

## Evaluation of Optical Coherence Tomography Angiography Parameters following Intravitreal Ranibizumab Biosimilar in Diabetic Macular Oedema

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### ABSTRACT

**Introduction:** Ranibizumab biosimilar (RbB) has emerged as a cost-effective treatment modality. There is paucity of literature on optical coherence tomography angiography (OCTA) parameters following use of RbB in DME.

**Objective:** To evaluate OCTA parameters following intravitreal ranibizumab RbB in DME.

**Methodology:** In an interventional study on treatment naïve eyes having DME, ocular examination for best-corrected visual acuity (BCVA), intraocular pressure (IOP), colour vision (CV) and contrast sensitivity (CS) was done. Further, optical coherence tomography (OCT) measured central foveal thickness (CFT). The OCTA imaging examined the foveal avascular zone (FAZ) and vessel density (VD) in six layers, including superficial capillary plexus (SCP), deep capillary plexus (DCP), outer retina (OR), outer retinal chorio-capillaries (ORCC), chorio-capillaries (CC) and choroid (C). Serum vascular endothelial growth factor-A (VEGF-A) levels were measured using an enzyme-linked immunosorbent assay (ELISA). One month after 0.5 mg/0.05 ml intravitreal injection of RbB, pre- and post-treatment parameters were compared.

**Result:** The study involved 44 eyes of 30 DME patients having a mean age of 56.0±8.66 years. The mean serum VEGF A levels were 539.11±336.44 pg/ml. Following treatment, the mean CFT reduced from 461.50±173.06 to 348.09±153.02 microns (p < 0.001). Distance BCVA improved significantly from a logMAR of 0.88±0.13 to 0.58±0.23 (p < 0.001). The mean FAZ area, perimeter and circularity reduced from 0.21±0.21mm<sup>2</sup>, 2.43±1.32 mm, and 0.38±0.11 to 0.16±0.15 mm<sup>2</sup> (p = 0.32), 2.32±1.27 mm (p = 0.71) and 0.36±0.12 (p = 0.47) respectively. The mean VD in SCP was 19.70±12.78, DCP 5±8.15, OR 1.80±3.91, ORCC 16.48±14.82, CC 9.11±11.44 and choroid was 20.09±18.06, and this increased to 23.63±17.62 (p = 0.24), 5.93±6.97 (p = 0.52), 2.77±4.97 (p = 0.08), 27.14±16.19 (p = 0.001), 17.60±15.64 (p = 0.002) and 29.05±17.95 (p = 0.011) respectively.

**Conclusion:** Treatment with a single injection of RbB significantly improved BCVA and reduced CFT in patients with DME one month after treatment. All the FAZ features, including area, perimeter and circularity, reduced, and VD across multiple retino-choroidal layers increased.

**Key words:** Diabetic macular oedema; foveal avascular zone; optical coherence tomography; optical coherence tomography angiography; ranibizumab biosimilar; vascular density.

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## INTRODUCTION

Diabetic macular oedema (DME) is primary cause of vision loss in diabetes (Cheong et al., 2020). Hyperglycaemia and subsequent oxidative stress trigger overexpression of vascular endothelial growth factor (VEGF) and inflammatory factors, such as interleukins and macrophage growth factors. The VEGF is critical mediator of physiological and pathological angiogenesis and has been shown to correlate with increased breakdown of blood retinal barrier (BRB) and severity of DME (Taylor et al., 2018).

Ranibizumab is one of the most commonly prescribed anti-vascular endothelial growth factor (anti-VEGF) for treating diabetic retinopathy (DR). It binds to three biologically active forms of VEGF-A, including VEGF<sub>165</sub>, VEGF<sub>121</sub>, and VEGF<sub>110</sub>, to interrupt interaction of VEGF with its receptors (Lowe et al., 2007). However, its high cost has become a significant concern, specifically as repeated injections must be given. Biosimilars are molecules similar to existing innovator biologic reference products with comparable pharmacokinetics, immunogenicity, safety and efficacy. Because of the use of the latest technology by biosimilar companies, these may be better than original biologics. The world's first biosimilar of Ranibizumab was developed in India to provide cost-effective treatment to patients with retinal diseases, including DME (Sameera et al., 2016).

There are a few studies on the efficacy and safety of RbB for the treatment of DME (Sameera et al., 2016; Verma et al., 2021; Sharma et al., 2018 & 2019; Gopal et al., 2020). It has been found that RbB improves visual acuity (VA), decreases

central foveal thickness (CFT), and reduces intraretinal and subretinal fluid. However, none of these studies have examined foveal avascular zone (FAZ) and vessel density (VD) changes using optical coherence tomography angiography (OCTA) following the use of RbB in subjects with DME.

