

Effectiveness of Intravitreal Ranibizumab for Diabetic Macular Edema with Serous Retinal Detachment

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Purpose: To evaluate the effectiveness of intravitreal injection of ranibizumab (IVR) in treating diabetic macular edema (DME) with serous retinal detachment (SRD) based on spectral domain optical coherence tomography (SD-OCT) patterns.

Methods: One hundred thirty-four eyes of 134 patients with DME who underwent SD-OCT evaluation were included in this study. We retrospectively analyzed the medical records of patients who received IVR for the treatment of DME. Their eyes were classified into three groups according to the following SD-OCT features: SRD, diffuse retinal thickness and cystoid macular edema. The three groups were compared regarding changes in best-corrected visual acuity and central foveal thickness (CFT) after IVR.

Results: The mean age was 61.4 ± 9.2 years (range, 44 to 81 years). The average length of the follow-up period was 9.4 ± 3.4 months (range, 6 to 24 months). The mean CFT value was significantly reduced in all groups ($p < 0.001$) after treatment. Increases in best-corrected visual acuity were statistically significant for the diffuse retinal thickness and cystoid macular edema groups ($p < 0.001$ and $p < 0.001$, respectively). However, there was no significant improvement after IVR injection in the SRD group ($p = 0.252$). In the SRD group, patients with ellipsoid zone disruption and external limiting membrane disruption demonstrated poorer visual gains at the last follow-up visit ($p < 0.005$ and $p = 0.002$, respectively).

Conclusions: A significant reduction in CFT with required IVR injections in DME with SRD was achieved but was accompanied by a worse functional outcome in the SRD group. The presence of subretinal fluid on SD-OCT in study eyes may be a poor prognostic factor for visual acuity.

Key Words: Diabetic macular edema, Ranibizumab, Serous retinal detachment, Spectral domain optical coherence tomography, Visual acuity

Macular edema occurs in a wide variety of ocular diseases and is a common cause of vision loss in patients with di-

abetic retinopathy [1]. Its complex and multifactorial pathogenesis is not yet fully understood. What is apparent is that the multifactorial disruption of inner and outer blood-retinal barriers leads to an abnormal inflow of fluid into the neurosensory retina that exceeds the outflow, producing intraretinal and subretinal fluid accumulation [2-5]. Using spectral domain optical coherence tomography (SD-OCT), Otani et al. [6] described three patterns of diabetic macular

Received: October 11, 2017 Accepted: December 20, 2017

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edema (DME): sponge-like swelling, cystoid macular edema (CME), and serous retinal detachment (SRD). SRD associated with CME can only be diagnosed using SD-OCT because it can be hidden beneath CME and therefore missed during fundus fluorescein angiography [7].

Vascular endothelial growth factor (VEGF) is a potent endothelial cell angiogenic factor and a powerful mediator of vascular permeability. It leads to the breakdown of the blood-retinal barrier in diabetic retinopathy, causing leakage of intravascular fluid from abnormal retinal capillaries and resulting in DME [8]. Therefore, treatment with anti-VEGF agents is one of the most promising approaches for the treatment of vision loss due to DME [9,10].

Various studies have established the safety and efficacy of anti-VEGF agents, including ranibizumab and bevacizumab, in the treatment of DME [11-13]. However, only a few publications have addressed the issue of why some eyes respond to this treatment more readily than others. The presence of SRD in retinal vascular diseases, such as diabetes, may affect the treatment results for macular edema associated with retinal vascular leakage and may also limit the ability to perform effective macular laser treatment.

There are few reports about the results of bevacuzimab injection on different optical coherence tomographic patterns of DME [14,15]. Koytak et al. [14] reported that the CME and SRD subtypes were associated with a greater reduction in central foveal thickness (CFT) than the diffuse retinal thickness (DRT) subtype. However, changes in visual acuity were not significantly different among the three groups.

The aim of this study was to evaluate the anatomical and functional outcomes based on various patterns of SD-OCT morphology in DME following treatment with intravitreal ranibizumab (IVR) injection.

