DOI: 10.14744/eer.2024.78941
Eur Eye Res 2024;4(3):193–201

EUROPEAN EYE RESEARCH

ORIGINAL ARTICLE

Investigation of subtypes of diabetic macular edema refractory to anti-VEGF treated with a single-dose dexamethasone implant

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Abstract

Purpose: The purpose of this study was to evaluate the subtypes of diabetic macular edema refractory to vascular endothelial growth factor (anti-VEGF) treated with a single-dose dexamethasone (DEX) implant.

Methods: In this retrospective study, 81 patients (118 eyes) with diabetic macular edema refractory to anti-VEGF treated with a single injection of DEX implant were evaluated. Diabetic macular edema was classified into four subtypes: Diffuse macular edema (DME) (n=36 eyes), cystoid macular edema (CME) (n=40 eyes), serous retinal detachment (SRD) (n=20 eyes), and cystoid macular degeneration (CMD) (n=22 eyes). Best-corrected visual acuity (BCVA) and central macular thickness (CMT) changes in 2, 4, and 6 months were examined.

Results: The baseline BCVA was significantly lower in CMD eyes compared with the CME eyes (p=0.005). The baseline CMT was significantly lower in CME eyes compared with CMD (n=0.002) and DME eyes (n=0.014). After the intravitreal DEX implant, BCVA increased significantly in the 2nd month in the SRD eyes (p=0.045), in the 4th month in the DME eyes (p=0.038), and in the 6th month in the CME eyes (p=0.014). BCVA changes in CMD eyes were not statistically significant for all months (p>0.05). The mean CMT of all groups decreased significantly in the 2nd month (p<0.001 for all). ΔCMT at 2 months was −231.20±221.12 μm in the SRD group, −112.97±141.02 μm in the CME group, −312.66±175.56 μm in the CMD group, and −190.77±173.04 μm in the DME group (p<0.001). According to post hoc Bonferroni analysis, ΔCMT was statistically significantly higher in CMD eyes than in CME eyes (p<0.001).

Conclusion: Different subtypes of diabetic macular edema suggest different etiopathogenesis and drug responses. The eyes with the fastest onset of both morphological and functional improvement of intravitreal DEX implant were eyes with SRD. Although anatomical improvement began early in CME and DME eyes (2nd month), functional recovery begins later (4th and 6th month). The eyes with the least functional recovery were the eyes with CMD.

Keywords: Best-corrected visual acuity; central macular thickness; cystoid macular degeneration; cystoid macular edema; diffuse macular edema; serous retinal detachment.

Cite this article as: Ismayilov AS, Kahkeci B, Kargin AM, Ulusoy MO. Investigation of subtypes of diabetic macular edema refractory to anti-VEGF treated with a single-dose dexamethasone implant. Eur Eye Res 2024;4(3):193–201.

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Submitted Date: 08.04.2024 **Revised Date:** 15.05.2024 **Accepted Date:** 10.06.2024 **Available Online Date:** 29.11.2024

Diabetic macular edema can be observed at any stage of diabetic retinopathy (DR) and is the most common cause of visual impairment in diabetic patients.[1,2] Inflammation, vascular endothelial growth factor (VEGF), angiogenesis, and cytokines such as monocyte chemotactic protein-1, interleukin-6 (IL-6), and interleukin-8 (IL-8) play roles in the etiopathogenesis.[3,4]

Anti-VEGF agents are used to block the VEGF pathway of diabetic macular edema, and steroids are used to suppress the inflammatory process. In addition, intravitreal steroid injection has been shown to block the expression of VEGF and other inflammatory mediators and reduce leukostasis and vascular leakage by improving the barrier function of endothelial cell tight junctions.[5] Dexamethasone (DEX) implant (Ozurdex; Allergan Inc, Irvine CA) is an effective slow-release delivery system established in the treatment of diabetic macular edema with common complications such as intraocular pressure (IOP) elevation and cataract formation.