The present study evaluated optical coherence tomography angiography parameters following the use of ranibizumab biosimilar (RbB) in diabetic macular oedema (DME).

## METHODOLOGY

The institutional ethical committee approved this interventional study (Reference number: F.1/IEC/MAMC/MD/MS (92/04/2022/No. 287; dated 2022/08/29). The research complied with the tenets of the Declaration of Helsinki. The study was carried out at the Department of Ophthalmology, Guru Nanak Eye Centre, affiliated with Maulana Azad Medical College, New Delhi, and involved patients with type 1 or 2 diabetes mellitus, aged 18-50 years, with diabetic macular oedema (DME). After informed written consent, treatment-naïve eyes with DME were recruited from 2022 December to 2023 December. The subjects had best corrected visual acuity of at least LogMAR 1 (6/60; 20/200). Subjects having other significant ocular or retinal diseases, especially those which affect macular perfusion and those at risk of thrombo-embolic events, were excluded from this study.

A detailed personal and family history was taken for visual complaints such as diminution of vision, defective colour vision (CV) and contrast sensitivity (CS).

The patients underwent ocular examination for VA, refractive error (RE), best corrected visual acuity (BCVA), intraocular pressure (IOP) with applanation tonometry, CV testing using Ishihara plates and Farnsworth test and CS test with Pelli Robson charts. A dilated fundus examination was performed for a colour fundus photograph and fundus fluorescein angiography (FFA). An Optical Coherence Tomography (OCT) scan (SD-OCT RTVue, Optovue Inc, Fremont, CA) of central 30 degrees around the fovea examined central foveal thickness (CFT), neurosensory detachment (NSD) and sub-foveal choroidal thickness (SFCT). The DME was diagnosed as a CFT greater than 300 microns.

A 3 x 3 mm macular OCTA scan (SD-OCT RTVue, Optovue Inc, Fremont, CA) was done before first anti-VEGF injection. The OCTA software automatically segmented the retina and choroid layers and examined the size and regularity of the foveal avascular zone (FAZ), microaneurysms and neovascularisation. The quantitative measurement was done for FAZ area, FAZ perimeter, FAZ circularity and vessel density (VD) of six retino-choroidal layers, including the superficial capillary plexus (SCP), deep capillary plexus (DCP), outer retina (OR), outer retinal chorio-capillaries (ORCC), chorio-capillaries (CC), and choroid (C).

The serum VEGF-A was estimated in a 3-millilitre blood sample obtained from venous puncture with an Enzyme Linked Immunosorbent Assay (ELISA) test using commercially available kits.

The patients received intravitreal injections of 0.5 mg/0.05 ml RbB (Razumab; Intas Pharmaceuticals Ltd., Ahmedabad, Gujarat,

India) inside the operation theatre. The injection was given about 3.5 to 4.0 mm posterior to the limbus with a 30-gauge needle. Post-operatively, tobramycin eye drops (0.3%) were given four times a day for one week. We measured the change in IOP at one day post injection and changes in visual, OCT, and OCTA parameters at one month following injection.

The primary outcome parameter was OCTA features in DME subjects. The secondary outcome parameters were BCVA and posterior segment OCT features. The pretreatment parameters were compared with post-treatment parameters at one month.

According to Elnahry and Elnahry (2021), mean VD before anti-VEGF was  $31.3 \pm 5.58$  and after anti-VEGF was  $28.8 \pm 5.18$ . For a study with 95% confidence level and 80% power, the sample size was calculated as 37 using the formula

$$N = [(Z_{\alpha} + Z_{\beta}) \sigma]^2 / \delta^2$$

$$N = [(1.96 + 0.84) 5.4]^2 / 2.5^2 = [2.8 \times 5.4]^2 / 2.5^2 = 228.6 / 6.25 = 36.57 = 37$$

$$\delta = \text{Difference between mean VD before and after anti-VEGF} = 31.3 - 28.8 = 2.5$$

$$\sigma = \text{pooled standard deviation of difference} = [5.58^2 + 5.18^2 / 2]^2 = 5.4$$

$$\text{If } p = 0.05, \text{ then } Z_{\alpha} = 1.96; \text{ if power} = 80\%, \text{ then } Z_{\beta} = 0.84$$

However, 44 eyes were enrolled for this study.

The collected data were entered in a Microsoft Excel sheet, analysed and statistically evaluated using IBM SPSS Statistics for Windows,

version 25 (IBM Corp., Armonk, N.Y., USA). The normality of each variable was assessed by using the Kolmogorov-Smirnov test. Data were presented as mean±standard deviation (SD) for the data set with normal distribution and compared using paired t-test. Data were presented as median with interquartile range for non-parametric data and compared using the Wilcoxon signed-rank test. The p-values less than 0.05 were considered statistically significant.

