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Optical coherence tomography findings predictive of response to treatment in diabetic macular edema

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Abstract

Objective: To evaluate the short-term efficacy of intravitreal bevacizumab (IVB) and posterior sub-tenon triamcinolone injections (PSTI) on the basis of spectral-domain optical coherence tomography (SD-OCT) patterns in diabetic macular edema (DME).

Methods: We retrospectively reviewed 73 eyes of 73 patients with DME. Based on the presence of serous retinal detachment (SRD), eyes were categorized into two groups, and either IVB or PSTI treatment was performed. Central macular thickness (CMT) and the degree of SRD were assessed preoperatively and 1 month postoperatively. The severity of intraretinal edema was approximated based on the distance from the external limiting membrane to the internal limiting membrane.

Results: In eyes with SRD, reduction of SRD was greater with IVB than with PSTI. Moreover, reduction of intraretinal edema was greater with PSTI than with IVB. In eyes without SRD, PSTI achieved greater CMT reduction, compared with IVB.

Conclusions: In DME patients with SRD, IVB achieved greater reduction of SRD, compared with PSTI; however, intraretinal edema responded more favorably to PSTI, regardless of the presence of SRD. Our results suggest that the classification of DME based on OCT findings may be useful to predict responses to IVB or PSTI treatments.

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Diabetic macular edema, optical coherence tomography, intravitreal bevacizumab, posterior sub-tenon triamcinolone, serous retinal detachment, diabetic retinopathy, retina, edema

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Introduction

Diabetic macular edema (DME) is a leading cause of visual impairment in patients with diabetic retinopathy. Although the precise pathophysiology of DME remains unclear,[1] vascular endothelial growth factor (VEGF) plays an important role in increasing vascular permeability in diabetic retinopathy;[2] moreover, the roles of many inflammatory cytokines have been reported in association with development of DME.[3–5] Grid/focal laser treatment, or the use of corticosteroid via intravitreal route or posterior sub-tenon space, constitute the conventional treatment modalities for DME. Recently, the use of anti-VEGF agents has provided effective treatment of DME, such that anti-VEGF therapy has become a common treatment modality for DME.[6]

The morphology of DME can be classified into cystoid macular edema, sponge-like diffuse retinal swelling, and serous retinal detachment (SRD).[7] However, DME often presents as combinations of multiple types, such that clear classification is difficult in some cases. Furthermore, little information is available with regard to pretreatment optical coherence tomography (OCT) patterns of DME and patterns associated with different treatments. In some patients, DME persists after repeated intravitreal bevacizumab injection (IVB), but may respond favorably to intravitreal triamcinolone acetonide injection (IVTA).[8] Likewise, refractory DME, unresponsive to IVTA, reportedly improved after IVB.[9] Thus, DME exhibits a variety of treatment responses to different pharmacologic agents, such that it would be beneficial to determine, based on OCT findings, which type of DME might demonstrate the most favorable response to each treatment (e.g., anti-VEGF or corticosteroid). This knowledge would support clinicians in making informed decisions for DME treatment. Thus, we hypothesized that clear discernment of patterns of DME, based on spectral-domain OCT (SD-OCT), may be useful for the prediction of anatomical outcomes following treatment with either anti-VEGF agents or corticosteroids. The aim of this study was to determine whether pretreatment morphology of DME was significantly correlated with response to different treatments, as determined by analysis of changes in the morphology of DME on OCT after corticosteroid or anti-VEGF treatment.

Methods

Study subjects

This retrospective study enrolled patients with type 2 diabetes mellitus who were initially treated with either 1.25 mg of IVB or 40 mg of posterior sub-tenon triamcinolone injection (PSTI) for the treatment of DME, from December 2007 to December 2012. Patients were not randomized to IVB or PSTI at the time. Patients had received PSTI for DME between 2007 and 2008 when IVB was not available at our institute. Those who visited our clinic after 2008 received IVB as their initial treatment for

