Comparison of Intravitreal Dexamethasone Implant and Aflibercept Therapy in Resistant Diabetic Macular Oedema Patients with an Inflammatory Phenotype: Short Term Results

Esra Vural[1], *Leyla Hazar*[2], *Ender Sırakaya*[3]

ABSTRACT

Purpose: To compare the effectiveness of dexamethasone and aflibercept therapy in diabetic macular oedema (DMO) patients with an inflammatory phenotype and insufficient response to bevacizumab.

Methods: Twenty-seven eyes of 27 patients who received a single dose of an intravitreal dexamethasone implant (group 1) and 32 eyes of 32 patients who received three doses of an intravitreal aflibercept injection (group 2) were included in the study. All the patients had DMO, accompanied by serous retinal detachment (SRD) and hyperreflective dots (HRDs), with an insufficient response to three doses of bevacizumab. The efficacy of the intravitreal dexamethasone implant and aflibercept injection was assessed 1, 2 and 3 mo later by analysing changes in best-corrected visual acuity (BCVA) and central macular thickness (CMT).

Results: The mean age of the patients in group 1 and 2 was 62.22 ± 7.49 and 63.06 ± 8.20 years. Although there was no significant difference in the BCVA between groups at the 1- and 3-mo follow-ups, there was a statistically significant increase in the BCVA in group 1 at the 2-mo follow-up. There was a statistically significant decrease in CMT at the 2- and 3-mo follow-ups in group 1 as compared to that in group 2.

Conclusions: In patients with DMO accompanied by an inflammatory phenotype and insufficient response to bevacizumab, dexamethasone implant was more effective in terms of both visual and anatomical results compared to aflibercept in a 3-mo follow-up study In refractory cases, switching to appropriate treatment before photodegeneration occurs affects visual results.

Keywords: Aflibercept, Dexamethasone, Hyperreflective dot, Inflammatory phenotype, Serous detachment.

INTRODUCTION

Diabetic macular oedema (DMO), which is the major cause of vision loss in diabetic patients[1]. DMO occurs when the blood–retinal barrier is disrupted, resulting in an increase in vascular permeability[2]. Based on fluorescein angiography, DMO is classified as focal or diffuse[3]. Morphologically, oedema patterns in DMO are classified using optical coherence tomography (OCT) as diffuse retinal oedema, cystoid macular oedema (CMO) and serous macular detachment[4]. Among macular oedema subtypes, serous retinal detachment (SRD), in particular, may not be detected using fundus fluorescein angiography and can only be diagnosed using SD-OCT[4]. SRD and hyperreflective dots (HRDs) serve as non-invasive biomarkers of retinal inflammation in DMO on OCT[5]. Both SRD and HRDs are associated with inflammation. The incidence of SRD-associated DMO ranges from 13% to 45%[6].

The pathogenesis of DMO includes inflammation, angiogenesis and oxidative stress processes triggered by cytokines, such as interleukins 6 and 8, monocyte chemotactic proteins and vascular endothelial growth factor (VEGF)[7]. VEGF plays an important role in abnormal vascular permeability in DMO, and anti-VEGF agents are used as first-line therapy for DMO[8]. Ranibizumab

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(Lucentis; Genentech, Inc., San Francisco, CA, USA), bevacizumab (Avastin; Genentech, Inc., San Francisco, CA, USA) and aflibercept (Eylea; Regeneron, Tarrytown, NY, USA) are the three main anti-VEGF agents most commonly used to treat the various sub-types of DMO. As bevacizumab is cheaper than the other two drugs, it is used as first-line therapy. In patients who respond poorly to bevacizumab, aflibercept is suggested[9, 10]. Aflibercept has a higher affinity for VEGF-A than does bevacizumab, and it also inhibits both placental growth factor (PIGF) and VEGF-B[11]. In diabetes mellitus patients with SRD, VEGF levels may not be correlated with baseline CMT[12]. In such cases, aflibercept is preferred due to it ability to bind PIGF, in addition to VEGF.

As mentioned above, inflammatory mediators, including VEGF, play important roles in the development of DMO. In some cases, long-term anti-VEGF treatment fails to induce an adequate response due to these inflammatory mediators. Intravitreal steroid administration for DMO treatment has been studied for many years due to its well-known and widespread anti-inflammatory effects. One such steroid, a dexamethasone implant (Ozurdex; Allergan Inc., Irvine, CA, USA), is a slow-release dexamethasone delivery system developed for intravitreal administration in DMO[13]. Considering that serous detachment and HRDs are signs of inflammation, a dexamethasone implant may be an important treatment agent in DMO.

