.<sup>11</sup> For these reasons, IVD injection has emerged as an alternative treatment in the treatment of diabetic DME resistant to anti-VEGF therapy.

Our study aims to evaluate the efficacy and possible complications of IVD implant in DME resistant to at least 3 doses of ranibizumab treatment.

## Methods

The study was conducted on 50 eyes of 38 patients, who were followed up with a diagnosis of DME between January 2014 and August 2016 in the Retina Unit of the Sakarya Education and Research Hospital. The patients who had macular edema according to ophthalmic examination and who had DME detected in fundus fluorescein angiography (FFA) and optical coherence tomography (OCT) and who had undergone intravitreal ranibizumab (IVR) were included in the study. Persistent DME was defined as macular edema where the central macular thickness (CMT, the mean central subfield thickness) is greater than 275  $\mu\text{m}$  with cystic spaces after at least three consecutive IVR injections. The mean central subfield thickness is defined as the mean retinal thickness within a 1-mm circle centered on the fovea.<sup>12</sup> Patients with persistent macular edema were considered resistant to ranibizumab treatment and treated with IVD. Patients who underwent one dose of IVD and followed up for 6 months were included in the study. A single-use applicator with a 22-gauge needle was used to place an IVD implant in the vitreal chamber through a self-sealing scleral injection. A topical antibiotic was used 5 times daily for one week.

Inflammatory diseases such as uveitis or retinal vascular occlusion which may cause macular edema, intense cataracts that may cause vision loss, age-related macular degeneration, epiretinal membrane, vitreomacular traction, macular non-perfusion in FFA<sup>13</sup> (non-perfusion areas of the retina are associated with the development of vascular occlusion or capillary closure<sup>14</sup>), glaucoma, ocular hypertension, cataract or

vitreoretinal surgery history in the last 6 months, history of LPC in the last 3 months, patients with previous history of intravitreal, periocular, and systemic steroid treatment were not included in the study. Patients with uncontrolled hypertension or nephropathy were also excluded. The patients who had HbA1c levels less than 8.0% at the beginning of the study and at the six-month follow-up period were included in the study.

Patients included in the study were informed about the DRP and possible course of the disease. The pre-treatment status of the eyes, the effectiveness of the previous treatments, and the treatment options were explained. The patients were informed about IVD injection, its application, expected effect, and possible complications, and informed consent forms were obtained from all patients. In addition, compliance with the principles of the Declaration of Helsinki was approved by the Ethics Committee of Sakarya University Faculty of Medicine.

All of the patients underwent ophthalmic examinations performed prior to treatment and at the 1st, 2nd, 4th, and 6th months after the injection. Detailed ocular examinations including best corrected visual acuity (BCVA) in Snellen scale, intraocular pressure (IOP) measurement using Goldmann applanation tonometry, slit-lamp biomicroscopic examination, and dilated fundoscopic examination using a 90-diopter lens were performed and recorded each visit. FFA and colored fundus photographs were taken in each patient, and CMT was evaluated by using macular thickness scanning protocol with spectral domain OCT (Cirrus HD OCT, Carl Zeiss Meditec, Dublin, CA, USA) device after pupil dilatation. Standard macular imaging consisted of the macular cube (512  $\times$  128) and the 5 Line Raster scanning protocols (Carl Zeiss, Carl Zeiss Meditec, Dublin, CA).

SPSS 21.00 for Windows (SPSS Inc., Chicago, IL, USA) statistics software was used for statistical analysis. Student's *t*-test was used to compare the parameters of normal distribution and Mann–Whitney *U* test was used to compare the abnormally distributed parameters. The paired sample *t*-test was used for intragroup comparisons of the parameters that were normally distributed, and Wilcoxon sign test was used for intragroup comparisons of abnormally distributed parameters. The results were evaluated in a confidence interval of 95% and a level of significance of  $P < 0.05$ .

## Results

Fifty eyes from 38 patients were included in the study. Of the patients, 20 (52.63%) were female, 18 (47.36%) were male, and the mean age was  $64.63 \pm 7.15$  (52–83) years. The right eye of 19 patients (50%), the left eye of 7 patients (18%), and both eyes of 12 patients (32%) were evaluated. At least 3 months before the injection, 16 (32%) eyes underwent pan-retinal LPC, 12 (24%) eyes had focal LPC, 1 (2%) eye underwent grid LPC, and 21 eyes had not undergone LPC. Of the studied eyes, 28 eyes (56%) were pseudophakic, and 22 eyes (44%) were phakic. No cataract was present in any of the phakic eyes.

