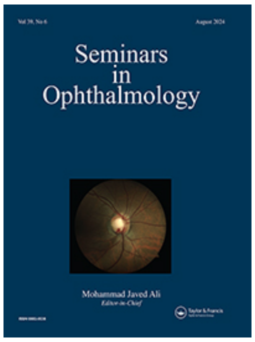

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One-Year Functional and Morphological Prognosis After Intravitreal Injection Treatments According to Different Morphological Patterns of Diabetic Macular Edema in Real-Life: MARMASIA Study Group Report No.13

Utku Limon[a], Fatih Bilgehan Kaplan[b], Işılay Saygın[a], Ecem Önder Tokuç[c], Işıl Kutlutürk Karagöz[d], Hatice Selen Kanar[e], Mehmet Orkun Sevik[f], Uğur Yayla[c], Erkan Çelik[g], Ayşe Sönmez[b], Aslan Aykut[f], Esra Kumral Türkseven[h], Nimet Yeşim Erçalık[h], Özlem Oncu Aydın[h], Erdinç Bozkurt[a], Tuğba Aydoğan[a], Ece Başaran Emengen[i], Abdullah Özkaya[j], Banu Açıkalın Öncel[b], Nursal Melda Yenerel[h], Özlem Şahin[f], and Levent Karabaş[i]

[a]Ümraniye Education and Research Hospital, Department of Ophthalmology, University of Health Sciences, Istanbul, Turkey; [b]Fatih Sultan Mehmet Education and Research Hospital, Department of Ophthalmology, University of Health Sciences, Istanbul, Turkey; [c]Derince Education and Research Hospital, Department of Ophthalmology, University of Health Sciences, Kocaeli, Turkey; [d]Şişli Hamidiye Etfal Education and Research Hospital, Department of Ophthalmology, University of Health Sciences, Istanbul, Turkey; [e]Kartal Dr. Lütfi Kırdar City Hospital, Department of Ophthalmology, University of Health Sciences, Istanbul, Turkey; [f]Department of Ophthalmology, Marmara University School of Medicine, Istanbul, Turkey; [g]Department of Ophthalmology, Sakarya University School of Medicine, Sakarya, Turkey; [h]Haydarpaşa Numune Education and Research Hospital, Department of Ophthalmology, University of Health Sciences, Istanbul, Turkey; [i]Department of Ophthalmology, Kocaeli University School of Medicine, Kocaeli, Turkey; [j]Department of Ophthalmology, Memorial Şişli Hospital, Istanbul, Turkey

ABSTRACT

Purpose: To evaluate the responses of different optical coherence tomography (OCT) patterns of diabetic macular edema (DME) to intravitreal injection therapy.

Methods: In this retrospective, comparative, and multicenter study, patients who had previously untreated DME, who received intravitreal ranibizumab (IVR) or aflibercept (IVA) and/or steroid treatment with the pro re nata (PRN) treatment regimen after a 3-month loading dose, and had a 12-month follow-up in the MARMASIA Study Group were included. Morphological patterns of DME were divided into four groups based on OCT features diffuse/spongious edema (Group 1), cystoid edema (Group 2), diffuse/spongious edema+subretinal fluid (SRF) (Group 3), and cystoid edema+SRF (Group 4). Changes in central macular thickness (CMT) and best-corrected visual acuity (BCVA) at months 3, 6, and 12, and the number of injections at month 12 were compared between the DME groups.

Results: 455 eyes of 299 patients were included in the study. The mean baseline BCVAs [Logarithm of the Minimum Angle of Resolution (logMAR)] in groups 1, 2, 3, and 4 were 0.54 ± 0.24, 0.52 ± 0.25, 0.55 ± 0.23, and 0.57 ± 0.27, respectively. There was no significant difference between the baseline mean BCVAs between the groups ($p = .35$). The mean BCVAs were significantly improved to 0,47 ± 0,33 in group 1, 0,42 ± 0,33 in group 2, 0,47 ± 0,31 in group 3, and 0,45 ± 0,43 at month 12. There was no significant difference between the groups in terms of BCVA change at month 12 ($p = .71$). The mean baseline CMTs in groups 1, 2, 3, and 4 were 387,19 ± 128,19, 447,02 ± 132,39, 449,12 ± 109,24, and 544,19 ± 178,61, respectively. At baseline, the mean CMT was significantly higher in Group 4 than in the other groups ($p = .000$). The mean CMTs were significantly decreased to 325,16 ± 97,55, 334,94 ± 115,99, 324,33 ± 79,20, and 332,08 ± 150,40 in four groups at month 12 respectively ($p > .05$). The groups had no significant difference in mean CMT at month 12 ($p = .835$). The change in CMT was significantly higher in Group 4 than in the other groups at month 12 ($p = .000$). The mean number of intravitreal anti-VEGF injections at month 12 was 4.51 ± 1.57 in Group 1, 4.63 ± 1.54 in Group 2, 4.88 ± 1.38 in Group 3, and 5.07 ± 1.49 in Group 4. The mean number of anti-VEGF injections in Group 1 and Group 2 was significantly lower than in Group 4 ($p = 0,014$ and $p = 0,017$).