Spectral-domain optical coherence tomography (SD-OCT) has allowed detailed morphological analysis of diabetic macular edema and revealed various biomarkers. Arf et al. defined three types based on SD-OCT: Diffuse macular edema (DME), cystoid macular edema (CME), and cystoid degeneration. They evaluated serous macular detachment (SMD), vitreomacular interface abnormalities, hard exudates, and photoreceptor status as additional morphological features.[6] Otani et al.[7] also reported three structural features of diabetic macular edema: Spongy retinal swelling, CME, and serous retinal detachment (SRD). In a different study,[8] the presence of vitreomacular traction (VMT) was taken into categorization and five OCT patterns were identified: Diffuse retinal thickening, CME, SRD, posterior hyaloidal traction, and tractional retinal detachment.

DME is thought to be the result of intracytoplasmic swelling of Müller cells in the outer plexiform layer. CME is characterized by the formation of cystoid cavities as a result of liquefaction necrosis of Müller cells. Serous macular detachment is a hyporeflective area under the neuroretina associated with the inflammatory component, seen in 15–30% of eyes with diabetic macular edema.[4,9] Cystoid macular degeneration (CMD) is a result of chronic macular edema and is associated with poor visual acuity. Each morphological subtype of macular edema, in addition to having common features, is likely to have unique pathophysiological aspects that may be responsible for different treatment responses.

The purpose of the present study is to evaluate the visual and morphologic outcomes of a single intravitreal injection of DEX implant in eyes with different subtypes of diabetic macular edema which was refractory to anti-VEGF agents.

Materials and Methods

In this retrospective study, 81 patients (118 eyes) with diabetic macular edema refractory to anti-VEGF treated with a single injection of DEX implant between September 2021 and March 2024 were evaluated. Ethics committee approval (Number: 2011-KAEK-25 2023/11–14) was obtained from the Local Ethics Committee of the hospital. The study adhered to the tenets of the Declaration of Helsinki. Refractory DME was defined as macular edema with central macular thickness (CMT) >300 µm or a reduction in CMT <10% after at least three prior anti-VEGF injections.[10]

Patients with glaucoma, a history of vitreoretinal surgery, other causes of retinopathies (e.g., age-related macular degeneration), received fewer than three anti-VEGF treatments, media opacities that decrease SD-OCT image quality, undergone cataract surgery within the past 6 months, history of macular focal, or grid laser were excluded from the study.

Demographic characteristics, duration of diabetes mellitus, number of previous anti-VEGF agents, and glycolyzed hemoglobin (HbA1C) levels before the therapy were recorded. At baseline and follow-up visits, all patients underwent an ophthalmologic examination including best-corrected visual acuity (BCVA) with a Snellen chart (converted to logMAR), IOP, slit-lamp examination, funduscopy, and OCT scans. Fluorescein angiography (FA) was performed to evaluate retinal ischemia and proliferation at baseline and repeated when necessary at follow-up.

OCT

SD-OCT was performed (RTVue XR AVANTI, Optovue, Inc., Fremont, CA, USA) with emitting light wavelength of 840 nm and capable of 70,000 A-scans per second and resolution of 5 µm. CMT, defined as the average thickness within a 1-mm circle centered over the fovea, was measured from the internal limiting membrane to the retinal pigment epithelium by manual calipers. ΔCMT: Calculated as the last visit of the CMT-baseline CMT.

Intraretinal or subretinal highly reflective dots were identified as hard exudates.[11] VMIA classifications were based on the International VMT Study Group.[12] The

conditions (intact/disrupted) of outer retinal layers within the central 1 mm external limiting membrane (ELM) and ellipsoid zone (EZ) were also evaluated.