## RESULT

The study included 44 eyes of 30 patients, including 15 (50%) males and 15 (50%) females, with a mean age of 56.0±8.66 (40-78) years. Seven patients (23.3%) had hypertension, and five (16.6%) had cardiovascular diseases. Among 44 eyes, 22 eyes had moderate non-proliferative diabetic retinopathy (NPDR), 20 eyes had severe NPDR, and two eyes had PDR.

The mean systolic blood pressure was 132.52±16.23 mmHg, diastolic blood pressure was 78.80±10.20 mmHg, fasting blood sugar was 141.59±56.03 mg/dl, postprandial blood sugar was 191.84±73.39 mg/dl and HbA1C was 7.53±1.33%.

The subjects presented with diminution of vision, metamorphopsia and scotoma in 44 eyes, 13 eyes and four eyes, respectively. At a pre-treatment stage, the mean VA was LogMAR 0.88±0.13, the mean refractive error (RE) was -0.45±0.99 and the mean BCVA was LogMAR 0.81±0.13. The mean IOP was 15.98±1.94 mmHg and the mean CS was 1.0±0.48.

While examining CV on 1-21 Ishihara plates, only seven eyes could read all 21 plates; the

mean number of plates read at pre-treatment was 18.77±1.64. In the 22-25 plates category, 23 eyes read all four plates; a mean number of plates read at pre-treatment was 3.41±0.69. The Ishihara plates testing showed that 23 eyes had a normal colour perception (CP) while nine were protans, seven were deutans, and five eyes had red-green CV defects. The Farnsworth test showed normal CV in 14 eyes, mild tritanopia in 12, moderate tritanopia in three, severe tritanopia in 11 and deuteranopia in three eyes. Only one eye had both severe tritanopia as well as protanopia, and this patient had PDR in both eyes.

The mean CFT was 461.50±173.06 microns, and the mean SFCT was 235.02±42.86 microns. All the eyes had DME located within 300 microns of the fovea, 43 eyes had intra-retinal cysts, 43 eyes had hard exudates (HE), 18 eyes had NSD, four eyes had epiretinal membrane (ERM), four eyes had disorganised retinal inner layers (DRIL) and eight eyes had thickened posterior hyaloid (TPH).

The FFA showed findings like hyperfluorescence in the early phase suggestive of microaneurysms, stellate pooling suggestive of cystoid macular oedema and distorted and enlarged FAZ. The FFA also showed blocked fluorescence from haemorrhages, collateral vessels and hyperfluorescence at abnormal vessels and disc suggestive of neovascularisation

The OCTA showed enlarged and distorted FAZ, microaneurysms, reduced vascularity and projection artefacts from intra-retinal cysts and NSD in slabs of DCP, OR and ORCC, but none showed neovascularisation in a 3 x 3 mm macular scan. The mean FAZ area was 0.21±0.21 mm<sup>2</sup>,

the FAZ perimeter was  $2.43 \pm 1.32$  mm, and the circularity was  $0.38 \pm 0.11$ . The mean VD in SCP whole was  $19.70 \pm 12.78$ , DCP whole  $5 \pm 8.15$ , OR whole  $1.80 \pm 3.91$ , ORCC whole  $16.48 \pm 14.82$ , CC whole  $9.11 \pm 11.44$  and choroid whole was  $20.09 \pm 18.06$ .

One month after intravitreal injections of RbB, the parameters were measured again and compared with pre-treatment parameters.

One day after RbB injection, the mean IOP was  $12.12 \pm 2.36$  mmHg. At one month, the mean VA improved to LogMAR  $0.58 \pm 0.23$ , mean RE decreased to  $-0.33 \pm 0.73$  i.e. eyes became less myopic and mean BCVA improved to LogMAR  $0.51 \pm 0.22$ . The mean CS improved to  $1.47 \pm 0.46$ .

During the examination on 1-21 Ishihara's plates, 16 eyes could read all the 21 plates and the mean number of plates read post-treatment was  $19.64 \pm 1.43$ . In the 22-25 plate category, 34 eyes read all the four plates and the mean number of plates read at post-treatment was  $3.68 \pm 0.64$ . Among 44 eyes, 34 had a normal CP, six were protans, and four were deutans. The Farnsworth test showed normal CV in 25 eyes, mild tritanopia in nine, moderate tritanopia in nine and deuteranopia in one eye.

Following treatment, the mean CFT reduced to  $348.09 \pm 153.02$  microns and the mean SFCT reduced to  $230.40 \pm 43.30$  microns. At post-treatment, 38 eyes had cystic spaces, 42 had HE, two had ERM, two had DRIL and two had TPH.