Conclusions: In real life, there was no significant difference between the DME groups in terms of visual improvement at month 12. However, better anatomical improvement was achieved in Group 4 than in the other DME groups.

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Anti-VEGF; diabetic macular edema patterns; Optical coherence tomography

INTRODUCTION

Diabetic macular edema is one of the leading causes of vision loss worldwide.[1] Complex and multifactorial mechanisms are responsible for forming the DME. The main changes are the thickening of the capillary basement membrane, loss of pericytes and endothelial cells, leukocyte dysfunction, increase of vascular endothelial growth factor (VEGF), and inflammatory cytokines released from the ischemic retina.[2] Afterward, capillary permeability increases, and DME forms.

Identifying patients with DME and treatment of DME is necessary to prevent vision loss or improve visual acuity. Systemic control of diabetes, hypertension, hyperlipidemia,

CONTACT Utku Limon utku_limon@hotmail.com Ümraniye Education and Research Hospital, Department of Ophthalmology, Health Sciences University Umraniye Training and Research Hospital Eye Clinic, Elmalıkent Mahallesi Adem Yavuz Cad. No:1, Ümraniye, Istanbul 34000, Turkey

nephropathy, and other diseases is of great importance in the treatment of DME.[3] Ocular treatment methods of DME include the use of lasers, injection of drugs (anti-VEGF or steroids), and pars plana vitrectomy (PPV).[4]

Because VEGF is the main cause of DME pathology, intravitreal anti-VEGF agents provide the most effective treatment of DME. The efficacy of intravitreal anti-VEGF drugs in the treatment of DME has been evaluated in various studies.[5–7] Laser treatments for DME have lagged due to their low effectiveness compared to anti-VEGFs. Intravitreal steroids are often used when anti-VEGF therapy either dries out the macula inadequately or frequent injections are prohibited for the patient or to reduce the frequency of injections or in the treatment of DME which have inflammatory biomarkers such as hyperreflective dots and SRF.[8] On the other hand, PPV is often performed in the presence of DME accompanied by an epiretinal membrane, thick posterior hyaloid, and vitreomacular traction.

The Early Treatment Diabetic Retinopathy Study (ETDRS) and the International Council of Ophthalmology (ICO) DME classifications were used for DME treatment for many years. ,[9], [10] Nowadays, optical coherence tomography (OCT) is the most commonly used technique for diagnosing, classifying, evaluating, following up, and determining the treatment response of DME. The OCT classification of patterns of DME was first described by Otani[11] et al. such as diffuse retinal thickening (DRT), cystoid macular edema (CME), and serous retinal detachment (SRD). Later, new DME classifications including the other OCT findings as ellipsoid zone and vitreomacular anomalies of DME were made in different OCT studies such as Arf et al.[12] and Panozzo et al.[13]

In recent years, many real-life studies have been published showing the efficacy of anti-VEGF in DME. However, the responses of different OCT patterns of DME to intravitreal anti-VEGF therapy in the new OCT-based DME classifications in real-life have not been adequately studied. Therefore, in this study, we evaluated the responses of different OCT patterns of DME to intravitreal therapy in a new DME classification in real-life.

MATERIALS AND METHODS

The protocol of the present study conformed to the Declaration of Helsinki. The protocol and design of this study were approved by the Kocaeli University Faculty of Medicine ethics committee. The institutional review board (IRB) approval number was E-80418770-020 -218,478 (14.04.2022). Written informed consent was obtained from all of the study participants.

In this retrospective, comparative, and multicenter (10 ophthalmology centers) study, the medical records of the patients in the MARMASIA Study Group[14] were analyzed between January 2015 and January 2021. Patients who meet the inclusion criteria and completed the follow-up period of 12 months were divided into four groups according to morphological patterns of DME based on OCT: diffuse/spongious edema (Group 1), cystoid edema (Group 2), diffuse/spongious edema+SRF (Group 3), and cystoid edema+SRF (Group 4).

The study group comprised patients who met the following eligibility criteria: 1-) either Type 1 or Type 2 diabetes mellitus 2-) previously untreated DME, 3-) intravitreal ranibizumab (IVR) or aflibercept (IVA) and/or steroid treatment (intravitreal dexamethasone), with PRN treatment regimen after a 3-month loading dose, 4-) baseline CMTof 300 µm or more, 5-) baseline BCVA between 1.3 and 0.2 logMAR.