We classified eyes of diabetic macular edema into four types with SD-OCT: 1, DME; 2, CME; 3, SRD; and 4, CMD. DME was defined as increased retinal thickness and enlarged areas of lower reflectivity with decreased intraretinal reflectance.[7,8] CME was called the localization of intraretinal cystoid-like spaces seen as high reflectivity, round or oval, low reflectivity areas separating cystoid-like spaces. Eyes with cystoid-like spaces of horizontal diameter ≥600 µm were graded as CMD.[13] SRD was considered by a shallow elevation of the retina and an optically clear gap between the retina and the retinal pigment epithelium.[4]

Our definition of DME only includes pure DME. If DME was combined with CME, it was classified as CME; if DME was combined with SRD, it was classified as SRD. When DME, CME, and SRD were all present, the type was classified as SRD. Severe CME (the horizontal diameter of cystoid spaces ≥600 µm) was accepted as CMD. Lesions on SD-OCT scans were evaluated by two independent observers (A.S.I and B.K). In case of disagreement, two other researchers evaluated the SD-OCT imaging (A.M.K. and M.O.U.).

FA

At first, a FA (Topcon TRC-50DX, Topcon Corporation, Tokyo, Japan) was carried out for all the patients to detect the presence of peripheral, macular ischemic areas and proliferation and repeated when necessary at follow-up.

Procedure

Intravitreal DEX implant (0.7 mg) injections were administered in the operating room under sterile conditions. The topical anesthetic was obtained by dropping 0.5% proparacaine hydrochloride (Alcaine, Alcon). Ocular surface cleaning was done with a 5% povidone-iodine solution. It was injected into the vitreous 4 mm behind the limbus (3.5 mm in pseudophakic eyes). Finally, 5% povidone-iodine drops were applied to the injection site. The patients were prescribed moxifloxacin 0.5% eye drops for 7 days following injection and monitored for adverse effects during the whole period of study.

Statistical Analyses

Statistical analyses were performed using the SPSS 22.0 software version (IBM Corp., Armonk, NY, USA), and statistical significance was established at two-tailed $p<0.05$. Variables were examined using the Shapiro–Wilk's test to determine distribution. Continuous data were presented as the mean±standard deviation. Categorical characteristics were presented as numbers (%). Statistical comparisons were performed in the 2nd, 4th, and 6th month with the baseline results. Demographic data, OCT findings, and treatment results of four different subgroups were performed with a Chi-square test and one-way ANOVA with a post hoc Bonferroni test. BCVA and CMT changes after intravitreal DEX for all DME patients were evaluated with paired sample t-tests.

Results

One hundred and eighteen eyes of 81 patients were included in the study. The mean age of patients was 65.01±8.23 (44–80) years. About 56.8% (n=46) of participants were female. About 33.1% (n=39) of patients were pseudophakic. The mean duration of diabetes mellitus was 19.22±4.73 years. The mean glycolyzed HbA1C value of patients before the treatment was 7.79±1.51. The mean number of previous anti-VEGF injections was 3.6±1.5 (3–11). The baseline BCVA was 0.97±0.43 (0.15–2) logMAR. The mean IOP was 14.2±3.1 mmHg. 42.3% (n=50) of eyes had ischemic maculopathy. The baseline CMT was 515.72±187.14 (300–1220) µm. Thirty-four patients (28.8%) had hard exudates and 6 patients (5.1%) had vitreomacular adhesion (VMA) or VMT. Thirty-four patients (28.8%) had epiretinal membrane (ERM). While 6 patients (5.1%) had ELM disruption, 10 patients (8.5%) had EZ disruption (Table 1).

The baseline BCVA was 0.92±0.34 logMAR in SRD eyes, 0.85±0.43 logMAR in CME eyes, 1.37±0.20 logMAR in CMD eyes, and 0.97±0.45 in DME ($p=0.009$). In post hoc analyses with Bonferroni, baseline BCVA (logMAR) in CME eyes was lower than in CMD eyes ($p=0.005$). The baseline CMT was 514.40±217.13 µm in SRD eyes, 440.0±139.61 µm in CME eyes, 620.38±203.23 µm in CMD eyes, and 568.69±186.39 µm in DME eyes ($p=0.001$). In post hoc analyses with Bonferroni, baseline CMT in CME eyes was lower than in CMD eyes ($p=0.002$) and DME eyes ($p=0.014$) (Table 2).

For all patients, there was a statistically significant decrease in mean BCVA (logMAR) and mean CMT in 2nd month, 4th month, and 6th month ($p<0.05$) (Table 3). The mean IOP at the 2nd, 4th, and 6th months was 17.1±5.1 mmHg, 15.9±3.5 mmHg, and 13.7±2.7 mmHg, respectively.