The OCTA showed a reduction in FAZ size, dilated vessels in SCP and an improvement in vascularity of six layers while projection artefact

of cysts and NSD in DCP, OR, ORCC were still seen. The mean FAZ area was  $0.16 \pm 0.15$  mm<sup>2</sup>, the FAZ perimeter was  $2.32 \pm 1.27$  mm, and the circularity was  $0.36 \pm 0.12$ . The mean VD in SCP whole was  $23.63 \pm 17.62$ , DCP whole  $5.93 \pm 6.97$ , OR whole  $2.77 \pm 4.97$ , ORCC whole  $27.14 \pm 16.19$ , CC whole  $17.60 \pm 15.64$  and choroid whole was  $29.05 \pm 17.95$ .

The difference between values for ocular and OCT parameters after treatment have been tabulated (Table 1). For parametric data, mean  $\pm$  SD with range and for non-parametric data, median with interquartile range have been written. There was a significant improvement in distance VA, distance BCVA, CS, number of Ishihara plates read and CFT (Table 1).

The blood sample analysis at baseline showed that the mean serum VEGF A levels were  $539.11 \pm 336.44$  (51.23 to 1243.5) [median 487.94; IQR 305 to 775.52] pg/ml.

The difference between mean values for OCTA parameters after treatment has been tabulated (Table 2). Following treatment, there was an insignificant reduction in mean FAZ area, perimeter, and circularity. However, the mean values of VD of all the retino-choroidal layers improved. The difference between median values for OCTA parameters after treatment is tabulated (Table 3).

Following treatment, the median values of FAZ area, perimeter and circularity decreased, though it was insignificant. However, the median values of VD of all the retino-choroidal layers improved. Any ocular or systemic side effects after using intravitreal injection of RbB was not observed.

**Table 1: Difference between values of ocular and optical coherence tomography parameters after treatment.**

S. N.	Ocular and OCT Features	Pre-treatment mean/median (range)	Post-treatment mean/median (range)	p-value
1.	Distance VA (LogMAR)*	0.88±0.13 (0.6-1.0)	0.58±0.23 (0.2-1.0)	<0.001†
2.	Spherical equivalent of distance refractive error (Dsph)	-0.50 (-1.0 to 0.18)	-0.50 (-0.75-0.00)	0.60
3.	Distance BCVA (LogMAR)*	0.81±0.13 (0.6-1.0)	0.51±0.22 (0.2-1.0)	<0.001†
4.	IOP (mmHg)*	15.98±1.94 (12.2-21.9)	12.12±2.36 (12.2-22.40)	0.062
5.	Contrast sensitivity	0.90 (0.75-1.53)	1.65 (0.80-1.85)	<0.001†
6.	Number of Ishihara 1-21 plates read*	18.77±1.64 (15-21)	19.64±1.43 (15-21)	0.005†
7.	Number of Ishihara 22-25 plates read*	3.41±0.69 (2-4)	3.68±0.64 (2-4)	0.027†
8.	CFT (microns)	448 (323-546)	330 (244-373)	<0.001†
9.	SFCT (microns)	241 (209-254)	236 (205-259)	0.83
10.	NSD number	1 (1-1)	0 (0-1)	0.60
11.	NSD height (microns)	130 (90.5 to 154.5)	135 (79.5-290.5)	0.86
12.	NSD width (microns)	1144 (734.5-1540.5)	1031 (603.5-2088)	0.73
13.	Number of eyes with oedema within 300 microns‡	44	41	0.78
14.	Number of eyes with cysts‡	43	38	0.27
15.	Number of eyes with HE‡	43	42	0.89
16.	Number of eyes with ERM‡	4	2	0.47
17.	Number of eyes with DRIL‡	4	2	0.47
18.	Number of eyes with TPH‡	8	6	0.51

\*Parametric data; †Statistically Significant difference; ‡Parameters for which neither mean nor median values can be calculated; OCT: Optical coherence tomography; VA: Visual acuity; LogMAR: Logarithm of the Minimum Angle of Resolution; BCVA: Best corrected visual acuity; IOP: Intraocular pressure; CFT: Central foveal thickness; SFCT: Sub-foveal choroidal thickness; NSD: Neurosensory retinal detachment; HE: Hard exudates; ERM: Epiretinal membrane; DRIL: Disorganisation of retinal inner layers; TPH: Thickened posterior hyaloid.