The mean number of IVRs performed before the IVD injection was  $3.4 \pm 0.38$  (range, 3–5 times). IVD injections

were administered on average  $1.2 \pm 0.22$  (range, 1–3 months) month after IVR.

The mean visual acuity of the patients was  $0.874 \pm 0.398$  logMAR before the IVD injection, and it was found to be  $0.598 \pm 0.306$  logMAR 1 month following the injection,  $0.602 \pm 0.340$  logMAR at 2 months after,  $0.708 \pm 0.359$  logMAR at the 4th month, and  $0.800 \pm 0.370$  logMAR at the 6th month. (Fig. 1) (Table 1). In the first month after IVD injection, BCVA increased in 42 (84%) eyes, decreased in 1 (2%) eyes, and remained the same as in 7 (14%) eyes. In the second month, it was 34 (68%), 3 (6%), and 13 (26%) eyes, respectively. The fourth month was 28 (56%), 4 (8%), and 18 (36%) eyes, respectively. At sixth month, 13 (26%), 31 (62%), and 6 (12%) eyes, respectively.

The increase in visual acuity was statistically significant at the 1st month, 2nd month, and 4th month compared to the preoperative visual acuity, whereas the increase in visual acuity at the 6th month was not statistically significant (Table 1).

The mean CMT of the patients was  $519.700 \pm 155.802$   $\mu\text{m}$  before the IVD injection, and it was found to be  $274.000 \pm 73.112$   $\mu\text{m}$  at the 1st month,  $307.98 \pm 87.869$   $\mu\text{m}$  at the 2nd month,  $387.82 \pm 110.503$   $\mu\text{m}$  at the 4th month, and  $478.54 \pm 163.743$   $\mu\text{m}$  at the 6th month (Fig. 2).

Although the decrease in CMT was found to be statistically significant at the 1st, 2nd, and 4th months, the decrease in the 6th month was not significant (Table 1).

The mean IOP was  $15.54 \pm 2.476$  mmHg before the injection, and it was found to be  $16.64 \pm 2.738$  mmHg at the first day after injection,  $17.08 \pm 2.988$  mmHg at the first month,  $17.30 \pm 2.97$  mmHg at the second month,  $15.90 \pm 2.922$  mmHg at the fourth month, and  $15.88 \pm 2.576$  mmHg at the sixth month (Table 1).

In the IOP comparison before and after IVD injection, the differences at the 1st day, 1st month, and 2nd month were found to be statistically higher ( $P = 0.002$ ,  $P = 0.000$ ,  $P = 0.000$ ). There was no significant difference between

preoperative IOP and postoperative IOP at the 4th month and 6th month ( $P = 0.348$ ,  $P = 0.325$ ).

No serious systemic complications associated with IVD were observed in any of the eyes during the study period. No endophthalmitis was experienced.

Based on the controls at the end of the injection, topical anti-glaucomatous medication was started in 3 (6%) patients with an IOP greater than 21 mmHg at the 1st month follow-up, and in 2 (4%) patients at the 2nd-month follow-up. None of the patients underwent trabeculectomy.

Cataract surgery was needed in one (2%) eye due to the progression of cataract. Phacoemulsification surgery and intraocular lens implantation were performed at the 4th month follow-up of this patient. No complication was observed during and after the operation.

The plan for the eyes refractory to IVD was re-injection of IVD implant and modified macular grid LPC 6 months after the first implantation of IVD. The mean interval from implantation of IVD to recurrence of DME (recurrence of sub- or intraretinal fluid in OCT) was  $4.9 \pm 0.58$  (range, 2–10) months. Only 7 eyes had complete DME resolution at 6 months after IVD implantation.

## Discussion

Although the efficacy of anti-VEGF injection treatment in DME has been clearly demonstrated, resistance to treatment is developed in some patients. In addition, the use of anti-VEGF injection is limited in patients with recent myocardial infarction, previous history of cerebrovascular disease, uncontrolled hypertension, and severe macular ischemia. Corticosteroids have been used for this purpose. Corticosteroids have been used for many years to suppress intraocular inflammation and to prevent extravasation from veins. They have been used as subconjunctival, subtenon, and intravitreal injections to avoid possible systemic side effects and to provide a maximum concentration in the desired area.

