

Visual and Morphologic Outcomes of Intravitreal Bevacizumab for Diabetic Macular Edema Based on OCT Patterns: A Retrospective Study

Rungrawin Khattiyawittayakun, M.D.*

Abstract

Purpose: To evaluate the visual and morphologic outcomes of intravitreal bevacizumab (IVB) injection in eyes with diabetic macular edema (DME) based on the morphologic patterns on the optical coherence tomography (OCT) at 6 months. **Method:** A retrospective comparative study of 64 eyes of type 2 diabetics with DME classified according to OCT patterns: diffuse retinal thickening (DRT), cystoid macular edema (CME), and serous retinal detachment (SRD) was performed. Every patient received 3 monthly IVB injections and as needed thereafter. The primary outcome was the changes in the best corrected visual acuity (BCVA) and central foveal thickness (CFT) measured by optical coherence tomography for duration of 6 months after the first injection. **Results:** The 64 eyes were classified as 24 (37.5%) of the DRT type, 21 (32.8%) of the CME type, and 19 (29.7%) of the SRD type. Before the injection, there were no significant differences in BCVA and CFT among different DME types ($P = 0.875$, 0.294 respectively). At 6 months after treatment, there were significant improvements of BCVA and CFT from baseline in all 3 DME types ($P < 0.001$) without significant difference among each OCT pattern ($P = 0.220$ for BCVA, $P = 0.635$ for CFT). The DRT type seemed to have the slightly more preferable results than the other types. **Conclusion:** Vision gain and anatomic improvement were achieved and maintained in all three DME types for at 6 months after intravitreal bevacizumab injections. **Key words:** Bevacizumab, Diabetic macular edema, Optical coherence tomography

*The Retina-Vitreous Service, Department of Ophthalmology, Maharat Nakhon Ratchasima Hospital, Nakhon Ratchasima, 30000

บทคัดย่อ: ผลการรักษาด้วยการฉีดยา Bevacizumab เข้าน้ำวุ้นตาในส่วนของ Visual outcome และ Morphologic outcome ผู้ป่วยที่มีจอประสาทตาบวมจากเบาหวานที่มีลักษณะที่แตกต่างจากการตรวจด้วย OCT รุ่งรวิน ชัตติยวิทยากุล, พ.บ.*

*อนุสาขาจอประสาทตาและน้ำวุ้นตาภาควิชาจักษุวิทยา โรงพยาบาลมหาราชนครราชสีมา

จังหวัดนครราชสีมา 30000

เวชสารโรงพยาบาลมหาราชนครราชสีมา 2560; 39: 91-100.

จุดประสงค์: เพื่อประเมินประสิทธิผลในการรักษาด้วยการฉีดยา bevacizumab เข้าน้ำวุ้นตาทั้งส่วนของ visual outcome และ morphologic outcome ต่อผู้ป่วยที่มีจอประสาทตาบวมจากเบาหวานที่มีลักษณะที่แตกต่างจากการตรวจด้วย optical coherence tomography (OCT) ที่ระยะเวลา 6 เดือน **ระเบียบวิธีวิจัย:** การวิจัยแบบ retrospective comparative study ในผู้ป่วยเบาหวานชนิดที่ 2 ที่ได้รับการวินิจฉัยเป็นจอประสาทตาบวมจากเบาหวาน (diabetic macular edema) จำนวน 64 ดวงตา โดยแบ่งชนิดของ DME ตามลักษณะที่พบใน OCT เป็น diffuse retinal thickening (DRT), cystoid macular edema (CME) และ serous retinal detachment (SRD) ผู้ป่วยทุกคนได้รับการฉีดยา bevacizumab เข้าน้ำวุ้นตาเดือนละครั้ง จำนวน 3 ครั้ง จากนั้นรับการฉีดตามความจำเป็น (as-needed regimen) ผู้วิจัยติดตามข้อมูล ผลการวัดการมองเห็น (best corrected visual acuity) จากเวชระเบียน และผลภาพถ่าย OCT เพื่อประเมินความหนาจอรับภาพ (central foveal thickness) หลังจากฉีดยาเข็มแรกแล้วจนถึง 6 เดือน **ผลการศึกษา:** ในจำนวน 64 ดวงตา ที่วินิจฉัยเป็นจอประสาทตาบวมจากเบาหวานมี 24 ดวงตา (37.5%) เป็นชนิด DRT, 21 ดวงตา (32.8%) เป็นชนิด CME และ 19 ดวงตา (29.7%) เป็นชนิด SRD โดยไม่พบความแตกต่างของการมองเห็น (BCVA) และความหนาจอรับภาพ (CFT) ระหว่างทั้งสามชนิดของ DME ($P=0.875$ และ 0.294 ตามลำดับ) หลังจากรับการรักษาด้วยการฉีดยา bevacizumab เข้าน้ำวุ้นตาเป็นเวลา 6 เดือน พบว่าการมองเห็นดีขึ้นอย่างมีนัยสำคัญทางสถิติ ($P<0.001$) และความหนาจอรับภาพลดลงอย่างมีนัยสำคัญทางสถิติ ($P<0.001$) ในจอประสาทตาบวมจากเบาหวานทั้งสามชนิด โดยไม่พบความแตกต่างอย่างมีนัยสำคัญทางสถิติทั้งในส่วนของการมองเห็นที่ดีขึ้น ($P=0.220$) และความหนาจอรับภาพที่ลดลง ($P=0.635$) ระหว่างกลุ่ม อย่างไรก็ตามพบว่า จอประสาทตาบวมจากเบาหวานชนิด DRT ได้รับผลการรักษาที่ดีกว่าชนิดอื่นเล็กน้อย **สรุป:** การรักษาด้วยการฉีดยา Bevacizumab เข้าน้ำวุ้นตาสามารถให้ผลการมองเห็นที่ดีขึ้น และความหนาจอรับภาพที่ลดลงได้ในภาวะจอประสาทตาบวมจากเบาหวานทั้งสามชนิดที่แตกต่างจากการตรวจ OCT ในช่วง 6 เดือนหลังการรักษา **คำสำคัญ:** Bevacizumab, จอประสาทตาบวมจากเบาหวาน, OCT