**Table 2: Difference between mean values of OCTA parameters after treatment.**

S. N.	OCTA Features	Pre-treatment Mean±SD (Range)	Post-treatment Mean±SD (Range)	Paired t test; p- value
1.	FAZ area (mm <sup>2</sup> )	0.21±0.21 (0.02-1.08)	0.16±0.15 (0.00-0.64)	0.322
2.	FAZ perimeter (mm)	2.43±1.32 (0.68-6.07)	2.32±1.27 (0.66-5.61)	0.706
3.	FAZ circularity	0.38±0.11 (0.15-0.63)	0.36±0.12 (0.20-0.65)	0.471
4.	SCP foveal VD	6.52±8.50 (0-44)	11.58±13.86 (0-53)	0.038*
5.	SCP parafoveal VD	17.98±13.56 (0-50)	19.98±14.14 (1-49)	0.540
6.	SCP perifoveal VD	24.70±14.53 (3-53)	27.77±14.94 (0-54)	0.385
7.	SCP whole VD	19.70±12.78 (2-49)	23.63±17.62 (0-91)	0.241
8.	DCP foveal VD	1.68±4.87 (0-30)	1.60±3.38 (0-17)	0.901
9.	DCP parafoveal VD	2.95±4.75 (0-26)	4.16±5.27 (0-22)	0.221
10.	DCP perifoveal VD	7.23±10.04 (0-53)	9.12±10.27 (0-42)	0.261
11.	DCP whole VD	5±8.15 (0-46)	5.93±6.97 (0-26)	0.521
12.	OR foveal VD	2±4.88 (0-25)	3.77±7.48 (0-35)	0.017*
13.	OR parafoveal VD	2.16±5.22 (0-24)	3.21±6.31 (0-28)	0.102
14.	OR perifoveal VD	1.39±2.75 (0-11)	2.16±3.25 (0-14)	0.117
15.	OR whole VD	1.80±3.91 (0-7)	2.77±4.97 (0-22)	0.082
16.	ORCC foveal VD	14.84±17.21 (0-56)	25.93±19.72 (0-64)	0.006*
17.	ORCC parafoveal VD	15.55±15.56 (0-54)	26.74±17.14 (0-59)	0.002*
18.	ORCC perifoveal VD	18.27±14.86 (0-52)	27.47±16.41 (0-55)	0.003*
19.	ORCC whole VD	16.48±14.82 (0-53)	27.14±16.19 (0-53)	0.001*
20.	CC foveal VD	9.07±13.08 (0-47)	19.26±18.90 (0-68)	0.001*
21.	CC parafoveal VD	8.70±11.67 (0-48)	17.63±15.77 (0-54)	0.001*
22.	CC perifoveal VD	9.50±11.61 (0-47)	17.16±15.79 (0-54)	0.005*
23.	CC whole VD	9.11±11.44 (0-47)	17.60±15.64 (0-55)	0.002*
24.	Choroid foveal VD	21.84±22.56 (0-67)	29.79±19.93 (0-65)	0.079
25.	Choroid parafoveal VD	19.70±18.42 (0-56)	29.40±18.38 (0-54)	0.009*
26.	Choroid perifoveal VD	20.20±17.40 (0-51)	28.65±17.94 (0-53)	0.012*
27.	Choroid whole VD	20.09±18.06 (0-52)	29.05±17.95 (0-53)	0.011*

Whole data was non-parametric; \*Statistically significant difference; OCTA: Optical coherence tomography angiography; SD: Standard deviation; FAZ: Foveal avascular zone; VD: Vessel density; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; OR: Outer retina; ORCC: Outer retinal chorio-capillaries; CC: Chorio-capillaries.