Exclusion criteria were 1-) other retinal diseases (age-related macular degeneration, retinal vein occlusion, retinal detachment, macular hole, and parafoveal telangiectasia), 2-) another ocular disease such as uveitis, ocular trauma, optic nerve disease, or glaucoma, 3-) pan-retinal laser photocoagulation, and/or focal/grid laser photocoagulation, and/or micropulse laser photocoagulation within 4 months of study enrollment, 4-) intraocular surgery within 1 month of study enrollment (Pars plana vitrectomy, phacoemulsification, and other ocular surgeries), 5-) patients with ischemic maculopathy (FAZ area larger than 600 microns in FFA) 6-) inadequate imaging or clinical data, 7-) history of stroke or myocardial infarction within 6 months, 8-) vitreomacular traction or epiretinal membrane or taut posterior hyaloid, 9-) lost to follow-up.

A detailed medical history, duration of diabetes, age, gender, BCVA, CMT, vitreomacular interface, and DME pattern on OCT, and intraocular pressure (IOP) at baseline, and months 3, 6, and 12 after intravitreal injections, the number of visits and number of injections during 12 months follow up were collected from the patient's medical records in different clinics.

Examinations

At all visits, BCVAs of all patients were measured with Snellen charts from 6 m, anterior segment, and dilated posterior segment examinations were performed with slit-lamp biomicroscopy, and IOP was measured with Goldman applanation tonometry. Spectral-domain–OCT was evaluated by each clinic's experienced physicians. The OCT scans were performed through dilated pupils within a 6 × 6 mm macular area. OCT measurements were calculated using device-generated software and repeated at all visits. [(Optovue, RTVue 100, CA, USA), (Spectralis OCT, Heidelberg Engineering, Heidelberg, Germany), (Spectral OCT-SLO, Optos, Scotland), (OCT Triton, Topcon,), (Cirrus HD-OCT system; Carl Zeiss Meditec, Inc., Dublin, Calif., USA] Fundus fluorescein angiography imaging was performed at baseline and repeated according to the physicians' opinion.

Classification of DME Using OCT

DME was classified into four types according to Panozzo et al.[13] studies and Euretina DME treatment guidelines.[15] (Figure 1). The diffuse/spongious edema type was defined as sponge-like retinal swelling of the macula with reduced intraretinal reflectivity. The cystoid edema type was defined as low-reflective intraretinal cystoid spaces with highly reflective septa that separate cystoid-like cavities in the macular area. The diffuse/spongious edema with SRF type was defined as diffuse/spongious edema accompanied

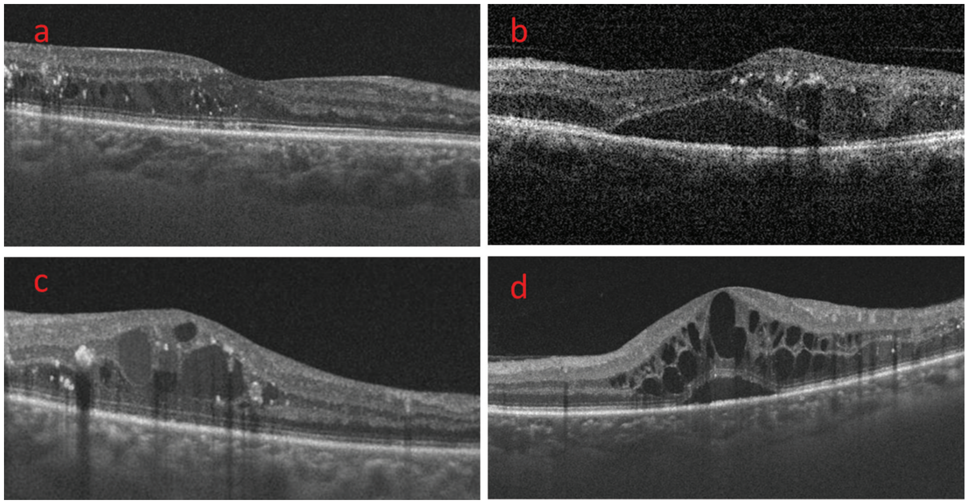

Figure 1. Different diabetic macular edema types on OCT.

by an optically clear space between the retina and retinal pigment epithelium. The cystoid edema with SRF type was defined as cystoid edema accompanied by an optically clear space between the retina and retinal pigment epithelium. If diffuse/spongious edema and cystoid edema coexisted, the predominant pattern in the OCT image was selected.

Intravitreal Anti-VEGF Injections

Intravitreal injections [0.5 mg/0.05 mL IVR (Lucentis; Novartis, Basel, Switzerland) or 2 mg/0.05 mL IVA (Eylea; Bayer, Berlin, Germany)] were done either in the operating room or injection rooms under topical anesthesia with proparacaine. The lids were sterilized with 10% povidone-iodine, and conjunctival sterilization was achieved with 5% povidone-iodine drops. After marking the superotemporal or inferotemporal quadrant (3–3.5 mm for pseudophakic and 3.5–4.0 mm for phakic patients away from the limbus) intravitreal injections were done with a 27 or 30-gauge needle.

