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ORIGINAL ARTICLE

The Responses of Different Types of Diabetic Macular Edema after Three Loading Doses of Anti-vascular Growth Factor: Outcomes in Two Medical Centers

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Background: Diabetic macular edema (DME) is currently treated by anti-vascular endothelial growth factor (anti-VEGF). **Aim:** The aim of this study was to evaluate the effect of intravitreal anti-VEGF in different types of DME classified by optical coherence tomography (OCT). **Methods:** This retrospective study included 161 treatment-naive eyes (116 patients) diagnosed with DME in two tertiary medical centers, which were classified into three groups according to initial OCT finding: diffuse retinal thickening (DRT), cystoid macular edema (CME), and serous retinal detachment (SRD). All eyes received three monthly loading doses of anti-VEGF. Primary and secondary outcomes were the improvement of best-corrected visual acuity (BCVA) and the decrease of central foveal thickness (CFT) on OCT, respectively. **Results:** Among the three groups, there was no significant difference in baseline BCVA ($P = 0.137$); however, the SRD group had the thickest baseline CFT ($P < 0.001$). After three loading doses of anti-VEGF, the BCVA of all three groups improved from baseline (DRT vs. CME vs. SRD, $P = 0.0002$, $P < 0.0001$, and $P < 0.0001$, respectively), while the SRD group seemed to have relatively better improvement among three groups although not significant ($P = 0.051$). The CFTs of all three groups significantly decreased from baseline ($P < 0.0001$ in all three groups). The CFT decreased the most in the SRD group, followed by the CME group, and the least in the DRT group ($P < 0.001$). **Conclusion:** Anti-VEGF therapy improved the anatomical structure and function in all types of DME; SRD responded the best.

Key words: Diabetic macular edema, optical coherence tomography, anti-vascular endothelial growth factor

INTRODUCTION

Globally, diabetic macular edema (DME) is one of the common complications of diabetes mellitus and the major cause of visual impairment in diabetic patients.[1] According to the International Diabetes Federation, the overall number of diabetic patients globally had already reached 425 million in 2017 and will reach 629 million by 2045.[2] Approximately 5.5% of people with diabetes have DME.[3] In 2020, the number of adults worldwide with diabetic retinopathy (DR), vision-threatening DR, and clinically significant DME was estimated to be 103.12 million, 28.54 million, and 18.83 million, respectively; by 2045, the numbers are projected to increase to 160.50 million, 44.82 million, and 28.61 million, respectively.[4]

DR is a disease characterized by the inflammation of retinal microvasculature and the following angiogenesis.[5] Clinical presentation of DR reveals initial retinal hemorrhage, lipid exudates, cotton-wool spots, and eventually the formation of neovascularization. The retinal neurovascular unit refers to the complex functional coupling between neurons, glial cells, and blood vessels. DR occurs after changes in this unit.[6] The breakdown of the blood–retinal barrier (BRB) and the increased retinal capillary permeability caused the formation of DME.[7]

Currently, spectral-domain optical coherence tomography (SD-OCT) is widely used as a standard evaluation of DME

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and an important basis for the tracking and judgment of treatment effects.[8] The different manifestations on the OCT images are also related to the prognosis of the disease itself and the effectiveness of treatment.[9]

The treatment option of DME includes laser therapy and intravitreal injection (IVI) of corticosteroids or anti-vascular endothelial growth factor (anti-VEGF); among which, IVIs of anti-VEGF agents have become the first-line treatment for center-involving DME.[10]

DME can be mainly classified into diffuse retinal thickening (DRT), cystoid macular edema (CME), and serous retinal detachment (SRD) according to OCT images.[11,12] It has been identified that the efficacy of anti-VEGF agents varies among different types of DME patients.[13] In this retrospective study, we evaluated the effect of three monthly loading doses of anti-VEGF on the treatment of DME patients with different OCT types, which was aimed to assess the treatment effect of anti-VEGF in different types of DME, and furthermore, provide a reference for the clinical practice while treating DME patients.