**Table 3: Difference between median values for OCTA parameters after treatment; Whole data was non-parametric.**

S. N.	OCTA Features	Pre-treatment Median with interquartile range	Post-treatment Median with interquartile range	Wilcoxon signed Rank; p-value
1.	FAZ area (mm <sup>2</sup> )	0.17 (0.04-0.26)	0.14 (0.3-0.27)	0.59
2.	FAZ perimeter (mm)	2.40 (1.28-3.18)	2.30 (1.16-3.29)	0.85
3.	FAZ circularity	0.36 (0.30-0.47)	0.33 (0.27-0.46)	0.34
4.	SCP foveal VD	4.50 (0.25-9.0)	7 (1-20)	0.05
5.	SCP parafoveal VD	14.50 (6-27)	18 (8-29)	0.40
6.	SCP perifoveal VD	22.50 (11.50-36)	26 (15-39)	0.22
7.	SCP whole VD	16.50 (8.25-30.25)	18 (11-32)	0.20
8.	DCP foveal VD	0.00 (0.00-1.0)	0.00 (0.00-2.0)	0.50
9.	DCP parafoveal VD	2.0 (0.00-4.0)	2 (0.00-7.0)	0.06
10.	DCP perifoveal VD	4.50 (1-8.50)	5 (2.0-13.0)	0.09
11.	DCP whole VD	3 (0.00-5.75)	3 (1.0-9.0)	0.12
12.	OR foveal VD	0.00 (0.00-1.0)	0.00 (0.00-5)	0.026
13.	OR parafoveal VD	0.00 (0.00-2.0)	1 (0.00-5)	0.068
14.	OR perifoveal VD	0.00 (0.00-1.0)	1 (0.00-3)	0.055
15.	OR whole VD	0.00 (0.00-2.0)	1 (0.00-4)	0.058
16.	ORCC foveal VD	7.50 (1.0-22.25)	21 (9-42)	0.004*
17.	ORCC parafoveal VD	12.50 (2-25.75)	25 (12-40)	0.003*
18.	ORCC perifoveal VD	15 (5.25-31.75)	26 (16-41)	0.005*
19.	ORCC whole VD	13.50 (3-24.75)	30 (11-40)	0.001*
20.	CC foveal VD	2 (0.00-12.75)	13 (3-34)	0.001*
21.	CC parafoveal VD	4 (1-10)	11 (5-28)	0.002*
22.	CC perifoveal VD	5 (1-13.75)	13 (4-25)	0.005*
23.	CC whole VD	4.50 (1-12.75)	14 (6-28)	0.002*
24.	Choroid foveal VD	14.50 (0.50-39)	32 (10-45)	0.03*
25.	Choroid parafoveal VD	14.50 (3-34)	35 (15-46)	0.009*
26.	Choroid perifoveal VD	16.50 (4.25-40)	33 (13-47)	0.01*
27.	Choroid whole VD	14.50 (3-37.50)	34 (15-45)	0.01*

\*Statistically significant difference; OCTA: Optical coherence tomography angiography; FAZ: Foveal avascular zone; VD: Vessel density; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; OR: Outer retina; ORCC: Outer retinal chorio-capillaries; CC: Chorio-capillaries.

## DISCUSSION

Intravitreal anti-VEGF therapy is the standard of care for DME, and this significantly improves vision and reduces fluid in DME (Falavarjani et al., 2017). RbB comes in a single-use glass vial with a concentration of 10 mg/mL in 0.05 mL and costs 30-40% less than the reference biologic Ranibizumab (Sameera et al., 2016; Sharma et al., 2018).

Sameera et al., (2016) conducted a prospective study in 123 eyes of 95 Indian patients suffering from wet age-related macular degeneration (ARMD), DME, and retinal vein occlusion (RVO) and found that in DME, a single intravitreal RbB injection caused a significant improvement in BCVA ( $p = 0.001$ ) and CFT ( $p = 0.0001$ ) at one month. The mean IOP at baseline was  $13.64 \pm 3.07$  mmHg, increasing to  $15.1 \pm 2.0$  mmHg at one month.

Verma et al., (2021) conducted a retrospective study to analyse the data of 153 eyes of 141 patients with a mean age of  $67.01 \pm 14.13$  years. Of these 153 eyes, 121 were treatment naïve eyes; among these 121 eyes 57 eyes had DME, 55 had choroidal neovascular membrane (CNVM), and nine had ME secondary to RVO. A total of three RbB injections were received by 94 eyes, two by nine eyes, and one by 18 eyes in a pro re nata regimen. Significant improvement in mean logMAR BCVA was observed from  $0.60 \pm 0.41$  to  $0.32 \pm 0.32$  and in mean CFT from  $436.70 \pm 174.33$  microns to  $275.04 \pm 120.09$  microns in naïve DME eyes ( $p < 0.001$ ) at three months follow-up. These authors observed that even one injection was followed by a significant improvement in VA and CFT at one month.<sup>5</sup>

The developers of the RbB (Intas Pharmaceuticals Ltd.) conducted the RE-ENACT (Real-Life Clinical Effectiveness of Razumab) study on 561 patients having wet ARMD, DME, and RVO receiving monthly injections of 0.5 mg RbB over 12 weeks. At week four, an improvement of 0.36% in VA ( $p = 0.0318$ ) and 2.02% in CFT ( $p < 0.0001$ ) was found (Sharma et al., 2018).

The RE-ENACT-2 studies evaluated the same variables for 48 weeks in 341 patients with wet ARMD, DME, RVO, and myopic CNVM receiving one to five RbB injections. Out of these, 73.6% were treatment naïve. There was a significant improvement in the BCVA from logMAR  $0.89 \pm 0.6$  to  $0.43 \pm 0.3$  and in CFT from  $467.09 \pm 159.6$  to  $296.56 \pm 49.7$  microns at 12 months. The IOP reduced from  $14.92 \pm 3.4$  to  $13.89 \pm 2.2$  mmHg ( $p = 0.4307$ ) at the end of the study (Sharma et al., 2019).

In both RE-ENACT and RE-ENACT-2 studies, the authors did not give the change in parameters separately for different disease groups (Sharma et al., 2018 and 2019).