DME. Inclusion criteria for this study were the following: 1) central macular thickness (CMT) of >300 μm; 2) presence of cystoid macular edema, with or without serous retinal detachment, within an area of 1 mm centered on the fovea; 3) absence of any mechanical traction exerted on the fovea; 4) absence of other retinal or choroidal pathologies; and 5) OCT images of sufficient quality to discern retinal morphological changes. Exclusion criteria included: 1) previous vitrectomy; 2) panretinal photocoagulation, IVB, PSTI, or cataract surgery within 6 months; 3) focal laser treatment within 1 year; 4) other ocular diseases; and 5) serum creatinine >3 mg/dL. In all eyes, CMT measurement by SD-OCT and a complete ophthalmic examination (including slit lamp biomicroscopic examination, fundus examination, and intraocular pressure measurements) were performed preoperatively and at 1 month postoperatively. Additionally, prior to treatment, fluorescein angiography was performed with a confocal scanning laser ophthalmoscope (HRA 2; Heidelberg Engineering, Heidelberg, Germany) after intravenous injection with 5 mL of 20% sodium fluorescein, excluding patients with evidence of macular ischemia.

To determine the effects of IVB and PSTI on DME, with respect to SD-OCT patterns, eyes with DME were divided into two groups based on the presence or absence of SRD under the macula within 500 μm from the fovea, as determined by SD-OCT findings. In each group, eyes were further divided into two subgroups on the basis of treatments with either IVB or PSTI; SD-OCT findings were analyzed both quantitatively and qualitatively at 1 month postoperatively to determine short-term anatomical responses to treatments. This study was approved by the Institutional Review Board of Yonsei University College of Medicine (IRB approval: 3-2013-0314), and was conducted in accordance with the tenets of the Declaration of Helsinki. Informed consent was obtained from all patients.

Optical coherence tomography image assessment

SD-OCT (Cirrus HD-OCT, Carl Zeiss Meditec, Dublin, CA, USA) was performed and CMT was defined as the distance from the retinal pigment epithelium (RPE) to the internal limiting membrane (ILM). CMT was measured on a 1-mm circle, centered on the fovea, by using the mapping protocol of the OCT software (Figure 1a). SRD was defined as the presence of subretinal fluid between the neurosensory retina and the RPE, and was measured as the greatest distance from the RPE to the external limiting membrane (ELM), within 500 μm of the fovea, by using digital calipers within the Cirrus OCT software (Figure 1b). Intraretinal edema was defined as the distance from the ELM to ILM, and was calculated as [CMT – SRD]. The proportion of improvement in CMT was assessed by the reduction ratio, which was calculated as [(CMT at baseline – CMT at 1 month post injection)/CMT at baseline × 100 (%)]. Independent measurements were performed twice by two different blinded examiners, and the average value was used for calculations.

Intervention

All patients were placed in the supine position; after topical 0.5% proparacaine hydrochloride and 5% povidone-iodine application, an eyelid speculum was used to stabilize the eyelids. After treatment, a small volume of topical 0.5% moxifloxacin eyedrops was instilled. For IVB, the injection of 1.25 mg (0.05 mL) bevacizumab (Avastin; Genentech, Inc., San Francisco, CA, USA) was performed at 3.5 to 4 mm posterior to the limbus, through the pars