The aim of this study was to compare the anatomical and functional success of an intravitreal dexamethasone implant versus aflibercept in DMO patients with an inflammatory phenotype and insufficient response to bevacizumab.

MATERIAL AND METHODS

Study design and participants

This was a retrospective, comparative trial performed at the ophthalmology department of Kayseri City Hospital. Ethical approval was obtained from the local clinical research ethics committee, and the study was performed according to the tenets of the Declaration of Helsinki.

In total, 59 patients with DMO accompanied by an inflammatory phenotype (SRD and HRDs) and an insufficient response to bevacizumab who presented to our retina clinic between March 2019 and September 2020 were recruited. These patients had previously received a dose of intravitreal bevacizumab once a month for 3 months but showed no response and then received a DEX implant (Ozurdex; Allergan, Inc.) or Aflibercept injection randomly. Criteria for nonresponse to anti-VEGF were determined as follows: despite 3 consecutive bevacizumab doses applied once a month, best corrected visual acuity (BCVA) had worsened by 2 ETDRS lines, a reduction of <%10 of retinal thickness or a reduction of central retinal thickness <50 μm[14].

The patients were divided into two groups: 27 eyes of 27 patients who received an intravitreal dexamethasone implant (group 1) and 32 eyes of 32 patients who received an intravitreal aflibercept injection (group 2). All the patients were followed up at regular intervals for 3 mo. Group 1 received single dose of the dexamethasone implant. Group 2 received three doses of the aflibercept injection which was administered at 1-mo intervals. The diagnosis of SRD was confirmed by OCT. SRD was defined as the presence of sub-retinal fluid between the retina and retinal pigment epithelium (RPE) (Fig. 1). Only eyes with central macular thickness (CMT) greater than 300 μm from the central macular subfield of 1 mm on SD-OCT and eyes without ischemic findings on fundus fluorescein angiography were included in the study.

Patients with a diagnosis of glaucoma, elevated intraocular pressure, a history of steroid-induced ocular hypertension and recent (i.e. in the last 3 mo) major cardiovascular or cerebrovascular events were excluded from the study. Patients with visually significant cataracts, other retinopathies or maculopathies, vitreomacular traction, peripheral ischemia, a history of pars plana vitrectomy or photocoagulation in the 3 mo prior to the dexamethasone implant and aflibercept treatment in the affected eye were also excluded from the study.

Data collection and SD-OCT measurements

Demographic characteristics (e.g. age and sex) and the duration of diabetes mellitus and HbA1c levels were recorded. Data on best-corrected visual acuity (BCVA), which was measured using the ETDRS protocol, and the findings of slit-lamp biomicroscopy and intraocular pressure, assessed using a Goldmann applanation tonometer, were obtained from the patients' medical records. The CMT was obtained from the central 1 mm sub-field area on SD-OCT. CMT was defined as the vertical distance between the RPE and internal limiting membrane in the central fovea and was automatically measured using the built-in mapping software of the OCT device. SRD was defined as a shallow elevation of the retina from the RPE due to sub-retinal fluid accumulation. The height of the SRD was manually measured using the software calliper in the OCT device.. HRDs were defined as small, round- or oval-shaped, well-circumscribed particles (no bigger

than 40 µm in diameter) and characterized by reflectivity that was higher than the background and by the presence of abnormalities spread over the retinal layers. The above data were recorded pre-treatment and 1, 2 and 3 mo after the aflibercept and dexamethasone implant treatments.

Statistical analysis

Data analysis was performed using the Statistical Package for the Social Sciences, version 25.0 (IBM, Armonk, NY, USA). The normality of the data was analysed using the Shapiro–Wilk test. The descriptive statistics were expressed as the mean ± standard deviation. Comparisons of the values between the two groups were analysed using an independent samples *t* test for parametric data and Mann–Whitney *U* test for nonparametric data. A repeated-measures test was used to analyse changes in variables over time between the groups. A chi-squared test was applied for the analysis of categorical variables among the groups, and Pearson's correlation test was used to examine the relationships between categorical variables. A *p* value ≤ 0.05 was considered statistically significant.

