Optical coherence tomography patterns of diabetic macular edema and treatment response to bevacizumab: a short-term study

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Abstract

Background: The purpose of this study was to evaluate the short-term response of intravitreal bevacizumab in diabetic macular edema (DME) and assess the variation in treatment outcomes in different morphology patterns using spectral domain–optical coherence tomography (SD-OCT).

Objective: To study different morphological patterns of DME based on OCT and compare their treatment response to bevacizumab.

Methods: Hundred and twelve eyes of 112 patients with DME were included and treated with intravitreal bevacizumab (1.25 mg/0.05 ml monthly for 3 months). The morphological patterns of DME were classified on the basis of OCT into three groups – diffuse retinal thickening (DRT), cystoid macular edema (CME), and serous retinal detachment (SRD) – and changes in central macular thickness (CMT) and best corrected visual acuity (BCVA) after treatment were compared.

Results: A total of 112 eyes with DME were included and consisted of 40 DRT, 37 CME, and 35 SRD. Treatment with bevacizumab resulted in decrease in central macular thickness and improvement in BCVA in all three groups. The baseline visual acuity and CMT of DRT group was better than that of the other two groups. The treatment outcome was measured in terms of CMT and BCVA. Change in CMT was statistically significant among three groups and was found to be better in DRT group ($p < 0.05$, 95% confidence interval). However, there was statistically no significant variation between the three groups regarding the change in BCVA ($p = 0.169$, 95% confidence interval).

Conclusion: Anatomic and visual improvement can be achieved by bevacizumab in all patterns of DME. However, individual pattern may respond differently. DRT, which appears to be the earliest form of DME, responds better than other types. Thus, the pattern of macular edema shown by OCT may provide an objective guideline in predicting the response of bevacizumab injection in DME.

Keywords: bevacizumab, diabetic macular edema, OCT

Introduction

Diabetic macular edema (DME) is one of the major causes of visual impairment in patients with diabetic retinopathy and can affect up to 15% of patients 20 years since diagnosis.[1] The alteration of blood–retinal barrier (BRB) in diabetic retinopathy leads to disruption of normal balance between inflow and outflow of fluid and thus causes accumulation of fluid in intraretinal and subretinal layers.

Multifactorial mechanisms may be responsible for the alteration of BRB, mainly the changes in cellular junctions, thickening of capillary basement

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membrane, loss of pericytes and endothelial cells, altered leucocyte function, and vitreoretinal traction.[2,3] Inflammatory response is initiated, and inflammatory mediators are secreted causing cellular hypoxia which leads to secretion of various growth factors and activation of oxidative stress reactants.[4]

Among the growth factors, vascular endothelial growth factor (VEGF) plays an important role in the development of changes in the vascular permeability, disruption of the BRB, and the induction of angiogenesis.[5]

Currently, principal techniques used in the diagnosis of DME are optical coherence tomography (OCT) and fundus fluorescein angiography (FFA). FFA is important for determining the presence of retinal ischemia, but is an invasive procedure with possible severe adverse effects. Thus, in clinical practice, OCT is the most commonly used technique for follow-up and determining treatment response.[5]

OCT can be used to assess qualitative data like macular morphology and vitreo-macular interface abnormalities, and quantitative data like macular thickness and macular volume, and thus helps to correlate macular thickness with visual acuity. As final visual acuity in DME is closely associated with integrity of inner segment–outer segment (IS/OS) junction and external limiting membrane (ELM),[6] evaluation of outer retinal layers with OCT is important in predicting the final visual outcome.

Different patterns of fluid accumulation have been reported in studies using OCT. Otani described three patterns of macular edema: diffuse retinal thickening (DRT), cystoid macular edema (CME), and serous retinal detachment (SRD).[7] DRT is caused by intracytoplasmic swelling of Müller cells in the outer plexiform layer or Henle fiber layer. Prolonged edema leads to liquefactive necrosis of the Müller cells with formation of cystoid cavities causing CME whereas SRD is the accumulation of fluid in the subfoveal layer.[8]

Along with other factors, morphological subtypes of macular edema could be one of the important factors for the variations of treatment response among patients with DME. The purpose of this study was to assess the variations among the different subgroups.

Methods

A hospital-based prospective study was conducted at a tertiary eye center (B.P. Koirala Lions Center for Ophthalmic Studies, Institute of Medicine, Maharajgunj, Kathmandu, Nepal) from January 2017 to June 2018. Exclusion criteria were (1) intraocular surgery, intravitreal injections, or focal/grid laser within 3 months of commencement of the study; (2) loss of vision/macular edema due to reason other than diabetes; (3) eyes with poor-quality OCT scans or any other process that prohibited proper interpretation; and (4) cases with vitreo-macular traction (VMT) or traction in macula.