Initially, the patients received a loading dose of three consecutive monthly ranibizumab or aflibercept injections and then continued with the PRN protocol.

Re-Treatment Criteria for Anti-VEGF Injections

The presence of new or persistent DME, intraretinal or subretinal fluid on OCT, and visual acuity loss of one or more lines at monthly visits.

Intravitreal Steroid Injections

When the presence of new or persistent DME, intraretinal or subretinal fluid on OCT, and visual acuity loss of one or more lines at monthly visits after three loading anti-VEGF doses, one dose of intravitreal 0.7 mg dexamethasone (Ozurdex, Allergan, Irvine, CA, USA) was added to the treatment at the physicians' discretion.

Laser Treatments

Pan-retinal photocoagulation (PRP) was applied to the patients who developed proliferative diabetic retinopathy during the follow-up. Focal/Grid laser photocoagulation was applied to all patients with clinically significant macular edema at month 6 and later.

Outcome Measurements

The primary outcome measures of this study were changes in CMT and BCVA at months 3, 6, and 12, and the number of visits and injections at month 12 in DME types.

Statistical Methods

Snellen BCVA values were converted to logMAR for statistical analysis. IBM SPSS Statistics 26 (IBM SPSS, Turkey) program was used for statistical analysis. The conformity of the parameters to the normal distribution was evaluated with the Shapiro-Wilks test. The normal distribution was evaluated by looking at the kurtosis values and skewness in the data that were unsuitable for the normality test. Independent sample t-test was used for comparisons between two groups, and one-way ANOVA test was used for comparison of more than two groups. Before the ANOVA test, the homogeneity of variances was tested and Welch's ANOVA test was used when necessary. Analysis of variance in repeated measures was used to evaluate the change in repeated measures and the variables affecting the change. Bonferroni correction was used to compare subgroups in the analysis of variance. Significance was evaluated at the $p < .05$ level.

RESULTS

A total of 455 eyes of 299 patients that met the eligibility criteria were included in the analysis. Of the eyes included in the study, 235 (51.6%) were female and 220 (48.4) were male. The mean age of all patients included in the study was 62.39 ± 8.99 years. Intravitreal aflibercept was applied to 131 (28.7%)

eyes and intravitreal ranibizumab was applied to 324 (71.3%) eyes. Intravitreal dexamethasone was applied to 110 (24.17%) eyes. Among the eyes divided into four groups, there were 81 (17.8%) eyes in the diffuse/spongious edema group (Group 1), 218 (47.9%) eyes in the cystoid edema group (Group 2), 49 (10.7%) eyes in the diffuse/spongious edema+SRF group (Group 3), and 107 (23.6%) eyes in the cystoid edema +SRF group (Group 4). The baseline demographics of each diabetic macular edema treatment group and all study patients are summarized in Table 1.

The mean baseline BCVAs of all patients was 0,54 ± 0,25, and the values at 3, 6, and 12 months after treatment were 0,42 ± 0,31, 0,42 ± 0,31, and 0,44 ± 0,35, respectively, which indicated a significant improvement over the baseline values ($p < .05$, for all time points). The mean baseline BCVAs in groups 1, 2, 3, and 4 were 0.54 ± 0.24, 0.52 ± 0.25, 0.55 ± 0.23, and 0.57 ± 0.27, respectively. There was no significant difference between the baseline mean BCVAs between the groups ($p = .35$). The mean BCVAs were significantly improved to 0,47 ± 0,33 in group 1, 0,42 ± 0,33 in group 2, 0,47 ± 0,31 in group 3, and 0,45 ± 0,43 at month 12 (respectively $p = .04$, $p = .000$, $p = .016$, $p = .026$). When the mean BCVA was compared between each type during the 12-month treatment period, there was no significant difference in mean BCVA at months 3 and 12 between the groups (respectively $p = .49$ and $p = .71$). There was a significant difference in mean BCVA between the diffuse/spongious (Group 1) and cystoid DME (Group 2) groups at month 6 ($p = .01$). The mean BCVA changes in groups showed in Figure 2 and Table 2.