RESULTS

There were 14 females and 13 males in group 1 and 19 females and 13 males in group 2 ($p = 0.432$). The mean age of the patients in group 1 and group 2 was 62.22 ± 7.49 y and 63.06 ± 8.20 y, respectively ($p = 0.685$). The duration of diabetes was 12.40 ± 4.20 y in group 1 and 11.18 ± 5.05 y in group 2 ($p = 0.323$). The HbA1c values were 8.60 ± 1.75% in group 1 and 8.92 ± 1.36% in group 2 ($p = 0.432$). Before dexamethasone and aflibercept treatment, 21/27 of the patients in group 1 and 25/32 of the patients in group 2 were phakic ($p = 0.360$). The height of the SRD at baseline was 94.92± 37.06 in group 1 and 110.43 ±36.65 in group 2 (p=0.113).

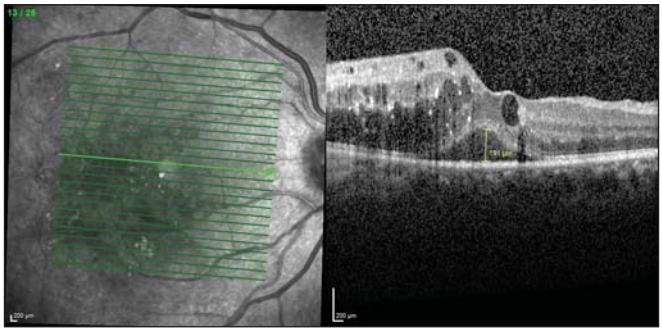

Figure 1: *Illustration of the measurement of the height of the serous detachment.*

The mean BCVA and CMT values in the follow-up periods are given in Table 1. Although there was no significant between -group difference in BCVA at the 1- and 3-mo follow-ups, there was a statistically significant increase in BCVA at the 2-mo follow-up in group 1 (table 2, figure 2). At the 3-mo follow-up, the rate of the gain of 10 or more letters was 66.6% (18/27) of the patients in group 1 and 28.1 % (9/32) of the patients in group 2. There was a statistically significant decrease in CMT in group 1 at the 2- and 3-mo follow-ups as compared to that in group 2 (Table 1-2, Fig. 3). However, there was no significant difference between the macular thicknesses in both groups at the 1-mo follow-up (Table 1-2, Figure 3). The mean of intraocular pressure in the group 1 was 12.5±2.6 mmHg, 16.2±2 mmHg, 18±2.9 mmHg and 17.4±2.6 mmHg at baseline, 1st month, 2nd and 3rd month, respectively (p<0.001). Compared to baseline, this difference was statistically significant at all times (p=0.004, p<0.001, p<0.001 respectively). The mean of intraocular pressure in the group 2 was 14.1±2.5 mmHg, 14.4±2.5 mmHg, 15±2.2 mmHg and 15.1±2.4 mmHg at baseline, 1st month, 2nd and 3rd month, respectively (p=0.06).

Table 1. *The mean value of CMT (µm) and BCVA (ETDR letters) (mean±SD) and comparisons in Dex group and Aflibercept group in follow up periods.*

	Dex Group	Aflibercept Group	[a]P value
Baseline BCVA	45.74 ± 7.63	45.53 ± 5.58	0.766
1st month BCVA	56.26 ± 10.53	53.06 ± 8.79	0.133
2nd month BCVA	60.7 ± 11.61	52.0 ± 7.3	**0.001**
3rd month BCVA	56.19 ± 10.17	51.94 ± 7.99	0.078
[b]P value	[b]p<0.001	[b]p<0.001	
Baseline CMT	525.3 ± 108.38	515.59 ± 105.95	0.73
1st month CMT	375.37 ± 86.99	370.44 ± 91.12	0.676
2nd month CMT	309.85 ± 47.87	390.28 ± 92.14	**<0.001**
3rd month CMT	339.41 ± 47.96	390.88 ± 78.54	**0.003**
[b]P value	[b]p<0.001	[b]p<0.001	

Mean±SD (standart deviation) [a] an independent samples t test for parametric data and Mann–Whitney U test for nonparametric data [b] Repeated measure test. p<0.05 was considered to be statistical significant, bold values denote statistical significance

Table 2: *Correlations between the height of the SRD at baseline and duration of diabetes mellitus, HBA1C levels, baseline BCVA, baseline CMT.*

	Duration of diabetes mellitus	HBA1C levels	Baseline BCVA	Baseline CMT
the height of the SRD at baseline	p=0.748 r=0.043	p=0.086 r=-0.225	**p=0.014** **r=-0.319**	**p<0.001** **r=0.564**

*Pearson correlation analysis was used. r=correlation coefficient. p<0.05 was considered to be statistical significant, bold values denote statistical significance