Materials and Methods

A retrospective chart review of patients with DME who underwent SD-OCT evaluation in the department of ophthalmology between January 2011 and August 2014 was performed. This study adhered to the tenets of the Declaration of Helsinki and was approved by our local ethics committee (2015/01-21). Informed consent was obtained before the investigation began.

In this study, the medical records of patients who had received an IVR injection for the treatment of DME were retrospectively analyzed. Eyes that had clinically significant macular edema and a CFT of 300 μm or more determined by SD-OCT (Spectralis HRA+SD-OCT; Heidelberg Engineering, Heidelberg, Germany) were included in the analysis, regardless of diabetic retinopathy stage. If both eyes of the same patient met the inclusion criteria, only one eye was assigned randomly for the study.

All patients underwent macular SD-OCT measurements prior to IVR injection. Eyes that had poor quality SD-OCT scans were excluded from the study. The causes of these poor scans included media opacities, excessive blinking, or persistent eye movement. Other exclusion criteria were ocular surgery or trauma, intravitreal or periocular injection of any drug, or laser photocoagulation within six months of the injection; history of any previous vitreoretinal surgical procedure; presence of concomitant retinal pathologies and glaucoma or evidence of vitreomacular traction on SD-OCT. Patients with a follow-up time shorter than six months were also excluded from the study.

During SD-OCT examination, the macula was scanned in six radial sections, including the horizontal, vertical, and oblique planes, through the center of the fovea. The macular thickness was measured automatically by the topography software built into the SD-OCT device.

The IVR injections were performed in the operating room under aseptic conditions. Topical anesthesia was achieved by instillation of at least three drops of 0.5% proparacaine hydrochloride (Alcaine; Alcon Laboratories, Fort Worth, TX, USA). Povidone iodine (5%) was applied to the lids and eyelashes and instilled in the conjunctiva before draping. Next, 0.5 mg/0.05 mL of ranibizumab (Lucentis; Novartis Pharma AG, Basel, Switzerland) was injected using a 30-gauge needle 4 mm posterior to the limbus (3.5 mm in pseudophakic eyes). Finally, a drop of 5% povidone iodine was instilled at the injection site. An eye pad was placed, and 0.5% moxifloxacin topical drops were prescribed for instillation four times daily.

Best-corrected visual acuity (BCVA) with a Snellen chart (BCVA measurements were converted to logarithm of the minimum angle of resolution [logMAR]) and CFT values assessed with SD-OCT prior to the IVR injection and at the last visit were recorded. Eyes were divided into SRD, DRT, and CME groups according to the assessment of macular edema morphology on SD-OCT (Fig. 1A-1C). When more