The BCVA and CMT results after intravitreal DEX according to the morphological subtype of diabetic macular edema are as follows: In SRD eyes, BCVA (logMAR) decrease at 2 months ($p=0.045$) and CMT decrease at 2 and 4 months were statistically significant ($p<0.001$ and $p=0.003$). In

Table 1. Characteristics of all diabetic macular edema patients before intravitreal DEX implant

Patient characteristics	All patients (n=118 eyes of 81 patients) (%)
Age (years)	65.01±8.23 (44–80)
Gender (male/female)	35/46 (43.2/56.8)
Laterality (R/L)	59/59
Lens status (phakic/pseudophakic)	79 (66.9)/39 (33.1)
Duration of diabetes mellitus (years)	19.22±4.73
HbA1c (%)	7.79±1.51 (5.59–11.80)
Number of previous anti-VEGF injections (n)	3.6±1.5 (3–11)
Baseline BCVA (log MAR)	0.97±0.43 (0.15–2)
Mean IOP (mmHg)	14.2±3.1 (7–20)
Proliferative/non-proliferative DR	17 (14.4)/101 (85.6)
Ischemic maculopathy (yes/no)	50(42.3)/68 (57.7)
Baseline CMT (µm)	515.72±187.14 (230–1220)
Hard exudates (yes/no)	34 (28.8)/84 (71.2)
Vitreomacular adhesion or vitreomacular traction (yes/no)	6 (5.1)/112 (94.9)
ERM (yes/no)	34 (28.8)/84 (71.2)
ELM zone disruption (yes/no)	6 (5.1)/112 (94.9)
EZ zone disruption (yes/no)	10 (8.5)/108 (91.5)

Anti-VEGF: Anti-vascular endothelial growth factor, HbA1c: Glycolized hemoglobin, BCVA: Best-corrected visual acuity, IOP: Intraocular pressure, DR: Diabetic retinopathy, CMT: Central macular thickness, VMA: Vitreomacular adhesion, VMT; Vitreomacular traction, ERM: Epiretinal membrane, ELM: External limiting membrane EZ: Ellipsoid zone, mean ± SD, n (%).

CME eyes, BCVA (logMAR) decrease at 6 months (p=0.014) and CMT decrease at 2, 4, and 6 months were statistically significant (p<0.001, p<0.001, and p=0.002). In CMD eyes, while BCVA changes were not statistically significant (p>0.05 for all months), only the CMT decrease at 2 months was statistically significant (p<0.001). In DME eyes, BCVA (logMAR) decrease at 4 months (p=0.038) and CMT decrease at 2, 4, and 6 months were statistically significant (p<0.001, p<0.001, and p=0.011) (Table 4 and Fig. 1).

The proportion of patients' diabetic macular edema completely resolved (p=0.725), decreased (p=0.526), and remained stable (p=0.426) after intravitreal DEX were similar in all groups (Table 5). The CME group had more recurrences after 6 months (63.6% in CME, 20% in SRD, 30% CME, and 30.5% DME) (p=0.032).

Between groups, ΔBCVA at the 2nd month (p=0.310), 4th month (p=0.126), and 6th month (p=0.640) and ΔCMT at 4th month (p=0.654) and 6th month (p=0.890) were similar. ΔCMT at 2 months was −231.20±221.12 µm in the SRD eyes, −112.97±141.02 µm in the CME eyes, −312.66±175.56 µm in the CMD eyes, and −190.77±173.04 µm in the DME group (p<0.001). According to post hoc Bonferroni analysis, this difference was statistically significantly higher in CMD than in CME eyes (p<0.001) (Table 6).