In a single-centre, retrospective observation study, Gopal et al., (2020) demonstrated that a single intravitreal RbB injection significantly improved the BCVA in 120 eyes with DME from logMAR 0.59 to 0.47 and markedly reduced the CFT from 393.49 to 321.70 microns after one month.

Sharma et al., (2020) conducted another retrospective study in 30 eyes of 20 subjects, with 13 eyes having DME. They did not see anterior and posterior segment inflammatory

reaction or a change in efficacy after switching from the biologic Ranibizumab to RbB, which was opted for by subjects due to financial reasons.

None of the above studies reported serious systemic or ocular adverse events. These studies did not measure serum VEGF-A levels. The serum VEGF A levels of  $539.11 \pm 336.44$  pg/ml found in our subjects were higher than average values (0 to 181 pg/ml) as reported in literature (Lopez et al., 2019).

Huang et al., (2021) demonstrated that VD could be used as a marker for quantifying capillary perfusion, and it has a negative relation with increasing severity of DR (Lee et al., 2016). The changes in OCTA parameters have been reported even in patients who do not have clinical signs of DR, suggesting a potential role of OCTA parameters to demonstrate early microvascular changes (Cheong et al., 2020).

A few studies evaluating OCTA changes following using other anti-VEGF in DME found that BCVA, CFT, FAZ, and VD parameters improved (Falavarjani et al., 2017; Pongsachareonnont et al., 2020; Couturier et al., 2019; Vujosevic et al., 2020; Sorour et al., 2019; Hsieh et al., 2019). However, Vujosevic et al., (2020) saw an increase in FAZ perimeter, Falavarjani et al., (2017) saw an increase in FAZ area, and Falavarjani et al., (2017) and Sorour et al., (2019) saw a reduction in VD of SCP and DCP.

This is the first detailed study for evaluating OCTA parameters following RbB injection in

DME patients. The strength of current study is that we included only treatment naïve eyes affected exclusively with DME. The limitation of our study was a smaller sample size and a shorter treatment period involving a single RbB injection and a short-term follow-up of one month. Additionally, equipment for OCTA used by us obtained only  $3 \text{ mm} \times 3 \text{ mm}$  scans.

## CONCLUSION

Similar to previous studies, it was observed that CFT and SFCT reduced, while mean BCVA improved significantly after a single RbB injection. The CFT is a significant anatomical parameter, and its normalisation was accompanied by an improvement in all visual functions, including VA, CV and CS. Among OCTA parameters, a reduction in FAZ area and perimeter was not accompanied by an improvement in the circularity index. The VD of all the retino-choroidal layers improved though it was significant in ORCC, CC and choroid. Our study demonstrates that RbB is a safe and effective low-cost therapy in patients with DME. The drug was well tolerated and had no ocular or systemic safety issues. Further studies on changes in OCTA features in DME while undergoing longer-duration treatment with RbB are recommended.