Introduction

Diabetic macular edema (DME) is a sight threatening complication of diabetic retinopathy⁽¹⁾ and the most common cause of permanent vision loss in work-age adult patients with DM^(2,3,4). It consists of localized expansion of the retinal intracellular and/or extracellular space in the macular area.

The morphologic characteristics of DME obtained by optical coherence tomography (OCT) are varies⁽⁵⁾ and may be classified into 3 major types: diffuse retinal thickening (DRT), cystoid macular edema (CME) and serous retinal detachment (SRD)⁽⁶⁾.

The pathophysiology of DME is thought to be multifactorial. One suggested etiology is the

breakdown of the inner and/or outer retinal blood barrier. Posterior hyaloid adhesion also plays a role in the pathogenesis of DME⁽⁷⁾.

The vascular endothelial growth factor (VEGF) is an endogenous mediator of DME. Pharmacologic therapies that inhibit VEGF directly target the main cause of pathology⁽⁸⁾. Recent studies have shown the effectiveness of intravitreal bevacizumab (IVB) in reducing DME^(9,10).

The therapeutic effect of the intravitreal bevacizumab on various DME morphologies has been sequentially reported^(11,12,13,14) but the comparative study of the effectiveness of IVB on different types of DME according to OCT patterns has never been previously done in Thailand.

Purpose

The purpose of this study is to evaluate the visual and morphologic outcomes of intravitreal bevacizumab (IVB) in eyes with diabetic macular edema (DME) based on the morphologic patterns on the optical coherence tomography (OCT).

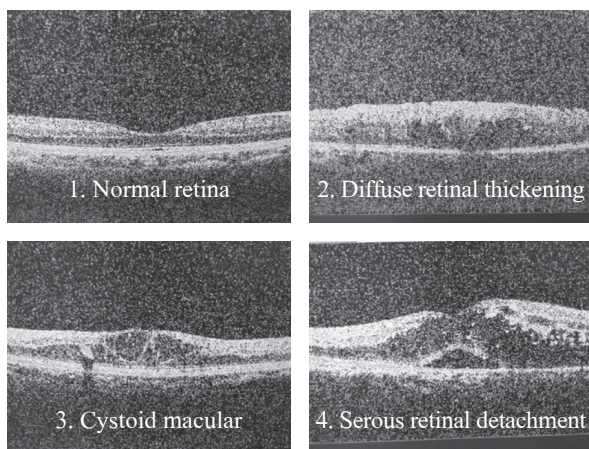


Figure Retinal morphologic patterns from OCT (counter-clockwise from the left)

Methods

Patient selection

A retrospective study was conducted recruiting the eyes with DME who were treated with intravitreal bevacizumab injections at the Maharat Nakhon Ratchasima Hospital between 1 August 2015 and 31 January 2016. The patients were treated with intravitreal bevacizumab 3 times at 1-month intervals, then as-needed all with a minimum follow-up of 6 months. A total of 64 eyes that met the eligible criteria were included in the analysis. Approval for this retrospective review was obtained from the Human Clinical Research Committee of the hospital.