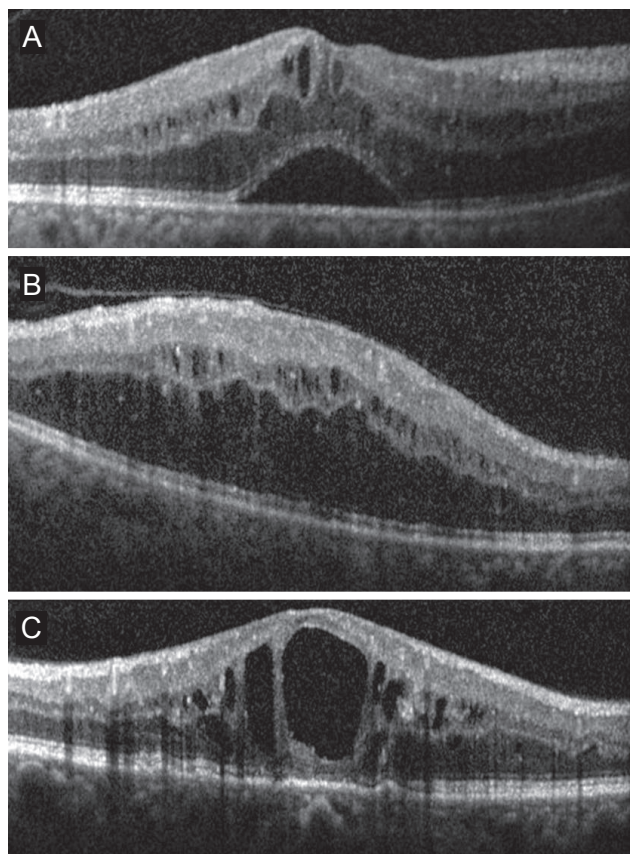


Fig. 1. Diabetic macular edema (DME) classification based on spectral domain optical coherence tomography. (A) Patients with predominant serous retinal detachment DME had an associated subretinal collection of fluid under the fovea. (B) Diffuse DME patients demonstrated widespread retinal thickening with a sponge-like appearance of the macula. (C) Patients with focal cystoid DME had a mound-like appearance of the fovea due to focal collection of fluid at the fovea.

than one edema pattern was observed, the eye was included in the group of the most obviously predominant pattern. In cases where more than one pattern was present and none was obviously predominant, the eye was not included in the study. The BCVA, macular appearance and SD-OCT findings were used to determine whether the patient should receive a repeat injection of IVR. However, it was left at the discretion of the treating physician to follow a specific regimen or treat patients on an as-needed basis.

All data were analyzed using the SPSS ver. 11.5 (SPSS Inc., Chicago, IL, USA). BCVA measurements were converted to logMAR equivalents for statistical analysis. Pearson chi-square test was used for comparative analyses of categorical variables. The independent sample *t*-test and paired *t*-test were employed to analyze changes in BCVA and CFT. One-way analysis of variance (post-hoc Tukey) was used to assess variations among the three groups. For all statistical tests, *p* < 0.05 was considered significant.

Results

One hundred thirty-four eyes of 134 patients with a minimum follow-up period of six months were included in the study. The mean follow-up time was 9.4 ± 3.4 months (range, 6 to 24 months). Of the 134 patients, 69 (51.5%) were female, and 65 (48.5%) were male. The mean age was 61.4 ± 9.2 years (range, 44 to 81 years). The baseline demographic and clinical properties of the patients in each group are summarized in Table 1. The three groups did not

Table 1. Demographic and clinical properties of the study groups

	SRD (n = 46)	DRT (n = 50)	CME (n = 38)	<i>p</i> -value
Age	59.8 ± 7.1	61.8 ± 10.4	63.0 ± 9.8	0.266
Sex (female / male)	24 / 22	27 / 23	18 / 20	0.822
Type of diabetes (type 1 / type 2)	18 / 28	20 / 30	16 / 22	0.961
Duration of diabetes	16.1 ± 5.7	14.5 ± 6.4	16.8 ± 7.2	0.214
Baseline HbA1c (%)	7.6 ± 1.1	7.5 ± 1.3	7.8 ± 0.9	0.560
PRP (yes / no)	38 / 8	37 / 13	26 / 12	0.311
MGL or focal laser (yes / no)	19 / 27	20 / 30	16 / 22	0.979
Mean number of intravitreal injections	4.2 ± 1.5	4.5 ± 1.5	4.4 ± 1.4	0.477
Lens (phakic / pseudophakic)	40 / 6	44 / 6	32 / 6	0.871
Rise in IOP	3 / 46	2 / 50	2 / 38	0.857

SRD = serous retinal detachment; DRT = diffuse retinal thickness; CME = cystoid macular edema; HbA1c = glycated haemoglobin; PRP = panretinal photocoagulation; MGL = macular grid laser; IOP = intraocular pressure.

Table 2. Pre-injection and post-injection measurements of BCVA (logMAR)

	Pre-injection BCVA	Post-injection BCVA	Change	<i>p</i> -value*
Serous retinal detachment	0.57 ± 0.32	0.56 ± 0.14	0.01 ± 0.0.7	0.252
Diffuse retinal tickness	0.63 ± 0.18	0.47 ± 0.24	0.16 ± 0.22	0.252
Cystoid macular edema	0.62 ± 0.11	0.48 ± 0.12	0.14 ± 0.10	<0.001
<i>p</i> -value [†]	0.063	<0.001	<0.001	

BCVA = best-corrected visual acuity; logMAR = logarithm of the minimum angle of resolution.