For each patient, the CMT was measured using a spectral domain–optical coherence tomography (SD-OCT) (OCT SPECTRALIS, Heidelberg Engineering, Heidelberg, Germany) by a single experienced operator.

Patients were treated with intravitreal bevacizumab (Avastin, Roche, Manheim, Germany) 1.25 mg in 0.05 ml in the operating room. Under sterile conditions, bevacizumab was injected into the vitreous cavity using a 30 G needle through pars plana, 3.5–4.0 mm posterior to limbus.

Injections were repeated monthly for 3 months, and patients were followed at 4, 8, and 12 weeks. On every follow-up, detailed examination was done including best corrected visual acuity (BCVA), intraocular pressure (IOP), dilated fundus examination, and OCT macula.

Eyes were divided into three groups on the basis of OCT morphology of macular edema – DRT, CME, and SRD. If DRT and CME coexisted, the predominant pattern in OCT image was selected. Suppose, if the OCT image showed mixed pattern of edema involving both diffuse thickening and cystoid edema, the eye was classified as DRT if DRT was predominant and vice versa. If none of the patterns appeared to be predominant, the eye was not included in the study. When serous detachment was also present with DRT or CME or both, the eye was grouped into SRD group.

Data processing and statistical analysis

Data were statistically described in terms of range, mean ± standard deviation (SD), frequencies, and percentages when appropriate. Pre-injection and post-injection BCVA and CMT in each subgroup were compared using paired *t*

Table 1. Demographic and clinical properties of the study groups.

	DRT	CME	SRD
No. of eyes	40	37	35
Age (Mean ± *SD*)	55.88 ± 7.39	55.35 ± 10.21	55.43 ± 9.68
Sex (male/female)	24/16	24/13	26/9
Laterality (right/left)	29/11	22/15	16/19
Duration of diabetes (Mean ± *SD*)	12.02 ± 5.62	10.95 ± 5.28	11.08 ± 5.08

CME, cystoid macular edema; DRT, diffuse retinal thickening; *SD*, standard deviation; SRD, serous retinal detachment.

Table 2. Change in central macular thickness (CMT) from baseline in three groups.

	Pre-injection	At 3 months	Change in CMT	*p* value
DRT	463.05 ± 86.31	251.73 ± 72.42	213.83 ± 69.47	<0.001
CME	480.97 ± 98.57	302.65 ± 73.75	183.73 ± 65.47	<0.001
SRD	504.54 ± 88.72	351.63 ± 77.74	147.20 ± 50.42	<0.001
p value	0.150	<0.001	<0.001	

CME, cystoid macular edema; CMT, central macular thickness; DRT, diffuse retinal thickening; SRD, serous retinal detachment.

test. To evaluate variations in the response of bevacizumab injection on three subgroups of DME, one-way ANOVA test was used. A p value of ≤0.05 was considered to be statistically significant.

Results

A total of 112 eyes of 112 patients were included with 40 patients in the DME group, 37 patients in the CME group, and 35 patients in the SRD group.

Baseline demographics of each treatment group are summarized in Table 1.

The influence of bevacizumab on CMT and BCVA and comparison among three groups of DME is summarized in Tables 2 and 3, respectively.

Mean CMT values were significantly reduced in all three groups ($p < 0.001$, $p < 0.001$, $p < 0.001$ in DRT, CME, and SRD group, respectively). DRT group had greater reduction in mean CMT than CME and SRD groups, and the amount of reduction was statistically significant between three groups ($p < 0.05$). In a post hoc test, change in CMT was statistically significant among DRT and SRD groups and CME and SRD groups. However, there was no significant difference between DRT and CME groups.

Pre-injection mean BCVA did not differ significantly between groups ($p = 0.009$). The mean improvement in log MAR (minimum angle of resolution) BCVA was 0.34 ± 0.25 ($p < 0.001$) in the DRT group, 0.38 ± 0.37 ($p < 0.001$) in the CME group, and 0.48 ± 0.35 ($p < 0.001$) in the SRD group. There was no statistically significant variation between the three groups regarding the change in BCVA.

No complications related to intravitreal injections occurred during the study period.

Discussion

Based on OCT, there are several classifications of DME. Our study uses the classification proposed by Otani, which classifies non-tractional DME into three types: DRT, CME, and SRD. As most

Table 3. Change in best corrected visual acuity from baseline in three groups.

