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ORIGINAL RESEARCH

Characteristics of diabetic macular edema on optical coherence tomography may change over time or after treatment

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Purpose: To investigate optical coherence tomography (OCT) characteristics in diabetic macular edema (DME) over time and after treatment.

Patients and methods: OCT morphological features in DME eyes treated with ranibizumab with at least 1 year of follow-up were retrospectively analyzed.

Results: Thirty-five eyes were included. From baseline to Month 12, mean visual gain was 7.2±13.6 letters and mean central retinal thickness reduction was 61.9±121.8 µm. Fovea-involving ellipsoid zone (EZ) disruption was significantly associated with final vision of <70 letters. Subretinal fluid at baseline was present only in eyes naïve to previous intravitreal pharmacotherapy and was related to better visual gain and fewer injections. Treatment-naïve eyes had shorter DME duration and less EZ damage.

Conclusion: DME characteristics on OCT may change over time or after treatment. Subretinal fluid may be associated with earlier change and less EZ damage in DME.

Keywords: diabetic macular edema, optical coherence tomography, OCT, subretinal fluid, SRF, vascular endothelial growth factor, VEGF

Introduction

Since the introduction of optical coherence tomography (OCT), it has become the most frequently used tool in the diagnosis and monitoring of many retinal diseases, including diabetic macular edema (DME). Although central retinal thickness (CRT) has been used to guide DME treatment and has served as the secondary efficacy endpoint in the majority of clinical trials related to DME, increasing evidence suggests that the morphological features of OCT are related to treatment course and response.[1–8] Furthermore, OCT biomarkers have been considered to be key identifiers in individualized pro re nata treatment regimens. However, patients recruited in clinical trials are typically treatment naïve; therefore, the findings are not fully applicable to real-world clinical practice. The purpose of this study was to investigate whether the characteristics of OCT change over time or with treatment in DME in real-world practice.

Patients and methods

A retrospective chart review of adult patients with type 2 diabetes mellitus and DME treated with ranibizumab according to the reimbursement policy of the Taiwan National Health Insurance in a single medical center from February 1, 2013 to December 31, 2014 was conducted. The reimbursement criteria were baseline best-corrected visual acuity of 3/60 to 6/12, presence of center-involved DME, CRT ≥300 µm on OCT

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and HbA1c ≦10%. The institutional review board and ethics committee of Kaohsiung Veterans General Hospital approved this study, which adhered to the tenets of the Declaration of Helsinki. Since this research was retrospective, using already existing information, patient's informed consent was not needed. All the patients were recorded with a number code without leakage of any personal information. Eyes with previous vitrectomy were excluded due to possible different drug bioavailability. Patients with <1 year of follow-up data were excluded. Of note, due to the required three-step reimbursement application with limit of maximum eight injections per eye for ranibizumab, patients were treated mostly on a pro re nata basis, leading to loss of follow-up in many patients who did not obtain the second approval. Data related to demographic characteristics, medical history, date of DME diagnosis, comorbidities, initial and final visual acuity (VA), slit-lamp biomicroscopy, intraocular pressure, fundus photography, fundus fluorescein angiography, CRT and optical characteristics according to OCT, and treatment were analyzed. Morphological features of OCT were identified as cystoid macular edema (CME), diffuse retinal thickening (DRT), subretinal fluid (SRF) and presence of epiretinal membrane involving the fovea. Ellipsoid zone (EZ) integrity was scored in a 3 mm scan into four grades (0–3), with "0" representing intact EZ, "1" representing partial disruption with weak reflectivity band, "2" representing loss at fovea but present elsewhere in the scan and "3" representing severe disruption with loss of signal along the entire scan.

Statistical analysis was performed using SPSS Version 12.0 (SPSS Inc., Chicago, IL, USA). Snellen VA measurements were converted to approximate Early Treatment Diabetic Retinopathy Study letter scores for statistical manipulations according to the methods described previously.[9] Descriptive statistics are expressed as mean with SD. Paired *t*-test was performed to evaluate the mean changes from baseline to endpoints. If a variable was not with a normal distribution, the Wilcoxon signed-rank test was adopted to compare the variable between two groups. A *P*-value of <0.05 was considered statistically significant. To understand the substantive clinical significance, effect size value (*d*) was calculated according to the methods described previously.[10] The denominator standardized the difference by transforming the absolute difference into SD units. The effect size was classified as small ($0.2 \leqq d < 0.5$), medium ($0.5 \leqq d < 0.8$) and large ($d \geq 0.8$).