MATERIALS AND METHODS

Ethics approval

The study was conducted in accordance with the Declaration of Helsinki, and approved by the Institutional Review Board of Tri-Service General Hospital (protocol code #A202005165, date of approval:2020/12/08) and Cathay General Hospital (protocol code #P109090, date of approval:2021/02/16). The patient consent was waived by institutional review boards.

Patient selection

The medical records of patients who were over 18 years old and with type 2 diabetes mellitus at two medical centers were retrospectively reviewed from January 2016 to December 2020. Among these patients, treatment-naive eyes with a diagnosis of central-involved DME with a central foveal thickness (CFT) of more than 300 μm measured by OCT and a complete loading treatment course with three monthly IVIs of anti-VEGF agents (either ranibizumab 0.5 mg/0.05 mL or aflibercept 2.0 mg/0.05 mL) were included. Before treatment, hemoglobin A1c (HbA1c) was checked for all patients. Detailed ocular evaluation, including a slit-lamp examination, indirect ophthalmoscopy, color fundus photography, OCT images cross fovea, and best-corrected visual acuity (BCVA) in the logarithm of the minimum angle of resolution (logMAR) units, was performed at baseline. The patients were then followed and treated every 4–5 weeks with routine eye examinations, including logMAR BCVA measurements, fundus examinations with dilated pupils or color fundus photography, and OCTs. Both eyes were included if they matched our inclusion criteria; however, baseline tests were performed independently if the diagnosis of DME was established at different periods. BCVA and CFT on OCT and their change after treatment were subsequently utilized as the primary and secondary outcomes.

Eyes with cloudy media or extreme refractive error affecting fundus observation and other retinal pathology that can cause macular edema or affect visual function were excluded.

Optical coherence tomography classifications

The vertical and horizontal OCT images cross fovea were obtained with an SD-OCT (Zeiss Cirrus 5000-HD-OCT, Carl Zeiss Meditec, Dublin, CA; or RTVue XR, Optovue, Fremont, USA).

DME was classified into three groups according to OCT images based on previous reports.[13-17] The DRT group was defined as a widespread retinal thickening with sponge-like hyporeflective edema of the macula. The CME group was defined as the formation of cystic spaces of fluid accumulation, leading to a focal mound-like area of hyporeflective edema in the foveal area. The SRD group was defined as the fluid accumulation in the subretinal space between the sensory retina and the retinal pigmented epithelium (RPE), leading to an elevated neuroepithelium and a transparent liquid dark area between the neuroepithelium and the RPE. These three retinal fluid accumulations are represented in Figure 1. If both DRT and CME are present, the eye is admitted to the CME group. When DRT or CME or both were concomitant with serous detachment, the eye was admitted to the SRD group.

To corroborate the diagnosis of all OCT characteristics, the two retinal doctors independently inspected the images. If the two specialists disagreed regarding the patient's diagnosis, a third retinal specialist was consulted, and the majority opinion served as the final decision.

Statistical analysis

All statistical analyses were performed with MedCalc softwar, version 19.6.1; (MedCalc Software, Ostend, Belgium; https://www.medcalc.org).

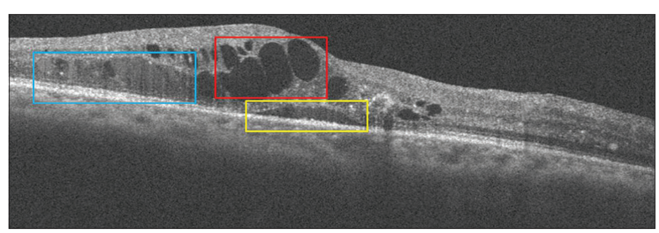

Figure 1: Optical coherence tomography image with the three different clinically defined types of diabetic macular edema: diffuse retinal thickening, blue box; cystoid macular edema, red box; and serous retinal detachment, yellow box

Baseline and posttreatment data, including age, sex, HbA1c value, lens status (phakia or pseudophakia), severity of DR (proliferative or nonproliferative), logMAR BCVA, and CFT, were compared between all groups using either the one-way analysis of variance (continuous variables) or the Chi-square test (categorical variables).