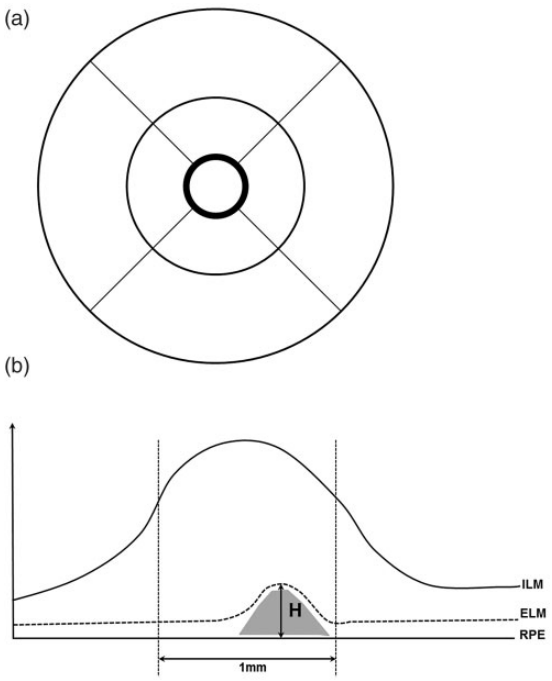

Figure 1. (a) Central macular thickness (CMT) was measured on the 1-mm Early Treatment Diabetic Retinopathy Study (ETDRS) circle (bold) centered on the fovea by using the mapping protocol of the OCT software. (b) Measurement of serous retinal detachment (SRD) was defined as the greatest distance (H) from the retinal pigment epithelium (RPE) to the external limiting membrane (ELM) within 500 μm of the fovea, as determined by using digital calipers. Intraretinal edema was defined as the distance from the ELM to the internal limiting membrane (ILM), and was calculated as [CMT – SRD].

plana, with a 30-gauge needle. For PSTI, a small incision (8 mm posterior to the limbus) was made through the conjunctiva and Tenon's capsule, to bare sclera, by using Westcott tenotomy scissors. The curved portion of the cannula was inserted, and the study medication was slowly injected behind the eye. One milliliter of a 40 mg/mL triamcinolone acetonide solution (Hanall Biopharma, Seoul, Korea) was delivered through the inferotemporal or superotemporal fornix, by using a curved cannula. When the depot application was complete, the cannula was withdrawn slowly, with gentle pressure maintained by a sterile swab, along the path of the cannula. No drug reflux was observed.

Statistical analysis

For descriptive purposes, quantitative data are reported as mean ± standard deviation. For comparison of baseline characteristics, Pearson's chi-squared test or Fisher's exact test were used for qualitative data and the Mann-Whitney U test was used for quantitative data. For comparison of CMT, intraretinal edema, and SRD between the groups, the Mann-Whitney U test was used and for comparison within the same group, the Wilcoxon signed rank test was used. *P* values less than 0.05 were considered statistically significant. Statistical analyses were performed using PASW Statistics for Windows, Version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

Demographic data

A total of 73 eyes of 73 patients that satisfied the inclusion and exclusion criteria were enrolled in the study. Thirty-two eyes were classified into the SRD group and 41 eyes into the non-SRD group. There were no statistically significant differences in age, sex, severity of diabetic retinopathy, previous history of treatment, serum level of glycohemoglobin, or creatinine levels. The baseline characteristics of each group are summarized in Table 1. There were only six patients (three in each group) who had received focal laser treatment at least 1 year before IVB or PSTI; none of the patients had received any injections, either intravitreally or via the sub-tenon route, for the treatment of DME.

Morphological changes after treatment of DME with SRD

The average preoperative CMT in eyes with SRD did not significantly differ between IVB and PSTI groups. At 1 month postoperatively, CMT was significantly reduced in both groups ($P = 0.001$ for both). There was no significant difference in total CMT reduction between the two groups (Table 2). With regard to changes in SRD, both groups exhibited significant reductions ($P = 0.001$ for both). Regarding changes in intraretinal edema, the IVB group showed mild but insignificant improvement, whereas the PSTI group, showed significant improvement ($P = 0.002$) (Figure 2; Table 2).

Overall, in DME with SRD, the IVB and PSTI groups achieved similar anatomical improvement in terms of the reduction of CMT. However, there was a greater degree of SRD reduction in eyes treated with IVB than in eyes treated with PSTI ($P = 0.001$). The improvement of intraretinal edema was greater in the PSTI group than in the IVB group ($P = 0.045$) (Table 2).

Morphological changes after treatment of DME without SRD

The average preoperative CMT in eyes without SRD improved in both IVB and PSTI groups ($P = 0.038$ and $P = 0.001$, respectively) (Figure 3; Table 2). Overall, in DME without SRD, PSTI was more

Table 1. Demographics and clinical characteristics of patients with diabetic macular edema.