All patients received a complete ocular examination, including best-corrected visual acuity (BCVA) testing, dilated fundus examination with slitlamp biomicroscopy and color fundus photography as baseline. The BCVA was measured with a standard Snellen chart at 6 meters by the skilled nurses who passed the official ophthalmologic course from the reliable institute and then converted to decimal visual acuity for statistical analysis.

Classification of DME Using OCT

OCT scans were performed through dilated pupils. A macular cube scan by SD-OCT (Advanced OCT/SLO system; Nidek co., ltd., Aichi, Japan) was performed to measure retinal thickness at the central fovea. The macular cube scan consisted of 128 raster scans with 53,000 A-scans, within a 6x6 mm. macular area. DME was classified into 3 morphologic patterns as follows. The Diffuse retinal thickening (DRT) pattern was characterized by a sponge-like retinal swelling of the macula with reduced intraretinal reflectivity. The Cystoid macular edema (CME) pattern was characterized by intraretinal cystoid spaces of low reflectivity with highly reflective septa separating cystoids like cavities

in the macular area. The Subretinal detachment (SRD) pattern was characterized by a shallow elevation of the retina, and an optically clear space between the retina and the retinal pigment epithelium. The definition of DRT allowed only pure DRT. If DRT was combined with CME or SRD, the pattern was classified as either CME or SRD, respectively; and when DRT, CME, and SRD were all present together, the pattern was classified as SRD.

Central foveal thickness (CFT) was defined as the mean retinal thickness in 1-mm diameter circular zone centered on the fovea. All OCT images were captured by a skilled technician and all OCT measurement was done by a single retinal specialist (Rungrawin K., M.D.)

Intravitreal bevacizumab injection

Each subject was given at least three monthly intravitreal injections of bevacizumab (Avastin; Genentech, Inc., South San Francisco, California, USA). Topical anesthetic drops were given first and then a lid speculum was inserted. After cleaning the injection site with 5% povidone iodine, a 30-gauge needle was inserted through the pars plana, and 0.05 ml (1.25 mg) of bevacizumab was injected. Patients were given topical antibiotics 4 times daily for 1 week after each injection.

Follow-up examination

The main outcomes measured included changes in the BCVA and CFT measured by OCT. A follow-up examination was performed every month. BCVA evaluation, fundus examination, and CFT measured by OCT were assessed at each follow-up visit. The data that were collected before the first injection and at 1, 2, 3, and 6 months after the first injection were used for the analysis.

Statistical analysis

Statistical analyses were performed using STATA software (ver. 11.0; STATA Corp., College station, Texas, USA). The changes of the BCVA evaluation and CFT measured with OCT over 6-month follow-up period were tested with the student T-test. The differences of the changes of the BCVA evaluation and CFT measured with OCT over 6-month period among three morphologic groups were tested using one-way ANOVA. A P-value of less than 0.05 was considered statistically significant.

Results

Sixty-four eyes of 64 patients were enrolled. Patient characteristics were summarized in table 1. DRT was presented in 24 eyes (37.5%), CME in 21 eyes (32.8%) and SRD in 19 eyes (29.7%). The baseline characteristics of each group based on the OCT pattern were not significantly different: age ($P=0.813$), baseline BCVA ($P=0.875$), and baseline CFT ($P=0.294$).

Changes in Mean BCVA

Figure 1 and table 2 showed the BCVA at baseline and after intravitreal bevacizumab injections based on the OCT patterns at baseline 1, 2, 3 and 6 months. At 6 months, the DRT type showed a better BCVA (0.38 ± 0.24) than the SRD (0.37 ± 0.22) and CME (0.29 ± 0.21) types. The BCVA at 6 months were significantly better than baseline BCVA in all three morphologic types ($P<0.001$). At 6 months, the change in mean BCVA in eyes with DRT was 0.19 ± 0.08 whereas with CME was 0.11 ± 0.04 and with SRD was 0.16 ± 0.01 . The changes in mean BCVA value at 6 months did not differ significantly among the three morphologic types ($P=0.22$) as shown in table 2. The DRT type had slightly better BCVA outcome than the other types.