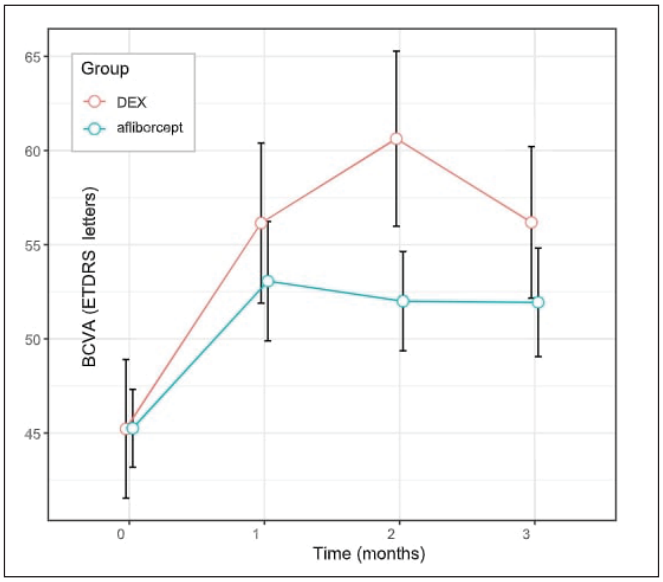

Figure 2: *Graph of BCVA change over time in group 1 and 2.*

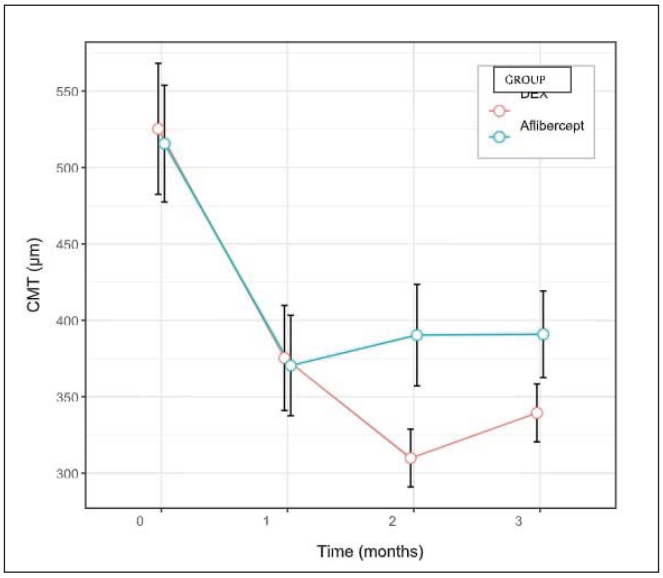

Figure 3: *Graph of CMT change over time in group 1 and 2.*

There was no correlation between the baseline height of SRD and the duration of diabetes and HBA1c levels in all patients (Table 2). There was a positive correlation between the baseline height of SRD and the baseline CMT but a negative correlation between the baseline height of SRD and the baseline BCVA in all patients (Table 2). There was a negative correlation between the baseline BCVA and CMT values (p = 0.001, r = - 0.430) in all patients. There was a positive correlation between increase in BCVA and decrease in CMT relative to the baseline at the 3-mo follow-up in all patients ($p < 0.001$ r = 0.450) (Figure 4). By the end of the 3-mo follow-up, SRD has completely regressed in 85.1% (23/27) of eyes in the dexamethasone group and 62.5% (20/32) of the eyes in the aflibercept group.

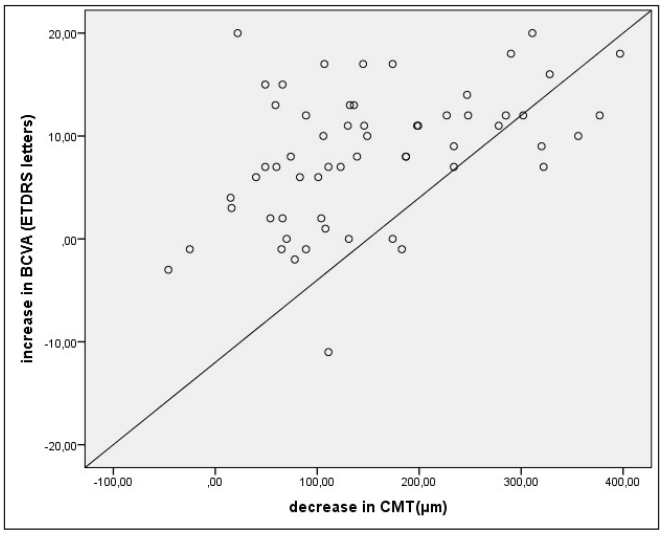

Figure 4: *Graph of the correlation between increase in BCVA and decrease in CMT relative to the baseline at the 3-mo follow-up in all patients ($p < 0.001$ r = 0.450).*