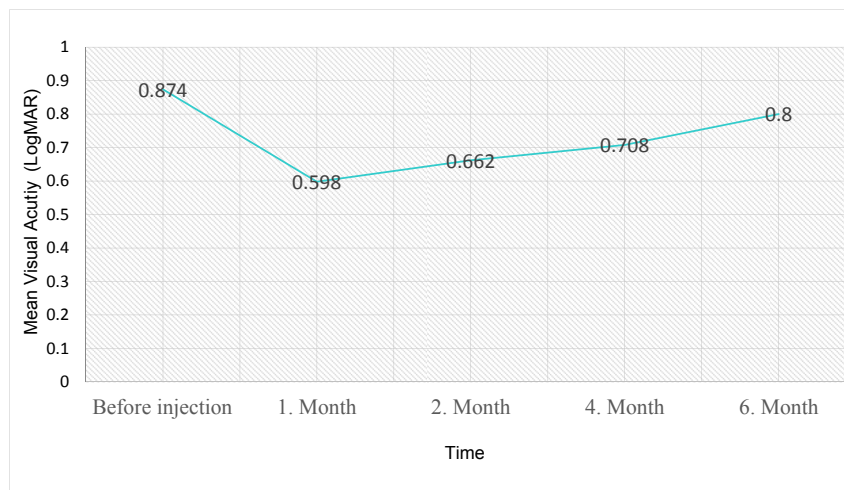


Fig. 1. Visual acuity changes after dexamethasone injection.

Table 1  
Best corrected visual acuity (BCVA), central macular thickness (CMT), and intraocular pressure (IOP) changes before and after intravitreal dexamethasone (IVD) injection.

	BCVA (logMAR)	CMT ( $\mu\text{m}$ )	IOP (mmHg)
Baseline	0.874 $\pm$ 0.39	519.70 $\pm$ 155.80	15.54 $\pm$ 2.476
1st day			16.64 $\pm$ 2.738 ( $P = 0.000$ )
1st month	0.598 $\pm$ 0.30 ( $P = 0.000$ )	285.32 $\pm$ 73.11 ( $P = 0.000$ )	17.08 $\pm$ 2.988 ( $P = 0.000$ )
2nd month	0.662 $\pm$ 0.34 ( $P = 0.000$ )	307.98 $\pm$ 87.86 ( $P = 0.000$ )	17.30 $\pm$ 2.97 ( $P = 0.000$ )
4th month	0.708 $\pm$ 0.35 ( $P = 0.000$ )	387.82 $\pm$ 110.50 ( $P = 0.000$ )	15.90 $\pm$ 2.922 ( $P = 0.348$ )
6th month	0.800 $\pm$ 0.37 ( $P = 0.06$ )	478.54 $\pm$ 163.74 ( $P = 0.114$ )	15.88 $\pm$ 2.576 ( $P = 0.325$ )

BCVA: Best corrected visual acuity; CMT: Central macular thickness; IOP: Intraocular pressure.

$P < 0.05$  was considered statistically significant (Student *t*-test). The  $P$  value was obtained by comparing with the baseline value.

The long-acting (6 months) dexamethasone on the Novadur platform has received Food and Drug Administration (FDA) approval as Ozurdex. Ozurdex is marketed with 22 G-tip intravitreal injector system in a single-use, pre-loaded form for intravitreal use that can be stored at room temperature, and it has a total of 0.7 mg dexamethasone with 6 months of activity. Rapid release was achieved in the first two months, and then slow release provides a 6-month drug effect. At the end of this period, the dexamethasone ends, and the platform, i.e. Novadur, is lost and converted to water and carbon dioxide.<sup>11</sup>

Several studies have been conducted to demonstrate the efficacy of the Ozurdex implant. In the multicenter study by Callanan et al. that evaluated 253 patients, the patients with DME treated with laser were compared to the DME patients that had both the laser and dexamethasone implant treatment. Visual acuity was found to increase significantly in the dexamethasone implant group.<sup>15</sup> In the meta-analysis of Khan et al., 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 in patients with persistent DME.<sup>16</sup>