Table 2. Functional and morphological baseline characteristics in morphological subtypes of diabetic macular edema

Characteristics	SRD (n=20 eyes)	CME (n=40 eyes)	CMD (n=22 eyes)	DME (n=36 eyes)	p
Age (years)	64.35±7.8	63.78±9.1	69.19.±6.9	63.83±7.6	0.063
Gender (male/female)	7//11	12/18	5/8	11/9	0.863
					0.929
Laterality (right/left)	10/10	21/19	10/12	18/18	0.929
					000
					0.820
HbA1c (%)	7.81±1.4	7.68±0.98	7.82±1.18	7.74±0.99	0.711
No. of previous anti-VEGF injections (n)	3.25±0.78	3.87±1.66	3.52±1.66	3.66±1.70	0.512
					0.254
Proliferative/nonproliferative (yes/no)	2/18	5/35	4/18	6/30	0.254
Ischemic maculopathy (yes/no)	10/10	15/25	9/13	16/20	0.149
Baseline BCVA	0.92±0.34	0.85±0.43	1.37±0.20	0.97±0.45	0.009*
Baseline CMT (µm)	514.40±217.13	440.0±139.61	620.38±203.23	568.0±186.39	0.001**
					0.0
Hard exudates (yes/no)	10/10	7/33	5/17	12/24	0.051
VMA or VMT (yes/no)	2/18	2/38	1/21	1/35	0.113
ERM (yes/no)	5/15	12/28	6/16	11/25	0.457
ELM disruption (yes/no)	1/19	2/38	2/20	1/35	0.746
EZ zone disruption (yes/no)	1/19	4/36	3/19	2/34	0.635

SRD: Serous retinal detachment, CME: Cystoid macular edema, CMD: Cystoid macular degeneration, DME: Diffuse macular edema, HbA1c: Glycolized hemoglobin, BCVA: Best-corrected visual acuity, CMT: Central macular thickness, VMA: Vitreomacular adhesion, VMT: Vitreomacular traction, ERM: Epiretinal membrane, ELM: External limiting membrane, EZ: Ellipsoid zone. Mean ± SD, Chi-square, one way ANOVA, post hoc Bonferroni test (P*: for CME and CMD eyes P=0.005 and P**: for CME and CMD eyes P=0.002 and for CME and DME eyes P=0.014).

Table 3. BCVA and CMT changes after intravitreal DEX for all diabetic macular edema patients

All patients	Outcomes	Period	Mean±SD	P-values	P´-values
	BCVA(logMAR)	Baseline	0.97±0.43		
		2 months	0.89±0.45	0.038	0.038
		4 months	0.90±0.46	0.048	0.643
		6 months	0.86±0.45	0.016	0.411
	CMT (µm)	Baseline	523.97±191.16		
		2 months	331.05±151.31	0.000	0.000
		4 months	348.74±153.83	0.000	0.100
		6 months	426.49±218.29	0.000	0.017

BCVA: Best-corrected visual acuity, CMT: Central macular thickness; P-values are obtained with Paired sample t-test and referred to change with baseline; P´-values are obtained with a Paired sample t-test and referred to change with the previous evaluation.

Table 4. Functional and morphological outcomes in morphological subtypes of diabetic macular edema

Subgroups	Outcomes	Period	Mean±SD	P-values	P´-values
SRD	BCVA (logMAR)	Baseline	0.92±0.34		
		2 months	0.79±0.34	0.045	0.045
		4 months	0.91±0.44	0.908	0.051
		6 months	0.91±0.37	0.944	0.770
	CMT (µm)	Baseline	530.15±211.43		
		2 months	284.25±108.14	0.000	0.000
		4 months	360.05±226.68	0.003	0.252
		6 months	412.46±255.10	0.079	0.535
CME	BCVA (logMAR)	Baseline	0.85±0.43		
		2 months	0.82±0.48	0.632	0.632
		4 months	0.81±0.52	0.592	0.633
		6 months	0.71±0.46	0.014	0.012
	CMT (µm)	Baseline	426.17±134.93		
		2 months	326.85±132.11	0.000	0.000
		4 months	302.24±151.40	0.000	0.214
		6 months	354.17±154.19	0.002	0.003
CMD	BCVA (logMAR)	Baseline	1.37±0.20		
		2 months	1.17±0.46	0.058	0.714
		4 months	1.03±0.47	0.127	0.630
		6 months	0.87±0.50	0.112	0.055
	CMT (µm)	Baseline	623.00±198.71		
		2 months	306.59±144.62	0.000	0.000
		4 months	487.18±263.23	0.130	0.131
		6 months	488.85±232.08	0.490	0.244
DME	BCVA (logMAR)	Baseline	0.97±0.45		
		2 month	0.92±0.43	0.460	0.460
		4 month	0.80±0.40	0.038	0.048
		6 month	0.93±0.56	0.562	0.045
	CMT (µm)	Baseline	568.69±186.39		
		2 month	377.91±186.97	0.000	0.000
		4 month	366.12±176.68	0.000	0.598
		6 month	498.76±233.43	0.011	0.227