Post hoc analysis with the Student–Newman–Keuls test was used to determine differences between paired groups.

Paired *t*-tests were employed to analyze baseline and posttreatment BCVA and the mean CFT in each subgroup.

$P < 0.05$ was considered statistically significant.

RESULTS

Baseline characteristics

A total of 161 eyes of 116 patients were included in this study.

There were 53 (32.9%) eyes of 46 patients in the DRT group, 62 (38.5%) eyes of 50 patients in the CME group, and 46 (28.6%) eyes of 38 patients in the SRD group. As shown in Table 1, the baseline parameters and measurements of the 161 research eyes were classified. The baseline characteristics were not statistically significant among the three groups, which comprised age ($P = 0.344$), gender ($P = 0.167$), HbA1c level ($P = 0.383$), status of lens (phakia or pseudophakia) ($P = 0.129$), and the stage of DR (nonproliferative or proliferative) ($P = 0.924$).

Baseline best-corrected visual acuity and changes in best-corrected visual acuity treatment

As shown in Table 2, there was no significant difference in baseline BCVA among the three groups (DRT vs. CME vs. SRD, 0.66 ± 0.355 vs. 0.65 ± 0.307 vs. 0.77 ± 0.385; $P = 0.137$), although the SRD group seemed to have slight worse baseline BCVA than the other two groups.

After three monthly loading doses of anti-VEGF, three groups had similar BCVA (logMAR BCVA after three IVIs, DRT vs. CME vs. SRD, 0.55 ± 0.381 vs. 0.49 ± 0.294 vs. 0.54 ± 0.330; $P = 0.0493$), while the SRD group seemed to have more BCVA improvement among three groups although not significant (logMAR BCVA change, DRT vs. CME vs. SRD, −0.11 ± 0.201 vs. −0.16 ± 0.260 vs. −0.23 ± 0.267; $P = 0.051$). Comparing the BCVA between baseline and posttreatment within each group, the DRT group showed a significant increase in BCVA ($P = 0.0002$), while the CME and SRD groups had a more significant increase of BCVA ($P < 0.0001$ in each group).

Baseline central foveal thickness and changes in central foveal thickness after treatment

Table 3 demonstrates the baseline and posttreatment CFT, and the changes of which between baseline and after three monthly IVI of anti-VEGF in different OCT types. OCT images of representative cases were shown in Figure 2.

At baseline, the SRD group had thicker CFT compared with the other two groups (DRT vs. CME vs. SRD, 371.7 ± 66.38 vs. 449.3 ± 114.10 vs. 506.0 ± 135.31; $P < 0.001$).

The posttreatment CFT showed no significant difference among the three groups (DRT vs. CME vs. SRD, 321.9 ± 79.78 vs. 339.0 ± 90.70 vs. 304.4 ± 68.63; $P = 0.094$). The SRD group had more CFT decrease than the other two groups (CFT decrease after three IVIs, DRT vs. CME vs. SRD, 49.8 ± 55.88 vs. 110.3 ± 98.94 vs. 201.6 ± 137.78; $P < 0.001$). Comparing the CFT between baseline and posttreatment within each group, all groups showed a significant decrease in CFT ($P < 0.0001$ in each group).

DISCUSSION

Retrospectively, we compared both the anatomical and functional effects of three monthly doses of anti-VEGF in different types of DME.