Haller et al. compared 0.7 mg and 0.35 mg dexamethasone implant with each other and follow-up group both in retinal vein branch occlusion and diabetes-induced macular edema. The highest visual acuity was in the 0.7 mg dexamethasone implant group. However, no significant difference was found

between the 3 groups on the 180th day.<sup>17</sup> Similarly, in the MEAD study, which compared 1048 patients in three groups, there was a 15-letter or more visual acuity increase by 22% in the 0.7 mg dexamethasone group, by 18% in the 0.35 mg dexamethasone group, and by 12% in the sham injection group. Visual acuity increase in the dexamethasone group was significantly higher than the sham injection group.<sup>18</sup>

In the CHAMPLAIN study, 55 vitrectomized eyes with treatment-resistant DME were evaluated. Patients received a single dose of 0.7 mg dexamethasone implant and were followed-up for 26 weeks. There was a statistically significant increase in visual acuity of these patients at the end of the 26th week. At the eighth week, a visual acuity increase of 10 letters or more was achieved in 30.4% of the patients.<sup>19</sup> Nil et al. applied 0.7 mg IVD to 25 eyes of 24 patients with DME who were resistant to IVR treatment and had a CMT of 300  $\mu\text{m}$  and above. Visual acuity was found to increase in all patients: there were 1–2 rows of increase in 22 (88%) patients and 3–4 rows of increase in 3 (22%) patients.<sup>20</sup>

Alshahrani et al. have applied IVD treatment in patients with the retinal vascular disease with macular edema resistant to treatment. Thirteen of the 53 eyes included in the study had central retinal vein occlusion, 14 had retinal vein branch occlusion, and 26 had DME seconder to DRP. The mean visual acuity of the patients before the injection was 20/160, and it was found to be 20/80 at the 1st month after the injection, 20/

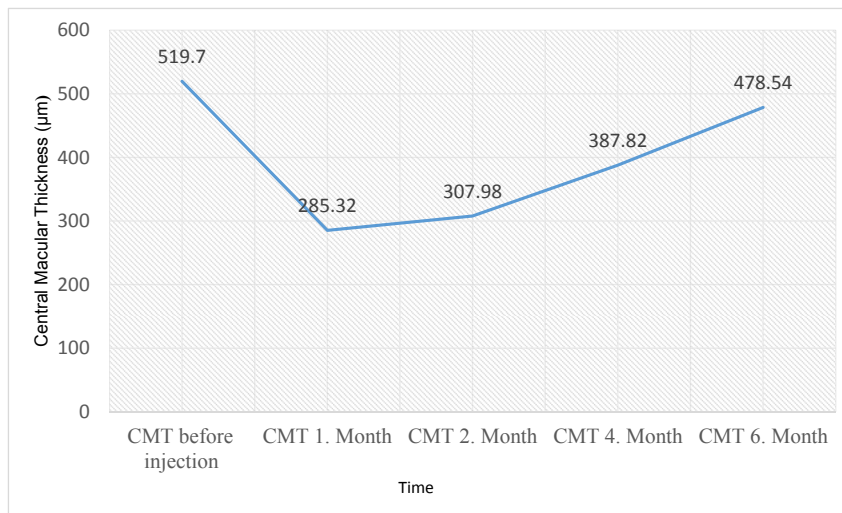


Fig. 2. Central macular thickness (CMT) changes after dexamethasone injection. CMT: Central macular thickness.

60 at the 3rd month, and 20/100 at the 6th month. The increases at the 1st and 3rd months were found to be statistically significant.<sup>21</sup>

In the study by Yıldırım et al., who applied IVD treatment to 11 eyes of 10 patients with macular edema secondary to retinal vein occlusion and DME resistant to LPC or intravitreal triamcinolone or IVR treatment, the visual acuity of the patients before the IVD injection was 0.17 compared to Snellen scale, whereas this value increased to 0.25 after injection. This increase, however, was not statistically significant.<sup>22</sup>

In our study, visual acuity increase was at the maximum in the first month after IVD. Macular edema increased due to decreased dexamethasone activity at the 6th month, and secondary to this visual acuity was decreased, but not to the pre-injection values in the majority of patients. Compared to the values before the IVD injection, lower visual acuity is believed to be caused by persistent hard exudates, impairment caused by macular edema, and degenerative changes in the retinal pigment epithelium.