DISCUSSION

In our study, the dexamethasone implant treatment was significantly better than the aflibercept treatment group in terms of visual outcomes at the 2-mo follow-up and superior in terms of anatomical results at the 2- and 3-mo follow-ups in patients with DMO accompanied by an inflammatory phenotype and insufficient response to bevacizumab. Thus, the slow-release dexamethasone implant treatment was better than aflibercept injections in a short-term follow-up, especially in terms of anatomical outcomes. Dexamethasone is a corticosteroid. Like all steroids, dexamethasone inhibits the arachidonic acid pathway and prevents the formation of prostaglandins and

leukotrienes, which are linked to inflammation of the cell membrane[9,13]. The positive outcomes of the dexamethasone implant in patients with an inflammatory phenotype in the present study can be attributed to the drug's anti-inflammatory activity.

SRD is found in many cases of DMO. Although the significance of SRD in DMO and its underlying pathophysiology have yet to be determined, it is thought to be the result of excessive leakage from the retinal or choroidal circulation and accumulation in the sub-retinal space[15]. There is no clear consensus on the effect of SRD on intravitreal treatment in DMO and its relationship with BCVA and CMT. Qu-Knafo et al. examined the efficacy of intravitreal ranibizumab on anatomical and functional outcomes in DMO patients with and without SRD[16]. In their study, the mean change in BCVA and mean decrease in CMT were higher in a group with SRD than without SRD. Gaucher et al. found that the height of SRD in DMO eyes was not correlated with visual acuity or retinal thickness[15]. Some studies evaluated responses to intravitreal treatment according to macular oedema subtypes (SRD, diffuse retinal thickening and CMO)[17],[18]. Kim et al. concluded that intravitreal bevacizumab injections were more effective in the diffuse type of macular oedema than in CMO and SRD subtypes and thus considered SRD a poor prognostic criterion for the response to intravitreal bevacizumab[17].

Koytak et al. found no statistically significant difference between all subtypes of DMO (diffuse ME, CMO and SRD) in terms of changes in BCVA after intravitreal bevacizumab injection therapy[18]. However, CMT was decreased in CMO and in macular oedema sub-types with SRD as compared with that in the diffuse mcular oedema sub-type[18]. However, studies investigated the effects of different drugs on SRD in DMO. The different efficacies of these drugs may explain the conflicting results of these studies. In our study, all the DMO patients had an inadequate response to bevacizumab prior to commencing treatment with the intravitreal dexamethasone implant or aflibercept. We found that dexamethasone was more effective than aflibercept in terms of anatomical outcomes at the end of the 3-mo follow-up period. Özsaygılı et al. showed that in treatment-naive diabetic macular oedema patients with an inflammatory phenotype, anatomical outcomes were better in a dexamethasone-treated group than in an aflibercept-treated group at 3-mo follow-up[19]. In the same study, visual outcomes were superior in the aflibercept-treated group at 3-mo follow-up[19]. But, patients with treatment-naive diabetic macular oedema were included in their study[19]. In our study, visual outcomes in the dexamethasone group were better than those in the aflibercept group at the 2-mo follow-up, when it was most effective. But at the 3-mo follow-up, although the visual result with dexamethasone implant was better than aflibercept, it was statistically insignificant. In our study, there was an increase in BCVA of more than 10 letters at the end of the follow-up in 66.6% (18/27) and 28.1% (9/32) of patients in the dexamethasone implant and aflibercept groups, respectively, as compared to 25% and 42% of patients in the dexamethasone and aflibercept-treated groups in the study by Ozsaygılı et al[19].