SRD: Serous retinal detachment, CME: Cystoid macular edema, CMD: Cystoid macular degeneration, DME: Diffuse macular edema, BCVA: Best-corrected visual acuity, CMT: Central macular thickness, P-values are obtained with a Paired sample t-test and referred to change with baseline. P-values are obtained with a Paired sample t-test and referred to change with the previous evaluation.

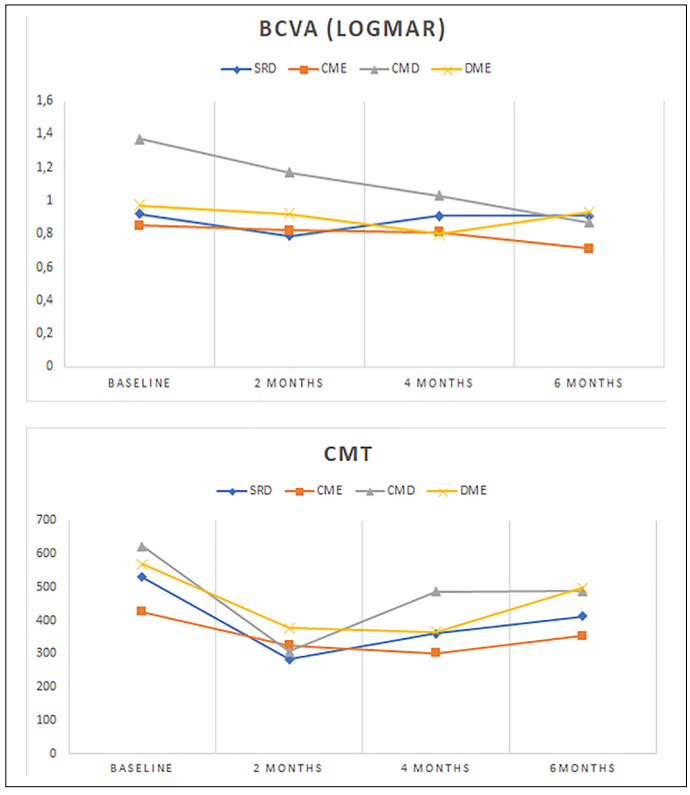

Fig. 1. Best-corrected visual acuity and central macular thickness changes in subtypes of diabetic macular edema.

After the intravitreal DEX implant, cataract surgery was performed in 11 eyes (9.3%) (within 6 months) and antiglaucomatous was started in 19 eyes (16.1%).

Discussion

Currently, the recommended and preferred first-choice treatment for diabetic macular edema is intravitreal anti-VEGF agents.[1] However, the need for frequent injections creates a treatment burden for many patients, and some patients also respond partially or do not respond to anti-VEGF treatments. In diabetics, macular edema, fluid accumulation, and macular thickening are the result of retinal capillary leakage or proliferation and are triggered by inflammation. Corticosteroids, which downregulate many of these inflammatory molecules, including VEGF, are used to repair the blood–retinal barrier and may offer an effective treatment option in unresponsive patients already treated with anti-VEGF.[1] The MEAD study, a Phase III clinical trial, evaluating the long-term safety and effectiveness of the DEX implant in previously treated patients, demonstrated the benefit of the DEX implant in improving visual acuity and reducing CMT in patients with diabetic macular edema.[14]