Results

A total of 35 eyes of 26 patients, including 6 women and 20 men, were included. Mean age was 60.62±7.28 years. Mean duration of DME was 22.11±23.71 months (range, 1–121). Nine eyes had history of DME-related anti-vascular endothelial growth factor (anti-VEGF) treatment. The interval from previous treatment was at least 3 months. Due to the reimbursement limitations, most patients were undertreated with a mean number of 4.43±2.05 injections over 12 months (range, 1–11). VA improved from 48.34±16.97 letters to 55.51±14.81 letters with a mean gain of 7.2±13.6 letters from baseline at Month 12. CRT was reduced from 399.83±97.35 to 337.89±130.5 μm with a mean reduction of 61.9±121.8 μm from baseline to Month 12.

More eyes with lower baseline VA had significant visual gain at Week 12 (Table 1). More eyes with higher baseline VA had final vision of ≥70 letters, though it was not significant

Table 1 Factors related to visual response at Week 12

Factor	Visual gain at Week 12 <5 letters	Adjusted *P*-value	Visual gain at Week 12 5–9 letters	Adjusted *P*-value	Visual gain at Week 12 ≧10 letters	*P*-value
	n=16		n=4		n=15	
Age	62.00±7.69	0.062	57.25±6.85	0.988	58.33±5.79	0.250[a]
Gender						
Male	12 (42.9%)	0.287	4 (14.3%)	0.985	12 (42.9%)	0.535[b]
Female	4 (57.1%)		0 (0.0%)		3 (42.9%)	
Baseline HbA1c (%)	7.15±1.63	0.499	7.68±1.10	0.987	7.33±1.08	0.781[a]
Baseline BCVA (letter)	53.63±15.25	0.109	61.75±13.87	0.946	39.13±15.97	0.012[a]
Baseline CRT (μm)	377.06±97.66	0.207	424.75±82.78	0.978	417.47±104.41	0.466[a]
Baseline volume (mm^3)	8.63±1.47	0.450	9.58±1.20	0.970	9.28±1.80	0.410[a]
Previous PRP	9 (56.2%)	0.609	2 (12.5%)	0.994	5 (31.2%)	0.433[b]
Previous anti-VEGF treatment	5 (55.6%)	0.202	1 (11.1%)	–	3 (33.3%)	0.773[b]
No of injections/12 months	5.06±2.54	0.289	4.50±1.92	0.987	3.73±1.34	0.208[a]
Duration of DME (month)	5.06±2.54	0.623	4.50±1.92	0.991	3.73±1.34	0.631[a]

Notes: [a]ANOVA test; [b]chi-squared test.

Abbreviations: ANOVA, analysis of variance; anti-VEGF, anti-vascular endothelial growth factor; BCVA, best-corrected visual acuity; CRT, central retinal thickness; DME, diabetic macular edema; PRP, pan retinal photocoagulation.

Table 2 Factors related to visual response at Month 12

Factor	Visual gain at 12 months <10 letters	Visual gain at 12 months ≧10 letters	Adjusted *P*-value	Final VA <70 letters	Final VA ≧70 letters	Adjusted *P*-value
	n=21	n=14		n=27	n=8	
Age	61.05±6.96	58.14±6.75	0.770	60.56±6.63	57.63±7.89	0.153
Gender						
Male	17 (60.7%)	11 (39.3%)	0.256	22 (78.6%)	6 (21.4%)	0.538
Female	4 (57.1%)	3 (42.9%)		5 (71.4%)	2 (28.6%)	
Baseline HbA1c (%)	7.35±1.56	7.19±0.95	0.815	7.45±1.42	6.73±0.86	0.255
Baseline BCVA (letter)	51.62±15.66	43.43±18.83	0.350	44.85±16.66	60.13±14.22	0.063
Baseline CRT (μm)	391.38±98.45	412.50±101.56	0.979	403.33±105.97	388.00±73.86	0.982
Baseline volume (mm^3)	8.74±1.33	9.43±1.91	0.345	9.01±1.70	9.03±1.29	0.319
Previous PRP	11 (68.8%)	5 (31.2%)	0.979	13 (81.2%)	3 (18.8%)	0.995
Previous treatments	7 (77.8%)	2 (22.2%)	0.155	9 (100.0%)	0 (0.0%)	0.999
No of injections/12 months	4.81±2.50	3.86±1.03	0.614	4.63±2.26	3.75±0.89	0.574
Duration of DME (months)	18.71±19.11	27.21±30.08	0.110	21.33±18.13	24.75±39.75	0.119

Abbreviations: BCVA, best-corrected visual acuity; CRT, central retinal thickness; DME, diabetic macular edema; PRP, pan retinal photocoagulation; VA, visual acuity.