	SRD group (n=32)			No SRD group (n=41)		
	IVB group	PSTI group	*P* value	IVB group	PSTI group	*P* value
Eyes	19	13		22	19	
Age (years)	52.6 ± 14.0	59.0 ± 13.4	0.305*	57.0 ± 12.1	64.2 ± 9.6	0.089*
Sex, Male/Female	10/9	5/8	0.491†	18/4	13/6	0.469†
NPDR/PDR	14/5	7/6	0.283†	13/9	12/7	0.790†
Previous focal laser	3	2	0.999‡	6	4	0.727‡
Previous anti-VEGF injection	0	1	0.406‡	0	3	0.091‡
Previous PSTI	2	2	0.999‡	4	3	0.999‡
HbA1c (%)	8.9 ± 2.5	8.6 ± 0.9	0.860*	8.2 ± 1.3	9.4 ± 2.4	0.200*
Creatinine (mg/dL)	1.04 ± 0.63	1.20 ± 0.52	0.485*	1.36 ±1.88	1.27 ± 1.07	0.067*

SRD = serous retinal detachment; IVB group = intravitreal bevacizumab group; PSTI group = posterior sub-tenon triamcinolone injection group; HbA1C = hemoglobin A1c; NPDR = nonproliferative diabetic retinopathy; PDR = proliferative diabetic retinopathy; VEGF = vascular endothelial growth factor.
*Mann-Whitney U test; †Pearson's chi-squared test; ‡Fisher's exact test.

Table 2. Quantitative changes of OCT parameters in eyes with diabetic macular edema.

	SRD group (n=32)			No SRD group (n=41)		
CMT (μm)	IVB group	PSTI group	*P* value*	IVB group	PSTI group	*P* value*
Reduction of (μm)						
CMT	136.53 ± 100.75	136.23 ± 96.89	0.773†	19.47 ± 13.49	139.56 ± 126.91	0.001†
Intraretinal edema	22.29 ± 7.39	83.23 ± 79.84	0.039†	–	–	–
SRD	114.24 ± 60.23	53.00 ± 39.76	<0.01†	–	–	–
% of improvement						
CMT	28.80 ± 18.96	28.10 ± 15.83	0.805†	3.87 ± 2.17	23.78 ± 20.10	0.001†
Intraretinal edema	4.94 ± 3.87	28.33 ± 22.58	0.045†	–	–	–
SRD	50.21 ± 19.62	27.61 ± 15.57	0.001†	–	–	–

CMT = central macular thickness; IVB = intravitreal bevacizumab; PSTI = posterior sub-tenon triamcinolone injection; SRD = serous retinal detachment, measured as perpendicular distance from RPE to ELM; intraretinal edema = [CMT – SRD]; ELM = external limiting membrane; RPE = retinal pigment epithelium; % of improvement = [(thickness at baseline minus thickness at 1 month postoperatively)/thickness at baseline × 100 (%)].
*Comparison between IVB and PSTI groups; †Mann-Whitney U test.

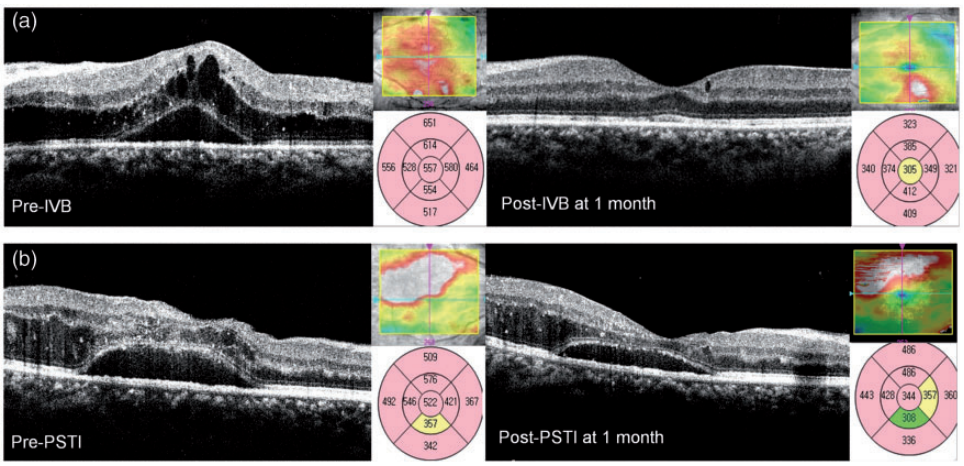

Figure 2. Morphological changes of diabetic macular edema with serous retinal detachment, as measured by SD-OCT. (a) One month after intravitreal bevacizumab treatment (IVB), macular edema, including all subretinal and intraretinal components, was resolved, and subretinal fluid had subsided completely. (b) One month after posterior sub-tenon triamcinolone injection (PSTI), macular edema had decreased slightly, but subretinal fluid components persisted.

effective in achieving greater CMT reduction than IVB ($P = 0.01$) by improvement of intraretinal edema (Table 2).