Examination of anatomical biomarkers on OCT may help predict response to the DEX implant. A study reported that in both naive and refractory to anti-VEGF patients, the presence of SRF, the absence of HRF, and the integrity of EZ were all predictive of better functional outcomes after with DEX implant.[15] Similarly, it is thought that different morphological edema types may respond differently to the DEX implant. The reason for this may be that edema types are due to different etiopathogenesis and may be related to different cytokine levels in the aqueous humor. In a histopathological study, it was reported that the initial type of diabetic macular edema was DME, and CME and SRD were more advanced forms,[16] but some studies say the opposite and show that the duration of diabetes is shorter in CME and SRD.[17,18] In one study, IL-6, IL-8, and VEGF levels were examined in aqueous samples of different types of diabetic edema, and IL-6 and VEGF values were found to be correlated with CMT in diffuse retinal thickening and SRD subgroups.[19]

There are conflicting results in the literature regarding macular edema type and visual acuity. In some studies, eyes with SRD are associated with worse BCVA,[20] while in others, the lowest BCVA and the highest CMT were found in the CME group.[21] On the other hand, Kim et al.[8] reported that DME was associated with the best BCVA, and Altinişik et al.[22] found the visual acuities of the subgroups to be similar. In the present study, eyes with CMD had the highest baseline CMT and the lowest baseline BCVA. About 18.5% of these eyes had proliferative DR and 40% had severe

Table 5. Diabetic macular edema after intravitreal DEX

Subtypes	Completely resolved	Decreased edema	Stable edema
SRD (n=20), n (%)	10 (50)	8 (40)	1 (5)
CME (n=40), n (%)	18 (45)	16 (40)	5 (12.5)
CMD (n=22), n (%)	12 (54.4)	6 (27.2)	2 (9)
DME (n=36), n (%)	12 (33.3)	10 (27.7)	3 (8.3)
P-value	0.725	0.526	0.426

SRD: Serous retinal detachment, Cystoid ME: Cystoid macular edema, Cystoid MD: Cystoid macular degeneration, DME: Diffuse macular edema, Chi-square, n (%).

Table 6. ΔBCVA and ΔCMT at 2, 4, and 6 months

Subtypes	ΔBCVA 2 months	ΔBCVA 4 months	ΔBCVA 6 months
SRD	1.33±0.86	1.56±0.84	1.44±0.97
CME	1.61±0.89	1.33±0.91	1.18±1.00
CMD	1.56±1.02	1.53±0.95	1.56±0.88
DME	1.39±0.80	1.16±0.68	1.40±0.87
P-value	0.310	0.126	0.640
	ΔCMT 2 months	**ΔCMT 4 months**	**ΔCMT 6 months**
SRD	−231.20±221.12	−204.62±217.61	−137.06±311.23
CME	−112.97±141.02	−133.88±139.76	−90.51±131.66
CMD	−312.66±175.56	−149.20±301.37	−76.28±274.88
DME	−190.77±173.04	−202.30±170.66	−106.56±194.60
P-value	<0.001*	0.654	0.890

SRD: Serous retinal detachment, CME: Cystoid macular edema, CMD: Cystoid macular degeneration, DME: Diffuse macular edema, ΔBCVA: Previous examination – baseline best-corrected visual acuity, ΔCMT: Previous examination – baseline central macular thickness, one-way ANOVA, post hoc Bonferroni test (P*: for CME and CMD eyes P<0.001).

non-proliferative DR. Among the groups, the group with the highest ELM and EZ disruption was also the eyes with CMD. Arf et al.[6] classified CMD, which is large cystoid cavities with a horizontal diameter ≥600 μm, consistent with long-term diabetic macular edema. They also found that eyes with CMD had the lowest baseline BCVA, the highest baseline CMT, and the highest outer retinal layer disruption.