(Table 2). None of the previously treated eyes had final vision of ≧70 letters. Patients with better response seemed to have fewer injections over 1 year, though the difference was not significant (Table 2).

Of the different morphological features of OCT at baseline, none were significantly associated with visual gain of <10 letters or final vision of <70 letters at Month 12, with the exception of EZ disruption score >1 (fovea involved). Fovea-involving EZ disruption was significantly associated with final visual outcome of <70 letters at Month 12 (Table 3). Compared to previously treated eyes, treatment-naïve eyes had shorter duration of DME and fewer had fovea-involving EZ disruption (Table 4). At baseline, SRF was present only in treatment-naïve eyes (Table 4). In eyes previously treated with panretinal photocoagulation, the proportion of eyes with SRF was similar to that of eyes with no previous treatment. In eyes with SRF at baseline, SRF disappeared rapidly after intravitreal ranibizumab treatment and recurred after a period of treatment discontinuation. The recurrence of SRF occurred mostly in treatment-naïve eyes. In one eye that was previously treated with intravitreal injection and macular and panretinal photocoagulation, SRF was not present at baseline but appeared during follow-up (Table 5). Compared to eyes without SRF, eyes with SRF at baseline were significantly more likely to be treatment naïve and have a shorter duration of DME. Although there was no statistically significant difference in visual gain at Week 12 or Month 12 or in the number of injections over 1 year between eyes with or without SRF at baseline, the

Table 3 Baseline OCT characteristics and visual outcome at Month 12

Factor	Visual gain at 12 months <10 letters	*P*-value	Final VA <70 letters	*P*-value
	n=21		n=27	
OCT pattern				
DRT	18 (60.0%)	1.000	23 (76.7%)	1.000
SRF	5 (62.5%)	1.000	6 (75.0%)	1.000
CME	12 (57.1%)	0.737	16 (76.2%)	1.000
DRT+SRF	5 (62.5%)	1.000	6 (75.0%)	1.000
CME+SRF	1 (50.0%)	1.000	1 (50.0%)	0.410
DRT+CME+SRF	1 (50.0%)	1.000	1 (50.0%)	0.410
ERM ≧1	2 (66.7%)	1.000	3 (100.0%)	1.000*
EZ >1	7 (50.0%)	0.483	14 (100.0%)	0.012*

Note: *Fisher's exact test.

Abbreviations: CME, cystoid macular edema; DRT, diffuse retinal thickening; ERM, epiretinal membrane; EZ, ellipsoid zone; OCT, optical coherence tomography; SRF, subretinal fluid; VA, visual acuity.

Table 4 Baseline OCT characteristics and duration of DME in naïve vs non-naïve eyes

Factor	Non-naïve	Naïve
	n=9	n=26
OCT pattern		
DRT	5 (55.6%)	25 (96.2%)
SRF	0 (0.0%)	8 (30.8%)
CME	8 (88.9%)	13 (50.0%)
DRT+SRF	0 (0.0%)	8 (30.8%)
CME+SRF	0 (0.0%)	2 (7.7%)
DRT+CME+SRF	0 (0.0%)	2 (7.7%)
ERM ≧1	1 (11.1%)	2 (7.7%)
EZ >1	6 (66.7%)	8 (30.8%)
Duration of DME (months)	32.44±18.48	18.54±25.02

Abbreviations: CME, cystoid macular edema; DME, diabetic macular edema; DRT, diffuse retinal thickening; ERM, epiretinal membrane; EZ, ellipsoid zone; OCT, optical coherence tomography; SRF, subretinal fluid.