Ocular/systemic complications

No patients developed any systemic complications, such as cerebrovascular accidents associated with the use of intravitreal anti-VEGF injections. No ocular complications, including cataracts, increased intraocular pressure, endophthalmitis, retinal detachment or RPE tears, blepharoptosis, and proptosis, were noted, with the exception of transient chemosis and subconjunctival hemorrhage.

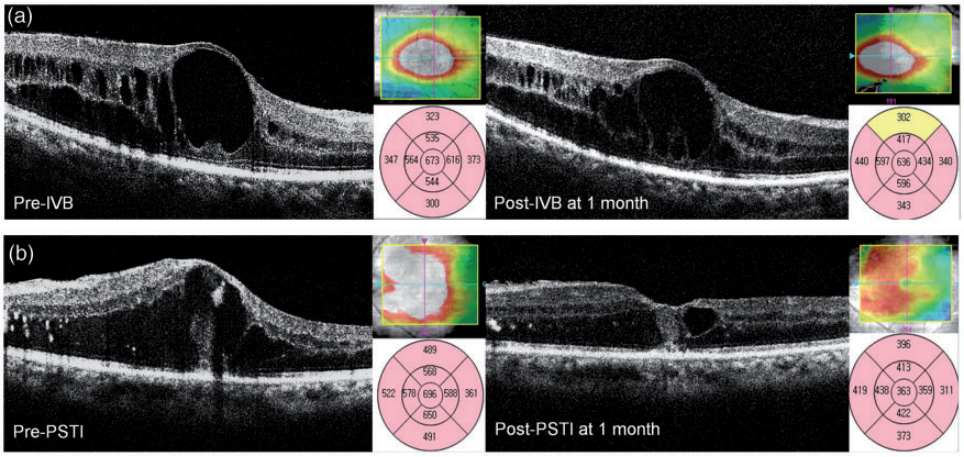

Figure 3. Morphological changes of diabetic macular edema without serous retinal detachment, as determined by SD-OCT. (a) At 1 month after intravitreal bevacizumab treatment (IVB), macular edema persisted, along with its intraretinal components. (b) At 1 month after posterior sub-tenon triamcinolone injection (PSTI), macular edema improved significantly, along with its intraretinal components.

Discussion

Despite major advances in the treatment of DME, many aspects of the disease remain unresolved. In particular, it would be highly beneficial to identify factors that can predict which type of DME would most benefit from a particular treatment. Our retrospective analysis of DME patients treated with either IVB or PSTI showed that, in DME with SRD, IVB resulted in greater reduction of subretinal fluid, compared with PSTI; however, PSTI showed greater improvement of intraretinal edema. Notably, DME without SRD also showed a greater improvement of retinal edema when treated by PSTI than when treated by IVB. This suggests that the classification of DME, based on OCT findings, may have important clinical implications for predicting anatomical improvement of DME in response to different pharmacologic agents.

The pathophysiology of DME is multifactorial and complex, and the precise causative mechanism for SRD has not been clearly elucidated. Although anti-VEGF treatment is effective in reducing the degree of DME, VEGF is one of many key factors involved in the pathogenesis of DME, and many inflammatory cytokines have been reported to contribute to the development of DME.[3,4] Past studies have shown higher concentrations of VEGF, as well as inflammatory cytokines, in patients with DME.[5] Moreover, recent studies revealed significant correlations between the OCT reflectivity of SRD and intravitreal VEGF concentration in eyes with DME.[10] Additionally, the concentration of interleukin-6 (IL-6) was found to be significantly higher in eyes with SRD than in eyes with CME or diffuse swelling; there was a significant correlation between the levels of VEGF and IL-6.[11] These results collectively imply that there may be different key mechanisms involved in the development of specific types of DME, based on OCT classification; this may explain the varying treatment responses to certain pharmacologic agents.[12]