In addition to leakage from the retinal or choroidal circulation, the pathogenesis of SRD is also linked to failure of the RPE pump mechanism[16]. RPE pump failure or disruption of tight junctions between adjacent RPE cells caused intraretinal oedema and SRD[15]. Cytokines caused leukostasis, increased vascular permeability and chronic inflammation, which led to impairment of the blood–retinal barrier in the retina[20]. Therefore, SRD is thought to accompany DMO when inflammation is present. Furthermore, steroids support tight junction protein expression and protect these proteins from degradation in RPE cells caused by oxidative stress[21]. Thus, preserving the integrity of tight junctions in the blood–retinal barrier helps to stabilize the retinal vascular system[21]. In a study on the effect of dexamethasone implant treatment on DMO, Kaldirim et al. reported improved BCVA in all sub-groups (SRD, CMO and diffuse macular oedema) at a 6-mo follow-up. In the same study, CMT values in the SRD sub-group were better than those in the macular oedama and CMO sub-groups at the 6-mo follow-up[22]. They asserted that their results supported the effectiveness of corticosteroid treatment in the presence of increased cytokine levels[22]. In our study, DMO accompanied by SRD and HRDs also showed a better response to dexamethasone due to the predominance of inflammation. Despite the aforementioned findings, some studies showed that DMO with SRD responded well to anti-VEGF therapy[22,23].

Jones et al. demonstrated that eyes with diabetic retinopathy had higher PIGF concentrations in aqueous and vitreous humor compared to controls[24]. Aflibercept has the ability to bind PIGF, in addition to VEGF. This property of aflibercept may make it more effective than other anti-VEGF agents (bevacizumab, ranibizumab) in DMO treatment[25]. Funk et al. examined inflammatory markers in anterior chamber fluids in a study that included 10 DMO eyes and 10 control eyes[26]. In the eyes with DMO, they detected increased expression of monocyte chemoattractant protein-1 and interleukin-8 but insignificant levels of interleukin-6 and VEGF[26]. These studies support the idea that dexamethasone and aflibercept may be effective in DMO cases where patients exhibit an inadequate response to bevacizumab.

Vujosevic et al. analysed and compared changes in retinal inflammatory biomarkers, such as SRD, after treatment with intravitreal dexamethasone ($N = 17$) and ranibizumab ($N = 10$)[27]. They reported no significant difference in SRD resolution between the two treatment groups but a greater decrease in CMT after the steroid therapy[27]. In our study, by the end of a 3-mo period, SRD had completely regressed in 85.1% (23/27) of eyes in the dexamethasone group and 62.5% (20/32) of the eyes in the aflibercept group, but the decrease in CMT was more pronounced in the dexamethasone group.

HRDs which are thought to be aggregates of microglia-activated cells, serve as a biomarker of inflammation on OCT imaging[28]. Studies also revealed that both SRD and HRDs constituted a specific inflammatory model of DMO that responded better to intravitreal steroids[27,29]. In our study, the presence of HRDs and SRD in patients unresponsive to bevacizumab supports the idea that inflammatory mediators other than VEGF are at the forefront in DMO. Thus, the patients with HRDs and SRD responded better to the dexamethasone implant treatment than they did to aflibercept

In our study, all the patients had previously received three doses of bevacizumab. Patients with a long duration of DMO and a history of DMO treatment exhibit photoreceptor degeneration as compared with newly diagnosed DMO cases. Previous research showed that delays in DMO treatment were associated with less of an improvement in visual acuity post-treatment[30]. In our study, we aimed to determine the effectiveness of intravitreal dexamethasone implant and aflibercept treatment over a 3-mo period in patients without photoreceptor degeneration or a treatment response after three doses of bevacizumab. Our results showed that the baseline BCVA was correlated with the baseline CMT values, despite prior treatment (i.e. three doses of bevacizumab). There was a correlation between the improvement in BCVA and CMT relative to the baseline at the 3-mo follow-up. Our findings highlight the importance of switching to an appropriate treatment regimen before photoreceptor degeneration occurs in DMO.

The limitations of this study are its retrospective design and short follow-up period. Long-term study results may differ, as dexamethasone, a steroid, may affect vision by causing cataracts and glaucoma.

In conclusion, although both intravitreal dexamethasone implant and aflibercept treatment significantly improved visual and anatomical outcomes in a 3-mo follow-up, dexamethasone was superior to aflibercept. In refractory cases, switching to appropriate treatment before photodegeneration occurs affects visual results. An additional advantage of dexamethasone versus aflibercept is that the former treatment requires fewer injections.

Author contribution: All authors read and approved the final manuscript

Study design: Esra vural

Data collection: Esra Vural, Ender Sırakaya

Analysıs And/Or Interpretatıon: Esra vural, Ender Sırakaya

Lıterature Revıew: Esra Vural, Leyla Hazar

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Compliance with Ethical Standards:

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Human and animal rights: Not applicable.

Informed consent: Not applicable.

Competing interest: Esra Vural declares that she has no conflict of interest. Leyla Hazar declares that she has no conflict of interest. Ender Sırakaya declares that he has no conflict of interest

Data Availability: Data available on request from authors

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