Table 5 The distribution of SRF at baseline and follow-up

No	Diagnosis/ previousTx	M0	MI	M2	M3	M4	M5	M6	M7	M8	M9	M10	M11	M12
1	NPDR	*	*	*										
2	NPDR	*	*	*										
3	NPDR	*	*		*		*			*				
4	NPDR	SRF/*	*				SRF		SRF/*		SRF		SRF	
5	NPDR	*	*			*		*					*	
6	NPDR	SRF/*												
7	NPDR	*	*				*							
8	NPDR	*	*	*										
9	NPDR	*		*	*		*							
10	NPDR	*	*	*			*	*	*	*	*	*	*	*
11	NPDR	SRF/*	*	*					*					
12	NPDR	*	*	*			*		*				SRF	
13	NPDR	*	*									*		
14	NPDR/PRP	SRF/*	*	*										*
15	NPDR/PRP	*	*	*				*	*			*	*	*
16	PDR	*	*	*										
17	PDR	*	*		*									
18	PDR	*	*		*		*	*						
19	PDR	*				SRF/*	*							
20	PDR	SRF/*	*		SRF/*			SRF		SRF				
21	PDR	SRF/*	*	*		*	*							
22	PDR	*	*	*			SRF/*		*				SRF/*	
23	PDR	*	*	*				*						
24	PDR/PRP	*			*			*		*	*			
25	PDR/PRP	SRF/*		SRF/*	*	SRF	SRF/*	*	*					
26	PDR/PRP	SRF/*		*	*		*	*						SRF
27	NPDR/*/macular pc/	*	*			SRF	*	*	*		SRF/*			*
28	PDR/*		*	*	*							*		
29	PDR/*	*		*	*				*	*				
30	PDR/*	*	*	*										
31	PDR/*	*	*	*										
32	PDR/*	*		*	*						*	*		
33	PDR/*/macular pc	*	*											
34	PDR/*/macular pc	*	*	*			*	*	*	*	*	*	*	
35	PDR/*/macular pc	*	*	*										

Notes: *IVI with RZB.

Abbreviations: IVI, intravitreal injection; NPDR, nonproliferative diabetic retinopathy; pc, photocoagulation; PDR, proliferative diabetic retinopathy; PRP, pan retinal photocoagulation; SRF, subretinal fluid.

effect size value revealed that eyes with SRF at baseline had higher probability of more visual gain at Week 12 (d=0.69) and Month 12 (d=0.66). Moreover, fewer injections were administered over 12 months in eyes with SRF at baseline compared to those without (d=0.34), as shown in Table 6. Besides, the effect size analysis showed EZ integrity had more impact on the baseline and final vision, but less impact on visual gain (Table 7).

Table 6 Clinical characteristics in eyes with SRF at baseline visit

	SRF (+)	SRF (–)	*P*-value	Effect size value (*d*)
	n=8	n=27		
Visual gain at Week 12 (letter)	13.50±16.57	5.63±9.61	0.234[a]	0.69
Visual gain at month 12 (letter)	16.88±26.48	5.07±14.74	0.261[a]	0.66
Final VA (letter)	54.75±15.73	55.74±15.11	0.877[a]	0.06
EZ ≦1	5 (62.5%)	16 (59.3%)	1.000[b]	–
Naïve patients	8 (100.0%)	18 (66.7%)	0.081[b]	–
Duration of DME (month)	9.13±14.29	25.96±25.19	0.025[a]	0.72
No of injections at month 12	3.88±1.55	4.59±2.21	0.316[a]	0.34

Notes: [a]Independent *t*-test; [b]Fisher's exact test.

Abbreviations: DME, diabetic macular edema; EZ, ellipsoid zone; SRF, subretinal fluid; VA, visual acuity.

Table 7 Clinical characteristics in eyes with EZ integrity at baseline visit

	EZ ≦1 n=21	EZ >1 n=14	*P*-value	Effect size value (*d*)
Baseline VA (letter)	57.52±14.10	34.57±11.35	0.000[a]	1.75
Visual gain at Week 12 (letter)	5.52±12.34	10.29±10.62	0.233[a]	0.41
Visual gain at month 12 (letter)	5.19±21.01	11.64±13.13	0.272[a]	0.35
Final VA (letter)	61.71±13.90	46.21±11.74	0.001[a]	1.18
Naïve patients	6 (42.9%)	3 (14.3%)	0.112[b]	–
Duration of DME (month)	19.29±27.55	26.36±17.70	0.362[a]	0.29
No of injections at month 12	4.67±2.52	4.07±1.14	0.351[a]	0.29

Notes: [a]Independent *t*-test; [b]Fisher's exact test.
Abbreviations: DME, diabetic macular edema; EZ, ellipsoid zone; VA, visual acuity.