In another study, the patients who underwent IVD due to DME had a pre-injection CMT average of 496  $\mu\text{m}$ , and the CMT averages for the first month, second month, third month, and fourth month after the injection was found to be 346  $\mu\text{m}$ , 232  $\mu\text{m}$ , 296  $\mu\text{m}$ , and 371  $\mu\text{m}$ , and the decrease in CMT was significantly lower compared to that before injection.<sup>20</sup> In the study by Alshahrani et al. conducted with patients who underwent IVD because of DME and retinal vein occlusion, CMT of the patients before the injection was 569  $\mu\text{m}$ , whereas their mean CMT was found to be 305  $\mu\text{m}$  1 month after the injection, 386  $\mu\text{m}$  at the 3rd month, and 446  $\mu\text{m}$  at the 6th month after the injection. The decrease in CMT after the injection was significant in all months.<sup>21</sup>

In our study, the mean CMT of the patients was 519.7  $\pm$  155.802  $\mu\text{m}$  before the IVD injection, and 274.0  $\pm$  73.1 at the 1st month, 307.9  $\pm$  87.8  $\mu\text{m}$  at the 2nd month, 387.8  $\pm$  110.5  $\mu\text{m}$  at the 4th month, and 478.5  $\pm$  163.7 at the 6th month. Despite the fact that the decrease in CMT was statistically significant at the 1st, 2nd, and 4th months, the decrease at the 6th month was not significant. Changes we observed in macular thickness after IVD injection were similar to those of previous studies. Although there was a decrease in CMT and anatomical improvement after the injection, especially starting from the 1st month, there was a significant increase in CMT at the 6th month.

Increased IOP and cataract development are the most common complication of IVD implant. The ratio of patients undergoing glaucoma surgery due to IOP elevation is 0.6% of patients with 0.7 mg IVD implant, 33.8% of the patients with 0.59 mg fluocinolone acetonide, 4.8% of the patients with 0.19 mg fluocinolone acetonide, and 1.2% of the patients with 4 mg triamcinolone acetonide.<sup>18</sup> Haller et al. found 15% 10 mmHg and above IOP increase in the groups that received 0.7 mg and 0.35 mg dexamethasone. This rate remained at 2% in the follow-up group.<sup>17</sup> In our study, the mean IOP was 15.54  $\pm$  2.4 mmHg before the injection, and it was found to be 16.64  $\pm$  2.7 mmHg at the first day after injection, 17.08  $\pm$  2.9 mmHg at the first month, 17.30  $\pm$  2.97 mmHg at the

second month, 15.90  $\pm$  2.9 mmHg at the fourth month, and 15.88  $\pm$  2.5 mmHg at the sixth month. IOP elevation was statistically significant on the 1st day, 1st month, and 2nd month. After the 4th month, IOP values started to decrease, and no significant difference was found between the pre-injection IOP values and the measurements at the 4th and 6th months. Topical anti-glaucomatous medication was initiated in 5 (10%) patients with an IOP greater than 21 mmHg, and no patients underwent glaucoma surgery. In our study, IOP increase was found to be 10%, and these results were similar to the literature.

Another common complication of dexamethasone is cataract progression. In the study by Boyer et al., the rates of cataract development were 67.9%, 64.1%, and 20.4%, in the patient groups receiving 0.7 mg and 0.35 mg dexamethasone and the control group, respectively. In this 3-year study, the rates of cataract surgery were 59.2%, 52.3%, and 7.2%, respectively.<sup>18</sup> In our study, cataract progression was observed in only 1 (2%) out of 22 phakic eyes. According to the literature, our low rates of cataract surgery can be attributed to short follow-up periods.

Our study included 50 eyes, and as the design of our study, we had strong inclusion/exclusion criteria, relieving a relatively homogenous study group, so we believe that the results of our study are reliable and intensify the effect of IVD in eyes with persistent macular edema. This study has many limitations such as its retrospective nature, short follow-up time, relatively small sample size, and lack of eyes treated with other anti-VEGF agents. In addition, we did not compare the results of phakic-pseudophakic eyes and eyes with lower/higher visual acuity. Also, this study did not include the long-term follow-up results of IVD implantation and additional treatments.

In conclusion, significant changes in visual acuity and CMT were observed in our study, with IVD implant treatment applied in the DME resistant to IVR treatment. The mean CMT was found to be lower after IVD than before. The decrease in CMT was statistically significant at 1st, 2nd, and 4th months. Although visual acuity increased in all months after IVD, the increase in 1st, 2nd, and 4th months were found to be statistically significant. No serious ocular complications were observed in any of the eyes during the study period. The intravitreal effect of dexamethasone is transient, with an average activity of 3–6 months and requires re-injection.

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