Table 1 Baseline characteristics of eyes with different types of OCT findings

	DRT (n=24)	CME (n=21)	SRD (n=19)	P value
Sex, male/female	11/13	16/5	8/11	-
Age, years	58.33±6.92	57.95±8.38	56.84±7.85	0.813
BCVA, decimal	0.19±0.16	0.18±0.17	0.21±0.21	0.875
CFT, µm.	469.42±100.20	527.38±156.65	511.42±122.33	0.294

ANOVA test, statistically significant at 5% level

Changes in Mean CFT

The effect of intravitreal bevacizumab on CFT based on OCT type at baseline, 1, 2, 3 and 6 months were summarized in figure 2 and table 3. Eyes with

DRT, CME and SRD patterns had CFT values at 6 months (308.96±87.45 µm, 322.33±127.93 µm and 321.15±150.06 µm, respectively) lower than that at baseline with statistical significance ($P<0.001$). At 6

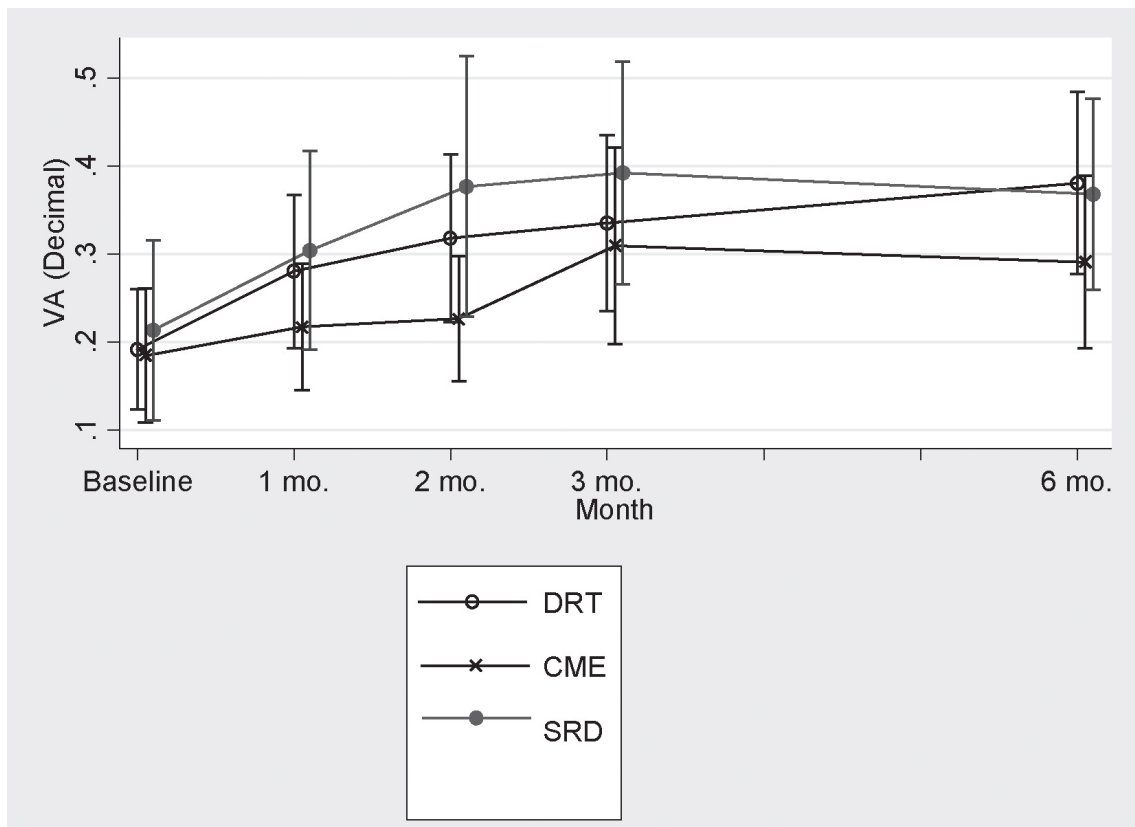


Figure 1 Changes in the mean BCVA over time after intravitreal bevacizumab injection. At 6 months, the DRT group shows slightly better BCVA than the other two groups. The CME group shows BCVA improvement less than the other groups without statistical significance.