Discussion

Study results showed a beneficial effect from ranibizumab in DME eyes with or without previous treatment, as well as in eyes with longer DME duration. Overall, mean VA gain was 7.2±13.6 letters and mean CRT reduction was 61.9±121.8 μm after a mean of 4.43±2.05 injections over 12 months. Presence of fovea-involving EZ disruption was significantly associated with final visual outcome of <70 letters at Month 12. At baseline, SRF was present only in treatment-naïve eyes, which had shorter duration of DME and less fovea-involving EZ damage compared to previously treated eyes. Eyes with SRF at baseline tended to be more likely treatment naïve and have shorter DME duration, more visual gain at Week 12 and Month 12 from baseline, as well as fewer injections over 1 year.

Compared to our previous prospective interventional study conducted at the same hospital, in this study, more patients were undertreated due to resource limitations in real-world practice, resulting in poorer visual outcome.[11] Studies conducted in different regions of the world have similarly reported that DME treatment in real-world settings are less intensive than treatment administered in trial settings.[12,13]

The pathogenesis of DME is complicated and involves not only vascular endothelial growth factor (VEGF) but also inflammatory cytokines and vitreoretinal interface abnormality.[14] Anti-VEGF agents are currently considered as appropriate first-line treatment for center-involved DME; however, certain degrees of macular edema persist even under the treatment protocol of controlled trials.[15] These findings support the hypothesis that in eyes with poor response, underlying mechanisms of pathogenesis other than VEGF may be involved. It is also possible that patients who are anti-VEGF non-responders were included in this study, which may account for the trend of poorer response to treatment in this series.

Accumulation of SRF typically arises from disruption of retinal pigment epithelium tight junctions or its protective function, whereas CME arises from compromised tight junctions in the retinal vasculature and Muller cell disturbances which affect water and potassium channels.[16,17] Although there is currently no consensus, several morphological features of OCT have been identified as possible biomarkers in DME, including SRF, CME, DRT, disorganization of retinal inner layer, status of vitreomacular interface, hyperreflective foci and changes in the integrity of the inner and outer photoreceptor segment border.[18–22] In the RESTORE study, eyes with SRF at baseline had greater visual gain at the end of the first study year than those without SRF at baseline, though there was no significant difference in VA at baseline between groups.[7] The protective role of SRF was further confirmed by a post hoc analysis of the RIDE/RISE studies.[23] Results of a post hoc analysis of the RESTORE/RESTORE-extension studies also showed a trend of positive impact from SRF on response to ranibizumab therapy and a negative impact on response to laser therapy.[24] Furthermore, eyes with SRF were reported to have better visual outcome in a study evaluating the effectiveness of vitrectomy for diffuse DME.[25] In a recent observational cohort study on the functional outcome of DME treated by dexamethasone implant, submacular fluid was predictive of better visual outcome.[26] However, a prospective study including 55 eyes with DME found that disruption of photoreceptor integrity at baseline correlated with poorer visual outcome and occurred more frequently in eyes with serous retinal detachment (SRD). The discrepancy may be due to the definition of SRD used in the study, which included eyes with DRT, CME and SRD together.[27] Our results showed that the absence of fovea-involving EZ disruption predicts better final vision, and that the presence of SRF at baseline predicts more VA gain and fewer injections over 1 year. Moreover, changes in OCT parameters were observed in chronic and previously treated cases.

As expected, previously treated eyes tended to have longer duration of DME and more fovea-involving EZ disruption. Baseline SRF presented only in treatment-naïve eyes in our series. SRF resolved rapidly after anti-VEGF treatment, but reappeared if treatment was discontinued for a period of time. According to these findings, SRF may be an indicator of earlier stage DME that would respond well to intravitreal anti-VEGF therapy. Improved visual gain may also be related to earlier intervention and possibly attributable to some eyes being good responders to anti-VEGF treatment.

This study was limited by the small sample size and lack of adequate treatment in the majority of the cases. Partial treatment as compared with treatment administered in trial settings, however, better reflects real-world conditions of DME treatment.

Conclusion

Our study showed that the characteristics of DME on OCT may change over time or after treatment. Presence of SRF in eyes with DME may indicate earlier change and lesser degree of EZ damage, and thus, may predict better outcome.

Disclosure

The authors report no conflicts of interest in this work.

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