The mean CMT of all patients showed significant improvement from 459,45 ± 150,64 at the baseline to 359,95 ± 106,41, 346,03 ± 117,81, and 331,38 ± 118,62 at 3, 6, and 12 months after treatment, respectively ($p < .05$, for all time points). The mean baseline CMTs in groups 1, 2, 3, and 4 were 387,19 ± 128,19, 447,02 ± 132,39, 449,12 ± 109,24, and 544,19 ± 178,61, respectively. At baseline, the mean CMT was significantly higher in Group 4 than in the other groups ($p = .000$). The mean CMTs were significantly decreased to 325,16 ± 97,55 in group 1, 334,94 ± 115,99 in group 2, 324,33 ± 79,20 in group 3, and 332,08 ± 150,40 in group 4 at month 12 ($p > .05$). When the mean CMT was compared between the DME types, there was a significant difference between the diffuse/spongious

Table 1. The baseline demographics of each diabetic macular edema treatment group and all study patients.

	Diffuse/spongious edema (*n* = 81)	Cystoid edema (*n* = 218)	Diffuse/spongious edema+SRF (*n* = 49)	Cystoid edema +SRF (*n* = 107)	All patients (*n* = 455)	p-value
Age	64,00 ± 7,45	62,77 ± 8,63	62,47 ± 10,18	60,36 ± 9,90	62,39 ± 8,99	0,43
Gender						0,69
Female	44	111	22	58	235	
Male	37	107	27	49	220	
Duration of DM	15,17 ± 5,92	15,39 ± 6,64	16,00 ± 6,39	15,31 ± 7,14	15,40 ± 6,60	0,91
DM Treatment	45	105	24	53	227	0,53
OAD	36	113	25	54	228	0,47
Insulin	51	107	27	55	240	
Accompanying disorders	10	28	7	14	59	
HT	1	2	0	1	4	
CAD	2	5	2	3	12	
CVA						
CKD						
Baseline BCVA	0,54 ± 0,24	0,52 ± 0,25	0,55 ± 0,23	0,57 ± 0,27	0,54 ± 0,25	0,35
Baseline CMT	387,19 ± 128,19	447,02 ± 132,39	449,12 ± 109,24	544,19 ± 178,61	459,45 ± 150,64	*0,000*

SRF: Subretinal fluid, DM: Diabetes mellitus, BCVA: Best corrected visual acuity, CMT: Central macular thickness, OAD: Oral antidiabetic, HT: Hypertension, CAD: Coronary artery disease, CKD: Chronic kidney disease, CVA: Cerebrovascular accident.
p <0,05.
One-way Anova test.

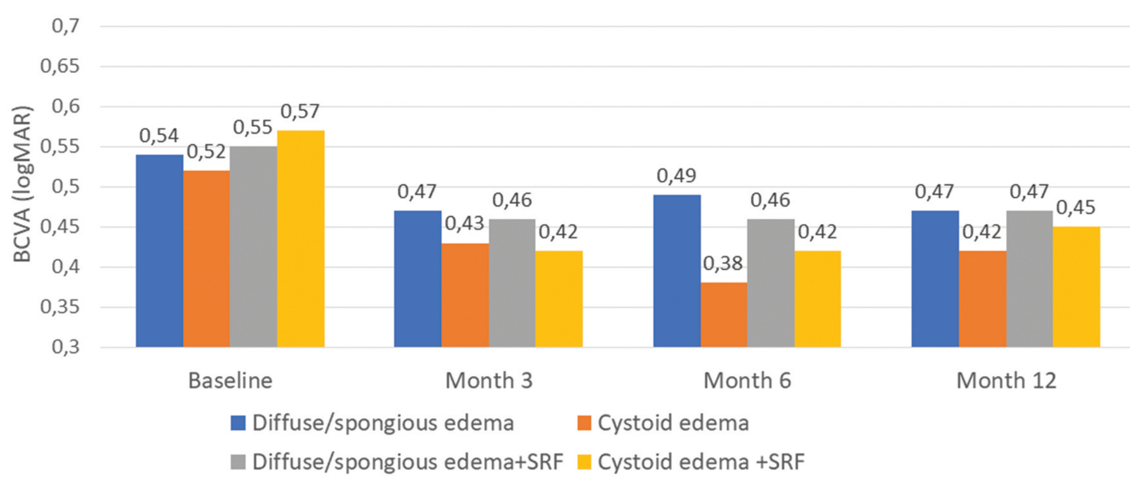

Figure 2. The mean best corrected visual acuity changes over time after intravitreal therapy between the diabetic macular edema types.

Table.2. The mean best corrected visual acuity (BCVA) and central macular thickness (CMT) changes over time after intravitreal therapy.