*Paired *t*-test; [†]One-way ANOVA (post-hoc Tukey).

Table 3. Pre-injection and post-injection CFT measurements

	Pre-injection CFT	Post-injection CFT	Change	<i>p</i> -value*
Serous retinal detachment	538.2 ± 163.9	382.3 ± 101.5	-155.9 ± 152.8	<0.001
Diffuse retinal thickness	531.2 ± 158.8	356.2 ± 88.7	-174.9 ± 160.2	<0.001
Cystoid macular edema	492.0 ± 145.4	326.5 ± 95.4	-165.5 ± 134.3	<0.001
<i>p</i> -value [†]	0.362	0.030	0.825	

CFT = central foveal thickness.

*Paired *t*-test; [†]One-way ANOVA (post-hoc Tukey).

differ significantly in terms of age and gender ($p = 0.266$ and $p = 0.822$ respectively). Table 2 and 3 summarize the BCVA (logMAR) and SD-OCT measurement data before and after the injection. Pre-injection mean BCVA did not differ significantly between groups ($p = 0.063$). The difference between mean pre-injection CFT values of the three groups was also not statistically significant ($p = 0.362$). When the pre-injection and post-injection data were compared within each group, increases in the BCVA were statistically significant in the DRT and CME groups ($p < 0.001$ and $p < 0.001$, respectively), but was not significant in the SRD group ($p = 0.252$). However, the mean CFT values significantly decreased in all three groups ($p < 0.001$). There was also a statistically significant difference between groups in terms of postoperative BCVA ($p < 0.001$). The three groups showed no significant variation in post-injection CFT ($p = 0.825$). In the SRD group, 34.8% (16 / 46) had visual improvement; 45.7% (21 / 46) had the same BCVA at the last visit as at preinjection; and 19.6% (9 / 46) of the patients demonstrated deterioration of BCVA at the last visit compared with the pre-injection BCVA. In the DRT group, 80% (40 / 50) experienced visual improvement; the BCVA was the same as the pre-injection BCVA at the last visit in 8.0% (4 / 50); and 12.0% (6 / 50) showed deterioration of the BCVA at the last visit compared with

pre-injection BCVA. In the CME group, 78.9% (30 / 38) displayed visual improvement; 13.2% (5 / 38) had no change in BCVA at the last visit; and 7.9% (3 / 38) experienced deterioration in BCVA at the last visit compared with pre-injection BCVA. A decrease $>50 \mu\text{m}$ in the CFT was accepted as a decreased CFT, while any change $\leq 50 \mu\text{m}$ was accepted as no change in CFT. An increase $>50 \mu\text{m}$ was defined as an increased CFT. In the SRD group, 71.7% (33 / 46) had a decreased CFT, while 80% (40 / 50) in the DRT group and 81.6% (31 / 38) in the CME group experienced a decreased CFT. Fig. 2 shows the results of all three groups with regard to the change in CFT. We also evaluated the improvement rates of BCVA in eyes with a decreased CFT. In the SRD group, 39.4% of eyes with a decreased CFT also demonstrated improvement in the BCVA; these rates were 82.9% and 74.2% in the DRT and CME groups, respectively (Fig. 3).

Shifts in the pathomorphology of the macular edema were assessed in each subgroup. In the DRT group, 48.0% (24 / 50) of the eyes became dry with no or minimal fluid, and 16.0% (8 / 50) retained DRT morphology; 28% became CME (14 / 50), while only 8% (4 / 50) were found to have SRT. In the CME group, 63.2% (24 / 38) of the eyes developed dryness, 36.8% (14 / 38) continued to have CME, and no patient was found to have SRD or DRT. For the SRD