Table 2 Change in BCVA from baseline

	DRT	CME	SRD	P value
Baseline (1 st inj.) BCVA (decimal)	0.19±0.16	0.18±0.17	0.21±0.21	0.875
6-month BCVA (decimal)	0.38±0.24	0.29±0.21	0.37±0.22	0.389
Change in BCVA from baseline (decimal)	0.19±0.08	0.11±0.04	0.16±0.01	0.220

ANOVA test, statistically significant at 5% level

months, the change in decreased mean CFT in DRT type was 160.45±12.75 µm. whereas in CME type was 205.15±28.76 µm and SRD type was 188.45±27.73 µm. The change in mean CFT value at 6 months did not differ significantly between the three morphologic types ($P=0.635$).

Adverse Events

During the follow-up period, none of patients developed any significant ocular adverse events including retinal tear, retinal detachment, and endophthalmitis. No other systemic side effects, such as cardio-vascular events or cerebral vascular accidents, were encountered in the study.

Discussion

Focal/grid laser has been the mainstay treatment for DME for decades. Several studies recently reported the effectiveness of the intravitreal administration of

antibodies against VEGF for treating DME, including a decrease in central foveal thickness (CFT) and the improved best corrected visual acuity (BCVA).

The largest published study of ranibizumab in DME, The Diabetic Retinopathy Clinical Research Network (DRCR. net), demonstrated that intravitreal ranibizumab with deferred (>24 weeks) or prompt focal/grid laser was superior to focal/grid laser alone for the treatment of DME involving the fovea through at least 2 years of follow-up⁽¹⁵⁾.

DME is classified into three different OCT patterns. Some earlier studies reported that the visual acuity was significantly better in the diffuse retinal thickening (DRT) type than in cystoid macular edema (CME) type^(16,17) and also better than in subretinal detachment (SRD) type⁽¹⁸⁾. In the present study, however, baseline BCVA was similar among the three OCT patterns.

Table 3 Change in CFT from baseline

	DRT	CME	SRD	P value
Baseline (1 st inj.) CFT (µm)	469.41±100.20	527.38±156.65	511.42±122.33	0.294
6-month CFT (µm)	308.96±87.45	322.23±127.93	321.97±150.06	0.920
Change in CFT (µm) from baseline	-160.45±12.75	-205.15±28.76	-188.45±27.73	0.635