	Pre-injection	At 3 months	Change in logMAR	p value
DRT	0.72 ± 0.26	0.38 ± 0.21	0.34 ± 0.25	<0.001
CME	0.84 ± 0.41	0.46 ± 0.26	0.38 ± 0.37	<0.001
SRD	0.97 ± 0.36	0.49 ± 0.19	0.48 ± 0.35	<0.001
p value	0.009	0.077	0.169	

CME, cystoid macular edema; DRT, diffuse retinal thickening; logMAR, logarithm of the minimum angle of resolution; SRD, serous retinal detachment.

of the tractional forms of DME required vitrectomy as a primary procedure, we have not included those cases in this study.

In our study, DRT was the most common OCT pattern of DME, whereas SRD was the least common, similar to findings in other studies.[8,10]

The DRT type had a better baseline BCVA and thinner CMT than the other types. The anatomical and visual outcome of anti-VEGF, visual improvement though not statistically significant, was seen better in cases of DRT in our study similar to Al Sayed *et al.*[11] and Shimura *et al.*[12] Kim *et al.*[13] also reported that the DRT type was associated with a greater improvement in visual acuity and decrease in the macular thickness than the CME and SRD types.

Conversely, in a retrospective study by Roh *et al.*,[14] they found that patients showing CME on OCT had greater improvement in visual acuity and central macular thickness after bevacizumab injection than patients with diffuse macular edema.

In some studies, patients with SRF seemed to achieve higher visual and anatomic gains.[14–16]

In a study by Koytak *et al.*,[9] no significant difference was found among the three groups in terms of visual acuity but change in CMT was comparatively lower in DRT group than in CME and SRD groups. But, only the result after a single injection of bevacizumab was taken into account in this study.

These differences could be due to differences in OCT classification of DME, frequency of injections of anti-VEGFs, and the duration of follow-up.

The pathological changes that occur during the course of DME is an initial damage, and impaired absorption of fluid by the Muller cells that causes intracytoplasmic swelling of the cells thus leads to DRT. Persistent edema is then followed by liquefaction necrosis of the Muller cells as seen by electron microscopy. This necrosis of muller cells and adjacent neural cells leads to formation of cystoid cavity in outer plexiform and inner plexiform layers in cases of CME. Also, apart from VEGF, prostaglandins and other inflammatory cytokines have an important association with CME in diabetes. Therefore, anti-VEGF alone may not have a profound effect in treating CME. The pathogenesis of fluid accumulation in SRD is mainly due to the breakdown of the outer BRB of retinal pigment epithelium (RPE) but may also occur due to the movement of fluid from the edematous retina to the subretinal space. The RPE dysfunction leads to extravasation of fluid and proteins from the retinal vessels and choroid. Thus, major role of VEGF in SRD is not proven.[17] Thus, it appears that DRT is the earliest form of DME, and VEGF has a major role in the development of edema and this explains better treatment outcome in cases of DRT.

Anti-VEGF therapy is an effective modality of treatment for DME. However, some cases appear to be refractory and often require alternative treatment measures.[18] Although DME is associated with increased VEGF level, there are also other inflammatory pathways as important as VEGF in the pathophysiology. So, anti-VEGF as a sole treatment modality may not lead to the desired outcome in all the cases. Also, anatomical improvement seen in OCT may not necessarily lead to visual improvement as one of the major OCT morphological features that have been shown to influence visual acuity is an intact IS-OS junction and ELM layer.[14] Thus, it can be said

that anatomical improvement usually correlates with functional improvement but irreversible damage to the photoreceptors may lead to permanent loss of vision and thus may not contribute to visual improvement despite decrease in the amount of edema.[19,20]

This study has few limitations. Important OCT parameters such as the IS-OS layer, ELM layer, and choroidal thickness were not evaluated, which could better explain the poor visual outcome in some cases despite the anatomical success. FFA or OCT angiography was not done in all the cases to look for macular ischemia, which could also affect the treatment outcomes. Apart from that, limited sample size and grouping method are other limitations of this study.

Thus, it is recommended that further prospective randomized controlled trial should be performed using detailed OCT morphology and FFA/OCT angiography to attain more accurate results.

Author contributions
Sadhana Sharma: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Software; Validation; Visualization; Writing – original draft; Writing – review & editing.

Pratap Karki: Conceptualization; Supervision; Validation; Visualization; Writing – review & editing.

Sagun Narayan Joshi: Conceptualization; Supervision; Writing – review & editing.

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Availability of data and materials
Datasets generated during and/or analyzed during the current study are available from the corresponding author on request.

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