After a single dose of intravitreal DEX, although BCVA increased in the 2nd month in all groups, a significant improvement was observed only in eyes with SRD compared to the others, and CMT decreased in the 2nd and 4th month. Campos et al.[18] suggested that SRD is more likely to occur in early-onset diabetic macular edema associated with increased choroidal thickness, choriocapillaris permeability, and external blood–retinal barrier dysfunction. The incidence of SRD in eyes with CMD is lower than in eyes with DME and CME. In this study, the reasons for the faster response in eyes with SRD to intravitreal DEX are; that permanent anatomical damage has not yet developed, and the role of the inflammation may be more dominant in the SRD type.[18] In CME eyes, while CMT decreased statistically significantly in the 2nd, 4th, and 6th month, a statistically significant change in BCVA was observed in the 6th month. Consistent with the literature,[23] more recurrence was observed in CME eyes. In DME eyes, CMT decreased significantly in the 2nd, 4th, and 6th months, and a significant improvement in BCVA was observed in the 4th month. The changes in BCVA and CMT in the 2nd and 4th months were greater in the DME group than in the CME group, but these differences were not statistically significant. Arf et al.[6] reported that DME is the earliest form of diabetic macular edema. Kim et al.[24] reported a better improvement in visual acuity in the DME eyes compared to the CME eyes after focal laser photocoagulation. However, Shulman et al.[25] reported better improvements in CME with intravitreal triamcinolone acetonide injection than in the DME group. In the present study, SRD eyes reached the best BCVA level in the 2nd month, DME eyes in the 4th month, and CME and CMD eyes in the 6th month. The lowest CMT levels were reached in SRD and CMD eyes at 2 months and DME and CME eyes at 4 months. Overall, the mean CMT showed a statistically significant reduction and the mean BCVA improved at all follow-up visits.

Hard exudates can often be seen together with macular edema in eyes with DR and consist of lipids and proteinaceous materials such as fibrinogen and albumin leaking from microaneurysms and capillaries.[26,27] Submacular hard exudates have been shown to cause severe visual loss in patients with diabetic macular edema.[28] The prevalence of VMT, including eyes with tense, thickened posterior hyaloid, and vitreoretinal adhesions, ranges from 4% to 25% in eyes with diabetic macular edema. A significant difference in mean BCVA was observed between patients with and without VMIA; patients with these abnormalities had worse vision.[29] In this study, 5.1% of the patients had VMA and VMT and 28.8% had ERM. However, their distribution among diabetic edema subgroups is not statistically significant. It is known that loss of the integrity of ELM and EZ is closely associated with poor visual acuity.[30] In our study, ELM and EZ disruption were most common in CMD eyes, as expected.

This study has some limitations, including its retrospective, open-label, uncontrolled nature involving a relatively small number of eyes.

Conclusion

The eyes with the fastest onset of both morphological and functional effects of intravitreal DEX implant were eyes with SRD. Although anatomical improvement began early in CME and DME eyes (2nd month), functional recovery begins later (4th and 6th month). The eyes with the least functional recovery were the eyes with CMD. Our results need to be supported by studies with larger patient numbers. This study, in which morphological and functional improvements were demonstrated, could suggest that different subtypes of diabetic macular edema can show different responses to intravitreal DEX implants. In the near future, specific treatment regimens can be performed on different morphological subtypes.

Ethics Committee Approval: Ethics Committee approval (Number: 2011-KAEK-25 2023/11–14) was obtained from the Local Ethics Committee of the Hospital.

Peer-review: Externally peer-reviewed.

Authorship Contributions: Concept: A.S.I., B.K., A.M.K., M.O.U.; Design: A.S.I., B.K., A.M.K., M.O.U.; Supervision: A.S.I., B.K., A.M.K., M.O.U.; Resource: A.S.I., B.K., A.M.K.; Materials: A.S.I., B.K., A.M.K.; Data Collection and/or Processing: A.S.I., M.O.U.; Analysis and/or Interpretation: A.S.I., M.O.U.; Literature Search: A.S.I., B.K., A.M.K., M.O.U.; Writing: A.S.I.; Critical Reviews: A.S.I., B.K., A.M.K., M.O.U.

Conflict of Interest: None declared.

Use of AI for Writing Assistance: Not declared.

Financial Disclosure: The authors declared that this study received no financial support.

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https://doi.org/10.1159/000458539

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