At the baseline, there was no difference in BCVA between all groups, while the SRD group had significantly thicker CFT than the other two groups. After three monthly doses of anti-VEGF therapy, all groups revealed a significant

Table 1: Basic characteristics

	Group			*P*
	DRT	CME	SRD	
Number of eyes	53	62	46	
Age (years)	62.5±8.46 (42~90)	61.7±9.11 (38~87)	60.0±7.75 (40~76)	0.344
Sex (male:female)	24:29	39:23	25:21	0.167
HbA1c	7.53±1.503 (4.8~12.0)	7.47±1.199 (5.7~11.3)	7.85±1.829 (5.0~13.6)	0.383
Lens status (phakia: pseudophakia)	35:18	39:23	37:9	0.129
DR (NPDR: PDR)	29:24	35:27	27:19	0.924

CME=Cystoid macular edema; DR=Diabetic retinopathy; NPDR=Nonproliferative DR; PDR=Proliferative DR; DRT=Diffuse retinal thickening; HbA1c=Hemoglobin A1c; SRD=Serous retinal detachment

Table 2: Best-corrected visual acuity at baseline and after treatment

	Group			P^b
	DRT	CME	SRD	
BL-BCVA (LogMAR)	0.6±0.355 (0.2~1.3)	0.65±0.307 (0.0~1.3)	0.77±0.385 (0.3~2.0)	0.137
BCVA after three IVIs (LogMAR)	0.55±0.381 (0.1~1.6)	0.49±0.294 (0.1~1.3)	0.54±0.330 (0.1~1.3)	0.493
P^a	0.0002	<0.0001	<0.0001	
BCVA improvement after three IVIs (post-IVI - BL) (LogMAR)	−0.11±0.201 (−0.6~0.3)	−0.16±0.260 (−0.9~0.8)	−0.23±0.267 (−0.8~0.3)	0.051

[a]Paired *t*-test (BL-BCVA vs. BCVA after three IVIs), [b]One-way ANOVA (among three groups). BCVA=Best-corrected visual acuity; BL=Baseline; CME=Cystoid macular edema; DRT=Diffuse retinal thickening; IVI=Intravitreal injection; SRD=Serous retinal detachment; LogMAR=Logarithm of the minimum angle of resolution

Table 3: Central foveal thickness at baseline and after treatment

	Group			P^b
	DRT	CME	SRD	
BL-CFT (μm)	371.7±66.38 (305~690)	449.3±114.10 (307~850)	506.0±135.31 (322~835)	<0.001
CFT after three IVIs (μm)	321.9±79.78 (233~656)	339.0±90.70 (211~634)	304.4±68.63 (191~488)	0.094
P^a	<0.0001	<0.0001	<0.0001	
CFT decrease after three IVIs (BL – post-IVI) (μm)	49.8±55.88 (−127~227)	110.3±98.94 (−23~401)	201.6±137.78 (−73~590)	<0.001

[a]Paired *t*-test (BL-BCVA vs. BCVA after three IVIs), [b]One-way ANOVA (among three groups). BL=Baseline; CFT=Central foveal thickness; CME=Cystoid macular edema; DRT=Diffuse retinal thickening; IVI=Intravitreal injection; SRD=Serous retinal detachment

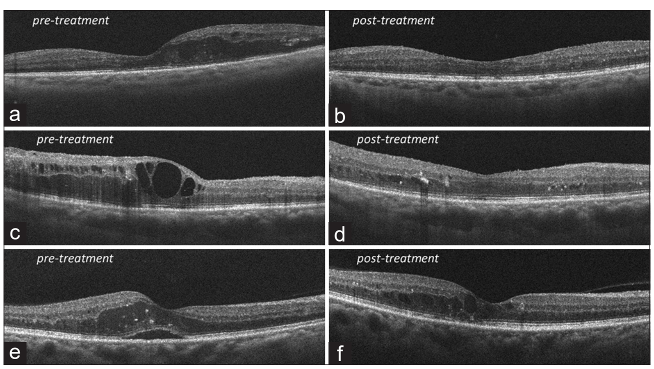

Figure 2: Representative optical coherence tomography images of three types of diabetic macular edema before and after intravitreal anti-vascular endothelial growth factor treatment. (a) Pre- and (b) posttreatment images of diffuse retinal thickening, (c) Pre- and (d) posttreatment images of cystoid macular edema, (e) Pre- and (f) posttreatment images of serous retinal detachment

improvement in both BCVA and CFT compared with baseline, while the SRD group showed the best result compared with the other two groups. The effect of anti-VEGF both anatomical and functional was, therefore, confirmed in our study; the different response to anti-VEGF therapy between different types of DME classified by OCT was also revealed.