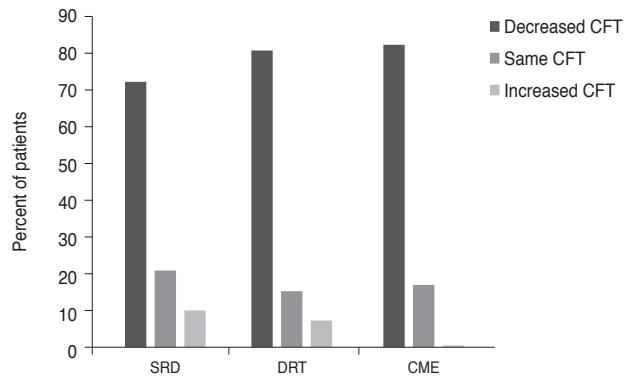


Fig. 2. Central foveal thickness (CFT) changes of the groups. SRD = serous retinal detachment; DRT = diffuse retinal thickness; CME = cystoid macular edema.

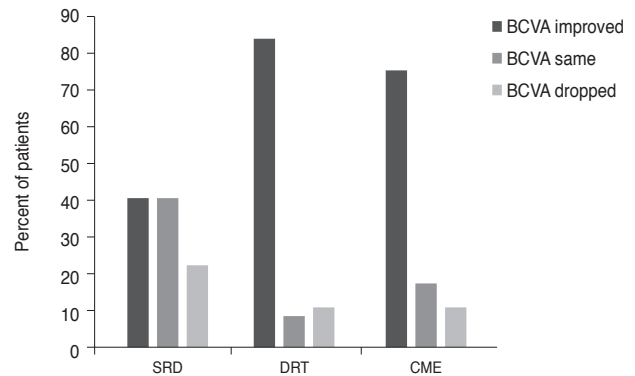


Fig. 3. Results of best-corrected visual acuity (BCVA) in eyes with decreased diabetic macular edema. SRD = serous retinal detachment; DRT = diffuse retinal thickness; CME = cystoid macular edema.

group, 21.7% (10 / 46) of the eyes became dry, 19.6% (9 / 46) and 17.4% (8 / 46) of the eyes converted to having DRT and CME, respectively, while 41.3% (19 / 46) remained with SRD.

An analysis of the outer retinal structures (including the external limiting membrane [ELM] and inner segment ellipsoidal band layer [previously known as the boundary of the inner segment and outer segment junction]) was carried out; ELM was found to be disrupted in 12 eyes (26%) in the SRD group, 6 eyes (12%) in the DRT group, and 6 eyes (15.8%) in the CME group. The ellipsoidal layer was disrupted in 10 eyes (21.7%) in the SRD group, 7 eyes (14%) in the DRT group, and 5 eyes (13.2%) in the CME group. In the DRT and CME groups, patients with an intact ELM and integrity of the ellipsoid zone layer showed significant visual improvement post-injection compared with eyes with disruptions of the ELM and the ellipsoid zone layer ($p = 0.004$ and $p = 0.008$, respectively). However, in the SRD group, patients with ellipsoid zone and ELM disruption experienced poorer visual gains at the last follow-up visit ($p < 0.005$ and $p = 0.002$, respectively).

No inflammation or severe decreases in vision immediately following the injection were noted, although 7 (5.2%) eyes (3 in the SRD group, 2 in the DRT group, and 2 in the CME group) showed elevated IOP. These cases were managed with conservative medical treatment. At the final follow-up, no ocular or systemic adverse events, such as thromboembolic events (cerebrovascular accidents, transient ischemic attacks, myocardial infarctions, or peripheral vascular diseases), were reported.

Discussion

The main cause of vision impairment in diabetic patients is DME. A large epidemiological study indicated that macular edema was present in 15% of patients with diabetic retinopathy [16]. The pathogenesis of DME is complex and multifactorial. Disruption of the inner and outer blood-retinal barriers leads to abnormal inflow of fluid into the neurosensory retina that exceeds the outflow, producing intraretinal and subretinal fluid accumulation [2,3]. However, the specific details of the pathogenesis of DME remain unclear. Classification of DME according to the SD-OCT findings might be helpful to obtain more information about the pathogenesis of DME. The first SD-OCT classification of DME was reported by Otani et al. [6]. Although various patterns of DME have been recognized on SD-OCT, few published studies have reported the visual outcomes for these SD-OCT patterns in DME patients treated with anti-VEGF therapy. Kim et al. [17] concluded that the intravitreal injection of bevacizumab was more effective in the DRT type than in the CME or SRD types of DME. Wu et al. [18] found that patients with cystoid changes gained greater improvements in visual acuity and macular thickness and volume after intravitreal bevacizumab injection. However, Koytak et al. [14] stated that there was no statistically significant variation between focal, cystoid, and neurosensory detachment groups regarding changes in BCVA after injection of intravitreal bevacizumab.