	Diffuse/spongious edema (*n* = 81)	Cystoid edema (*n* = 218)	Diffuse/spongious edema+SRF (*n* = 49)	Cystoid edema +SRF (*n* = 107)	All patients (*n* = 455)	p-value
BCVA						
Baseline	0,54 ± 0,24	0,52 ± 0,25	0,55 ± 0,23	0,57 ± 0,27	0,54 ± 0,25	0,35
Month 3	0,47 ± 0,33	0,43 ± 0,29	0,46 ± 0,25	0,42 ± 0,27	0,42 ± 0,31	0,49
Month 6	0,49 ± 0,42	0,38 ± 0,28	0,46 ± 0,25	0,42 ± 0,27	0,42 ± 0,31	*0,04*
Year 1	0,47 ± 0,33	0,42 ± 0,33	0,47 ± 0,31	0,45 ± 0,43	0,44 ± 0,35	0,71
CMT						
Baseline	387,19 ± 128,19	447,02 ± 132,39	449,12 ± 109,24	544,19 ± 178,61	459,45 ± 150,64	*0,000*
Month 3	331,69 ± 94,19	357,24 ± 101,32	364,92 ± 112,77	384,59 ± 117,36	359,95 ± 106,41	*0,009*
Month 6	350,35 ± 129,01	326,07 ± 89,11	340,51 ± 87,77	385,96 ± 157,11	346,03 ± 117,81	*0,003*
Year 1	325,16 ± 97,55	334,94 ± 115,99	324,33 ± 79,20	332,08 ± 150,40	331,38 ± 118,62	0,835

SRF: Subretinal fluid, BCVA: Best corrected visual acuity, CMT: Central macular thickness.
p <0,05.
One-way Anova test.

Table 3. The number of intravitreal injections, and the number of visits during 12-month follow-up.

	Diffuse/spongious edema (*n* = 81)	Cystoid edema (*n* = 218)	Diffuse/spongious edema+SRF (*n* = 49)	Cystoid edema +SRF (*n* = 107)	All patients (*n* = 455)	p-value
Number of visits	8,47 ± 2,30	8,19 ± 2,63	7,49 ± 2,01	7,96 ± 2,36	8,11 ± 2,46	0,07
Total number of anti-VEGF injections						
Month 6	3,21 ± 1,17	3,24 ± 0,99	3,37 ± 0,83	3,43 ± 0,98	3,30 ± 1,01	0,36
Year 1	4,51 ± 1,57	4,63 ± 1,54	4,88 ± 1,38	5,07 ± 1,49	4,74 ± 1,53	0,04
Total number of steroid injections						
Year 1	0,21 ± 0,56	0,20 ± 0,44	0,27 ± 0,53	0,36 ± 0,59	0,25 ± 0,51	*0,03*

SRF: Subretinal fluid, DM: Diabetes mellitus, BCVA: Best corrected visual acuity, CMT: Central macular thickness.
p <0,05.
One-way Anova test.

(Group-1) and cystoid DME (Group-2) groups at month 3 ($p = 0,049$). There was a significant difference between the diffuse/spongious+SRF (Group 3) and cystoid+SRF DME (Group 4) groups at month 6 ($p = 0,022$). The groups had no significant difference in mean CMT at month 12 ($p = .835$). The change in mean CMT was significantly higher in Group 4 than in the other groups at month 12 ($p = .000$). The mean CMT changes in groups are shown in Figure 3 and Table 2.

The steroid use was included in the measurement as a covariate and its effect on the treatment process of the patients was evaluated (With Variance Analysis in Repeated Measurements). No significant effect of steroid use was detected in terms of visual acuity change in the 1-year follow-up of the patients. p:0.000 (F:32.68) A significant effect of steroid use was detected in terms of central macular thickness change in the 1-year follow-up of the patients in the cystoid edema+SRF group than the other groups p:0.000 (F:21.79).

The mean number of visits of all study patients was 8,11 ± 2,46 at month 12. The mean number of visits in groups 1, 2, 3, and 4 were 8,47 ± 2,30, 8,19 ± 2,63, 7,49 ± 2,01, and 7,96 ± 2,36, respectively. There was no significant difference between the groups in the mean number of visits at month 12 ($p = .07$).

The mean number of intravitreal anti-VEGF injections at the 12-month follow-up was 4.51 ± 1.57 in Group 1, 4.63 ± 1.54 in Group 2, 4.88 ± 1.38 in Group 3, and 5.07 ± 1.49 in Group 4, respectively. The number of anti-VEGF injections in