There was not yet a commonly accepted classification system for DME morphology on OCT images; each author used different determinations in studies. In our study, the proportion of SRD type was 28.6%, followed by 32.9% of the DRT group and 38.5% of the CME group. The relatively lesser proportion of DRT type compared with previous reports[18,19] with more DRT could be explained by more sensitive detection of cystoid spaces by newer OCT machines and our classifying strategy, by which once included eyes exhibited cystic change or subretinal fluid, they would be categorized into CME and SRD types.

To date, the efficacy and prognosis of different types of DME patients treated with anti-VEGF agents still remain controversial. When it comes to predicting treatment outcomes, it seems that both anatomic and visual parameters are essential for monitoring patients with DME. Chen *et al*.[14] reported a most CFT decrease in the SRD type of DME, followed by CME type and then the DRT type, at 1-month and 2-year follow-up after IVI of ranibizumab treatment. Roh *et al*.[20] also reported better anatomical and functional outcomes of CME compared with DRT after IVI of bevacizumab treatment. Koytak *et al*.[19] reported relatively lower CMT changes in the DRT group than those in the CME and SRD groups after a single IVI of bevacizumab. These reported data were consistent with our findings while several reports showed different results. Shimura *et al*.[16] reported better CFT reduction and visual improvement of DRT and CME than SRD type after intravitreal bevacizumab injection. Wu *et al*.[15] found that the CME group was associated with a greater reduction in CFT with superior visual acuity (VA) improvement after intravitreal bevacizumab injection compared with the DRT or SRD. Gu *et al*.[13] reported the most VA benefit and the most significant CFT reduction in DME with DRT type than CME and SRD types after intravitreal aflibercept treatment. These controversial findings may be consistent with incomplete agreement in DME classifications, different anti-VEGF drugs, different treatment regimens, and different duration of follow-up and sample size. The longer duration of diabetes and/or edema might be associated with worse outcomes; however, it was difficult to trace back the exact timing of onset.

Referring to the possible mechanism of DME, DRT, the diffuse thickening of the retina with reduced intraretinal reflectivity on OCT, is caused by intracytoplasmic swelling of Müller cells in the outer plexiform layer; CME, the cystic fluid accumulation mostly within the outer retina, is a result of the liquefaction necrosis of the Müller cells which form cystoid cavities after longstanding edema; SRD, the subfoveal accumulation of fluid, indicates a combination of BRB breakdown and RPE pump damage.[21] The different mechanism and pathophysiology may explain to some extent why and how different DME types respond differently to anti-VEGF treatment.

Although most patients respond well to anti-VEGF agents, some patients showed only moderate or even poor response. There is no clear consensus as to how to manage these patients or define them.[22] Since the era of anti-VEGF in ophthalmology, ophthalmologists worldwide kept working to find out factors that might be relevant in clinical practice to help guide physicians in treatment decisions. The simple classification of DME types by OCT images can act as a powerful tool to quickly predict treatment effect and design treatment and follow-up regimen during clinical practice. Finally, this study has several limitations requiring consideration, which include the retrospectively collection of data, the small number of cases, and the probability of transformation between types during treatment.

CONCLUSION

In summary, different OCT patterns defined different types of DME, which might affect the therapeutic effect of anti-VEGF agents and could be used to predict both anatomical and functional outcomes.

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Data availability statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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