Our study showed that the reduction of intraretinal edema was greater than the

reduction of subretinal fluid in eyes receiving PSTI, compared with IVB; this implies that PSTI may be more effective in DME predominantly comprising fluid accumulation within the retinal layers, such as CME or diffuse swelling, but not in DME with SRD. Several previous studies have shown the effectiveness of either IVTA or IVB. In a retrospective analysis of the effect of IVTA in DME patients, Shimura et al.[13] reported that IVTA was more effective in patients with CME, while IVTA was less effective in patients with SRD. Although the pathogenesis of DME remains unclear, CME is thought to be caused by intracytoplasmic swelling of Müller cells.[14] Shimura et al.[13] suggested that triamcinolone may reduce hypoxia-induced inhibition of fluid absorption, which could stimulate the Na^+ transporter and Na^+/K^+-ATPase to reduce cytoplasmic swelling, similar to the mechanism exhibited by pulmonary alveolar cells.[15] Further, the effect of triamcinolone was reported to be protective against oxidative stress-induced disruption of the RPE tight junction.[15] Thus, we hypothesize that the resorption of fluid within the inner and outer retinal layers may be more effectively achieved by the action of triamcinolone delivered by PSTI. In contrast, other studies have shown that IVB is more effective for sponge-like diffuse retinal thickening, but less effective for SRD.[16,17] Liu et al.[16] reported that IVTA was superior to IVB in treatment of DME combined with SRD, but was inferior to IVB in treatment of diffuse macular thickening. Unlike the present study, the prospective study by Liu et al.[16] used IVTA in place of PSTI for the treatment of DME; it further differed in that the study population comprised three different groups (DME combined with SRD, diffuse macular thickening, and CME). Additionally, the prior study population did not receive any treatment before either IVTA or IVB. Shimura et al.[17] revealed that the improvement of foveal thickness and visual acuity after IVB was greater in the group with sponge-like diffuse retinal thickening than in the SRD group; their prospective study focused on the effect of IVB only in patients with DME, such that a direct comparison between IVTA and IVB was not possible. The different outcomes of these studies may be attributable to the significant differences in baseline CMT among the different treatment groups in each study.[16] Furthermore, their study results occasionally demonstrated complete resolution of SRD after a single injection of IVB.[17] Therefore, because the pathogenesis of SRD remains unclear, further studies are warranted to elucidate the precise correlation between morphological patterns of DME on OCT and observed therapeutic responses.

Although intravitreal delivery of triamcinolone has shown therapeutic effects on refractory DME,[18] it has also been associated with complications such as cataract and endophthalmitis.[19,20] Notably, PSTI delivers a large amount of drug to the posterior segment of the eye, via transscleral absorption,[21,22] and has been widely used as treatment for CME secondary to uveitis.[23,24] Additionally, several studies have reported significant reduction in CMT after PSTI in DME patients.[24,25] In our study, we used the posterior sub-tenon route for safer delivery of triamcinolone, in order to minimize complications associated with the intravitreal use of triamcinolone; no complications were noted in the study.

Our study has several limitations, namely a lack of randomization to either IVB or PSTI treatments owing to the retrospective nature of the study, a relatively small number of patients, and short duration. However, our study was intentionally designed to analyze the short-term anatomical response of DME based on pretreatment morphological patterns of DME by OCT. The 1-month follow-up period seemed most appropriate to observe the

immediate effects of a single pharmacologic agent on DME, because longer follow-up evaluations of eyes would have resulted in a combination of different treatments administered to the eyes after the initial treatment with either IVB or PSTI. Because this was only a 1-month follow-up study, correlations between visual acuity and OCT patterns were not evaluated. Furthermore, some patients had received other treatments for DME before the initiation of the study, which may have affected the results of our study. To investigate this relationship further, a large prospective randomized controlled trial is warranted.

In conclusion, in patients with DME, the degree of SRD reduction was greater in eyes treated with IVB than in those treated with PSTI; intraretinal edema showed a more favorable response to PSTI than IVB, regardless of the presence of SRD. Our study indicated that morphological classification of DME, based on OCT results, might be useful to predict short-term anatomical responses to different treatments. Further OCT studies are warranted to clarify the clinical relationships between the pathophysiology and morphological features of DME.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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