Shimura et al. [19] reported that the foveal thickness in all patterns was reduced, but the reduction ratios in the DRT and CME groups were significantly greater than that

seen in the SRD group following intravitreal bevacuzimab injection. Similarly, improvement in visual acuity in the DRT and CME groups was significantly greater than that in the SRD group; therefore, it was concluded that the effectiveness of intravitreal bevacuzimab injection in reducing macular edema varied depending on the SD-OCT pattern and was greatest in the DRT group, intermediate in the CME group, and weakest in the group with the SRD pattern. In our study, the pre-injection BCVA and CFT values were similar in all three groups. The observed decrease in CFT at the last follow-up visit was not statistically significant between the three groups, whereas the improvement in BCVA was statistically worse in the SRD group compared with the DRT and CME groups. The ELM and ellipsoid zone integrities were significantly correlated with post-treatment visual acuity and were significantly lower in the SRD type than in the other types. In eyes with SRD, outer retinal structures were found to be associated with poor visual recovery. In our series, 34 of 41 DRT eyes (82.3%) with a decrease $>50 \mu\text{m}$ also showed improvement in BCVA. In the CME group, 23 of 31 (74.2%) eyes with a decrease $>50 \mu\text{m}$ demonstrated improvement in BCVA. However, in the SRD group, only 13 of 33 (39.4%) eyes with a decrease $>50 \mu\text{m}$ experienced an improvement in BCVA. In 2016, Seo et al. [20] reported that vision gains and retinal anatomy improvement were maintained in all three types during the first year of IVR administration, which is in agreement with our study findings. Additionally, the BCVA of SRD (20 / 60) patients was significantly worse than that of the other types (DRT = 20 / 38; CME = 20 / 43) after 12 months. In contrast, Giocanti-Auregan et al. [21] found in 2017 that similar BCVA gains were observed regardless of the presence of SRD. The higher visual gain usually observed in DME with SRD could be associated with a lower baseline BCVA.

The pathogenesis of DRT involves the persistent breakdown of the inner blood retinal barrier from the loss of anchor proteins in the tight junctions of the capillary endothelial cells [22]. Vascular endothelial growth factor is a pluripotent growth factor that acts as an endothelial cell-specific mitogen and vasopermeability factor and thus plays a critical role in promoting angiogenesis and vascular leakage [23-25]. Therefore, IVR reduces hypervasopermeability, leading to a reduction of DRT. Although the pathogenesis of CME remains unknown, the reduction of CME seen with intravitreal bevacuzimab and IVR injections

suggests that CME formation is partly dependent on VEGF. The pathogenesis of SRD associated with DME occurs due to transient migration of fluid from the cystoid spaces in the retina to the subretinal space [7]. Another theory is that SRD occurs subsequent to failure of the retinal pigment epithelium (RPE) pump mechanism [26]. The breakdown of the RPE pump or disruption of the tight junctions between adjacent RPE cells results in intraretinal edema and SRD [27-29]. IVR may have little efficacy in the regression of diabetes-induced RPE impairment, which suggests that VEGF is not primarily responsible for SRD formation in DME.

In conclusion, the visual improvement noted in DME eyes with SRD was lower than that experienced by eyes with DRT and CME. Disruption of the photoreceptor integrity was correlated with a poorer visual outcome and appeared more frequently in the SRD group. Based on our findings, we believe that different treatment modalities should be considered for DME with SRD. More prospective studies are warranted to better understand the pathogenesis of DME.

Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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