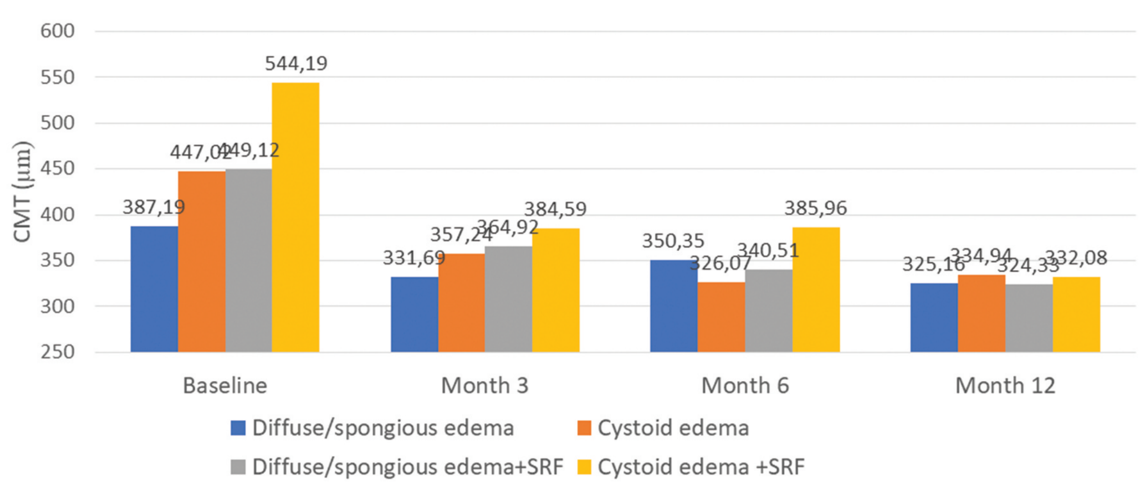

Figure 3. The mean central macular thickness changes over time after intravitreal therapy between the diabetic macular edema types.

Group 1 and Group 2 was significantly lower than in Group 4 ($p = 0,014$ and $p = 0,017$). The mean number of intravitreal steroid (dexamethasone) injections at the 12-month follow-up was 0,21 ± 0,56, 0,20 ± 0,44, 0,27 ± 0,53 and 0,36 ± 0,59 in 4 groups respectively ($p > .05$) Table 3.

No serious ocular complications such as endophthalmitis and retinal detachment and no serious systemic complications, such as cerebrovascular accidents and myocardial infarctions, related to intravitreal injections occurred during the study period.

DISCUSSION

The pathophysiology of each type of DME is different. Diffuse/spongious DME occurs as a result of intracytoplasmic swelling of Müller cells after impaired fluid absorption of Müller cells secondary to increased vascular permeability and leakage after the breakdown of the blood-retinal barrier. VEGF plays an important role in the formation of diffuse/spongious types of edema by causing the breakdown of the inner blood-retinal barrier.[16] In cystoid, DME, prolonged edema and inflammatory factors develop liquefaction necrosis in Müller cells. Thus, cystoid cavities are formed that cause cystoid macular edema. SRF is the accumulation of fluid into the subfoveal area secondary to the damaged external limiting membrane (ELM), ELM dysfunction, retinal pigment epithelium (RPE) impairment, and increased oncotic pressure.[17] ELM barrier dysfunction (causes transient fluid migration from the cystoid spaces in the retina to the subretinal space) and RPE pump dysfunction might lead to fluid accumulation in the subretinal space forming a SRD.[18] Each of these edema types may accompany the other. To the best of our knowledge, the intravitreal therapy response to different types of DME in a new OCT classification in a large patient group in real life has not been adequately studied.

In the present study, DME was classified into four different OCT patterns, which were compared in terms of changes in BCVA and CMT after intravitreal injections of ranibizumab or aflibercept, and/or dexamethasone. In this study, we did not consider SRF as a morphological pattern of DME. We classified it as a comorbid finding in the early stage of DME as in the Arf et al.[12] study. Cystoid type ($n = 218$) and cystoid+SRF type ($n = 107$) were the most common OCT patterns, whereas diffuse/spongious type ($n = 81$) and diffuse/spongious+SRF types ($n = 49$) were the least common patterns in our study. In contrast to our study, Kim et al.[19] evaluated 276 OCT scans of 164 eyes of 119 patients and reported that DRT was the most common pattern. Roh et al.[20] examined 56 eyes of 43 DME patients and they reported that 28 (50%) eyes of 21 patients showed diffuse retinal swelling, and 28 (50%) eyes of 22 patients showed cystoid edema. Cystoid type appears to be the latest form of DME. However, the diffuse/spongious type appears to be the earliest form of DME and responds better than other types. The higher incidence of cystoid edema type in our patients may be related to the later admission of our patients for treatment.

Our findings demonstrate that visual and anatomical improvements were maintained in all four types of DME during the first year of intravitreal administration. However, better anatomical improvement was achieved in the cystoid edema+SRF group than in the other DME groups. This may be due to the cystoid+SRF type having a significantly higher baseline CMT (544,19 µm) and the mean number of anti-VEGF and steroid injections was more than the other types in the cystoid+SRF type (5,07 anti-VEGF and 0,36 steroid injections) in 12 months follow-up. Similar to our study Wu et al.[21] reported a greater reduction in CMT in patients with CME after intravitreal bevacizumab injection. Shimura et al.[22] reported that the DRT type has a better response to anti-VEGF treatment than the CME and SRD types. Some of the other studies have confirmed the same results as the Shimura et al. study.[23,24] However, a small number of studies have reported that SRD is good for visual prognosis.[25]

Most of the studies related to DME types used the Otani[11] classification and DME was classified into three groups DRT, CME, and SRD. However, SRD often accompanies both diffuse/spongious DME and cystoid DME. Differences in DME classifications may be the cause of different responses to intravitreal treatment in some eyes than others. Therefore, the classification of SRD within these DME groups will be correct in evaluating the treatment responses given by DME groups.