ANOVA test, statistically significant at 5 % level

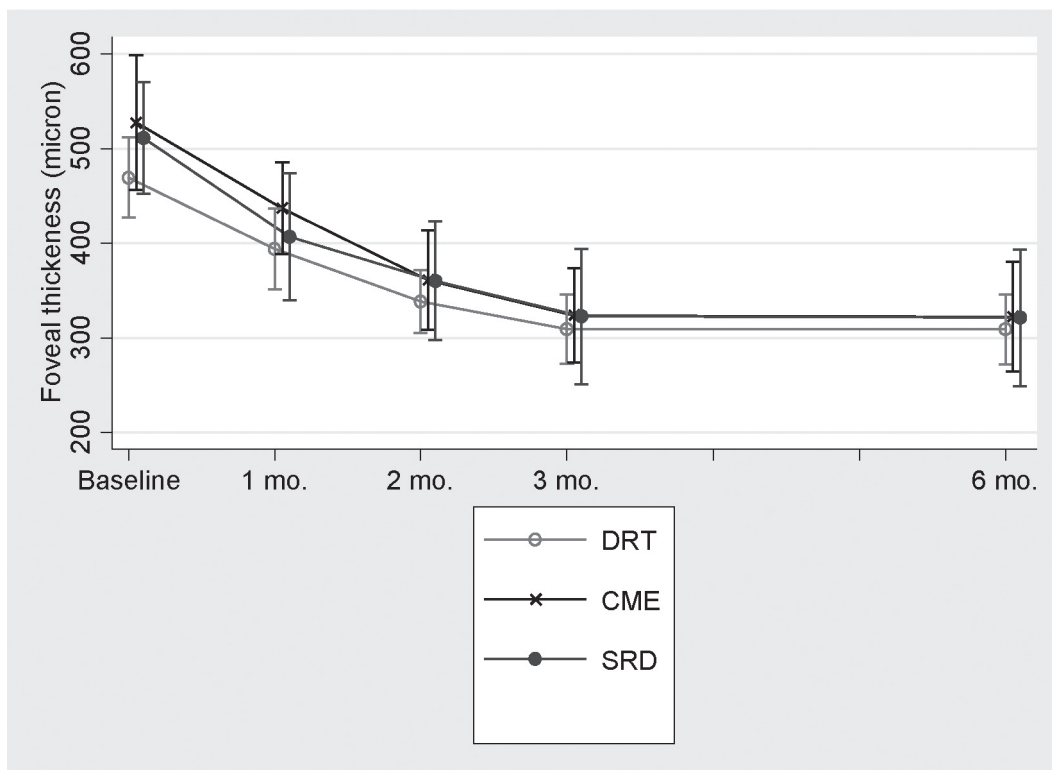


Figure 2 Change in mean CFT over time after intravitreal bevacizumab injection. At 6 months, the reduction in CFT was evident in all three groups while the DRT group showed slightly more reduction than the other groups with no statistical significance.

The results of this study reported that the BCVA and CFT at 6 months after intravitreal bevacizumab injections were significantly better than the baseline in all three OCT morphologic patterns with no significant difference among each pattern. However, the DRT type showed more change in BCVA and CFT than CME and SRD types at 6 months. (Figure 1, 2)

The significance of the morphologic pattern in term of predicting the response to intravitreal bevacizumab had been reported by some studies. One previous study reported that the effectiveness of intravitreal bevacizumab was dependent on the OCT pattern and found that after one intravitreal injection, the BCVA and foveal thickness was better in DRT type than CME and SRD types at 12 weeks follow-up⁽¹¹⁾. The retrospective study of Kim et al reported that the

BCVA in DRT type was significantly better than in CME and SRD type and the CFT in the DRT and SRD types were significantly lower than in CME type at 6 months follow-up after three consecutive intravitreal bevacizumab injections⁽¹³⁾.

The pathogenesis of diffuse retinal thickening is likely to originate from the destruction of the tight junctions in retinal capillary endothelial cells resulting in the persistent breakdown of the inner blood retina barrier which causes the diffuse accumulation of the fluid in the extracellular space of the retina^(8,19). Consequently, the capillary destruction causes the retinal ischemia inducing the cytotoxic edema and intracytoplasmic swelling of the Muller cells. Liquefaction necrosis of the Muller cells and adjacent neural cells close to persistent extracellular edema

and ischemia lead to the cystoid cavity formation or CME type in OCT pattern prominently in the outer retinal layer^(21,22). The retinal ischemia also aggravates the release of permeability disturbing substances as vascular endothelial growth factors (VEGFs) and prostaglandin^(23,24).

Bevacizumab suppresses the hypervasopermeability by its anti-VEGF effect, leading to reduction of macular edema in all DME types especially in DRT type. The CME formation involves the cytotoxic edema which cause the deformation of retinal structure and is partly dependent on the VEGF as well as prostaglandin and other inflammatory cytokines therefore bevacizumab seems to have less therapeutic effect in the CME type because it suppresses only the VEGF and does not have the effect to repair the retinal structure. The present study also showed that DRT type received better BCVA than CME type after IVB injections although it was not statistically significant. Shimura et al⁽²⁵⁾ reported that adding triamcinolone to suppress various inflammatory cytokines was expected to have better therapeutic effect than anti-VEGF treatment alone.

The edema in the SRD type may result from the decreasing in the retinal pigment epithelium (RPE) function that may result from the ischemic disorder and/or the inflammation which leads to the accumulation of intraretinal and subretinal fluid⁽²⁶⁾. The RPE abnormality also allows for increased fluid from choriocapillaris pass into the retina. Kang et al⁽²⁷⁾ suggests that the SRD usually precedes the CME for the following reasons. First, the visual acuity in the CME type is significantly worse than that in the SRD type. Second, foveal thickness is thicker in the CME

type than in the SRD type. Third, foveal detachment often leads to cystoid foveal change. In the present study, the SRD type achieved better BCVA than the CME type at 6 months after treatment although it was not statistically significant probably due to its earlier in pathogenesis.

Our study has several limitations that require consideration, including the retrospective study, relative small number of patients, and short follow up period. In conclusion, intravitreal injection of bevacizumab is the effective treatment for all OCT morphologic types of DME in duration of 6 months but the therapeutic effect is temporary and repeated injection should be considered. The therapeutic effect seems to be less in CME type than the other types. Findings from this study suggest that the understanding in the structural macular change in DME based on OCT before intravitreal bevacizumab injection would help predict the treatment outcome. The prospective study with a large number of participants will be required to confirm the conclusion of this study.

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