In cystoid+SRF type with chronicity of the edema cystoid spaces increase, SRF occurs, and CMT increases in accordance with the pathophysiology of macular edema. More intravitreal anti-VEGF injections are needed for the treatment of this type of DME. At the same time, the accumulation of SRF does not respond well to anti-VEGF therapy because of the different pathophysiological mechanisms mentioned above. Therefore, this group may have needed more steroid injections. Ozsaygili et al.[26] compared the efficacy and safety of intravitreal dexamethasone and aflibercept in patients with DME with SRD. They reported better anatomical reports with dexamethasone implants. In our study, statistically significant steroid injections were done in cystoid+SRD and diffuse/spongious+SRD DME groups than in cystoid and diffuse/spongious DME groups.

On the other hand, in this real-life study, our favorable results indicate that, in the diffuse/spongious type, anatomical and visual improvement was achieved with fewer intravitreal anti-VEGF and steroid injections (4.51 anti-VEGF and 0.21 steroids) than in the other types. This is because the baseline CMT of this group was significantly lower than the other groups (387,19 µm) in accordance with the pathophysiology of macular edema. In contrast to our study, Kim et al[27] reported that there was no significant difference between the three morphologic types of DME ($p = .914$) in the mean number of injections during the 12-month follow-up. (3.67 in the DRT group, 3.97 in the CME group, and 3.79 in the SRD group).

In this study, our results suggest that although CMTs at baseline and month 12, and intravitreal injection numbers at month 12 were different between DME types, BCVAs at baseline and month 12 were similar. In our study, the similarity of BCVAs at baseline and 12 months between DME types may be related to the fact that it is based on real-life data.

The limitations of our study are that it has a retrospective design, and the number of patients is relatively small in each type. However, we evaluated subgroups of treatment-naïve

DME patients. Our findings should be supported by randomized prospective trials with larger sample sizes.

In conclusion, in real life, Cystoid type ($n = 218$) DME was the most common OCT pattern. This may be related to the fact that diabetic patients do not seek examination and treatment early. SRF is not a separate DME type. According to the pathogenesis of DME, SRF develops in advanced DME. All types of DME respond well to anti-VEGF and steroid therapy at the clinician's discretion in real life. There was no significant difference between the DME groups in terms of visual improvement at month 12. Better anatomical improvement was achieved in the cystoid edema+SRF group. However, cystoid edema+SRF DME type requires more anti-VEGF and steroid treatment. The reason for this is that DME becomes chronic and SRF accompanies this type of DME. Therefore, determining the morphological patterns of DME on OCT can predict treatment response and visual outcome when formulating a treatment plan for patients with DME.

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ORCID

Utku Limon http://orcid.org/0000-0002-4998-1896
Fatih Bilgehan Kaplan http://orcid.org/0000-0001-7580-5514
Işılay Saygın http://orcid.org/0000-0003-0101-1900
Ecem Önder Tokuç http://orcid.org/0000-0002-6260-6716
Işıl Kutlutürk Karagöz http://orcid.org/0000-0001-7367-2906
Hatice Selen Kanar http://orcid.org/0000-0001-6505-9714
Mehmet Orkun Sevik http://orcid.org/0000-0001-7130-4798
Uğur Yayla http://orcid.org/0000-0002-0073-4747
Erkan Çelik http://orcid.org/0000-0002-8681-7868
Ayşe Sönmez http://orcid.org/0000-0003-0523-5979
Aslan Aykut http://orcid.org/0000-0001-5426-1992
Esra Kumral Türkseven http://orcid.org/0000-0001-6285-6566
Nimet Yeşim Erçalık http://orcid.org/0000-0002-8730-2495
Özlem Oncu Aydın http://orcid.org/0000-0001-7299-9528
Erdinç Bozkurt http://orcid.org/0000-0002-5570-799X
Tuğba Aydoğan http://orcid.org/0000-0002-2624-7496
Ece Başaran Emengen http://orcid.org/0000-0003-4894-7116
Abdullah Özkaya http://orcid.org/0000-0002-1940-8669
Banu Açıkalın Öncel http://orcid.org/0000-0002-6791-2915
Nursal Melda Yenerel http://orcid.org/0000-0001-9940-8599
Özlem Şahin http://orcid.org/0000-0003-2907-2852
Levent Karabaş http://orcid.org/0000-0001-7860-4603

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