## REFERENCES

- Cheong KX, Lee SY, Ang M, et al., (2020). Vessel density changes on optical coherence tomography angiography after vascular endothelial growth factor inhibitor treatment for diabetic macular oedema. *Turkish Journal of Ophthalmology*; 50(6): 343-350. DOI: [10.4274/tjo.galenos.2020.81592](https://doi.org/10.4274/tjo.galenos.2020.81592) PMID: 33389934
- Couturier A, Rey PA, Erginay A, et al., (2019). Widefield OCT-Angiography and fluorescein angiography assessments of nonperfusion in diabetic retinopathy and oedema treated with anti-vascular endothelial growth factor. *Ophthalmology*; 126(12): 1685-1694. DOI: [10.1016/j.ophtha.2019.06.022](https://doi.org/10.1016/j.ophtha.2019.06.022).
- Elnahry AG, Elnahry GA (2021). Optical Coherence Tomography Angiography of Macular Perfusion Changes after Anti-VEGF Therapy for Diabetic Macular Edema: A Systematic Review. *Journal of Diabetes Research*; 22;2021: 6634637. DOI: [10.1155/2021/6634637](https://doi.org/10.1155/2021/6634637).
- Falavarjani KG, Iafe NA, Hubschman JP, et al., (2017). Optical coherence tomography angiography analysis of the foveal avascular zone and macular vessel density after anti-VEGF therapy in eyes with diabetic macular oedema and retinal vein occlusion. *Investigative Ophthalmology and Visual Science*; 58(1): 30-34. DOI: [10.1167/iovs.16-20579](https://doi.org/10.1167/iovs.16-20579)
- Gopal S, Kasturirangan S, Madhivanan N, et al., (2020). Clinical effectiveness and safety of razumab (a biosimilar of ranibizumab). *TNOA Journal of Ophthalmic Science and Research*; 58: 154-158. DOI: [10.4103/tjosr.tjosr\\_41\\_20](https://doi.org/10.4103/tjosr.tjosr_41_20)
- Hsieh YT, Alam MN, Le D, et al., (2019). OCT angiography biomarkers for predicting visual outcomes after ranibizumab treatment for diabetic macular oedema. *Ophthalmology Retina*; 3(10): 826-834. DOI: [10.1016/j.oret.2019.04.027](https://doi.org/10.1016/j.oret.2019.04.027)
- Huang WH, Lai CC, Chuang LH, et al., (2021). Foveal microvascular integrity association with anti-VEGF treatment response for diabetic macular oedema. *Investigative Ophthalmology and Visual Science*; 62(8): 41. DOI: [10.1167/iovs.62.9.41](https://doi.org/10.1167/iovs.62.9.41)
- Lee J, Moon BG, Cho AR, et al., (2016). Optical coherence tomography angiography of DME and its association with anti-VEGF treatment response. *Ophthalmology*; 123(11): 2368-2375. DOI: [10.1016/j.ophtha.2016.07.010](https://doi.org/10.1016/j.ophtha.2016.07.010)
- Lopez Yomayuzza CC, Preissner KT, Lorenz B, et al., (2019). Optimizing measurement of vascular endothelial growth factor in small blood samples of premature Infants. *Scientific Reports*; 9(1): 6744. DOI: [10.1038/s41598-019-43108-7](https://doi.org/10.1038/s41598-019-43108-7)
- Lowe J, Araujo J, Yang J, et al., (2007). **Ranibizumab inhibits multiple forms of biologically active vascular endothelial growth factor in vitro and in vivo.** *Experimental Eye Research*; 85(4): 425-430. DOI: [10.1016/j.exer.2007.05.008](https://doi.org/10.1016/j.exer.2007.05.008)
- Pongsachareonnont P, Charoenphol P, Hurst C, et al., (2020). The effect of anti-vascular endothelial growth factor on retinal microvascular changes in diabetic macular oedema using swept-source optical coherence tomography angiography. *Clinical Ophthalmology*; 14: 3871-3880. DOI: [10.2147/OPTH.S270410](https://doi.org/10.2147/OPTH.S270410)
- Sameera VV, Apoorva AG, Joshi S, et al., (2016). Safety and efficacy of Razumab - The new biosimilar in India: Our experience. *Kerala Journal of Ophthalmology*; 28: 180-185. DOI: [10.4103/kjo.kjo\\_18\\_17](https://doi.org/10.4103/kjo.kjo_18_17)
- Sharma A, Hafeez Faridi M, Kumar N, et al., (2020). Immunogenicity and efficacy after switching from original Ranibizumab to a Ranibizumab biosimilar: Real-world data. *Eye*;34(6):1008–1009. DOI: [10.1038/s41433-019-0745-z](https://doi.org/10.1038/s41433-019-0745-z)
- Sharma A, Reddy P, Kuppermann BD, et al., (2018). Biosimilars in ophthalmology: “Is there a big change on the horizon?” *Clinical Ophthalmology*; 12:2137-2143. DOI: [10.2147/OPTH.S180393](https://doi.org/10.2147/OPTH.S180393).
- Sharma S, Khan MA, Chaturvedi A and RE-ENACT Study Investigators Group (2018). Real-life clinical effectiveness of Razumab® (world’s first biosimilar ranibizumab) in wet age-related macular degeneration, diabetic macular oedema, and retinal vein occlusion: A retrospective pooled analysis. *International Journal of Ophthalmology and Eye Science*; 6 (4): 377-383. DOI: [10.19070/2332-290X-1800076](https://doi.org/10.19070/2332-290X-1800076)



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Sharma S, Khan MA, Chaturvedi A and RE-ENACT Study Investigators Group (2019). A multicentre, retrospective study (RE-ENACT 2) on the use of Razumab™ (World's First Biosimilar Ranibizumab) in Wet AMD, DME, RVO and Myopic CNV. *Journal of Clinical and Experimental Ophthalmology*; 10 (5): 826. DOI: [10.4172/2155-9570.1000826](https://doi.org/10.4172/2155-9570.1000826)

Sorour OA, Sabrosa AS, Yasin Alibhai A, et al., (2019). Optical coherence tomography angiography analysis of macular vessel density before and after anti-VEGF therapy in eyes with diabetic retinopathy. *International Ophthalmology*; 39(10): 2361-2371. DOI: [10.1007/s10792-019-01076-x](https://doi.org/10.1007/s10792-019-01076-x)

Taylor SC, Montana C, Shah M, Agarwal A, (2018). Diabetic macular oedema. In Kumar A, ed. *Retina Medical & Surgical Management*. First Edition. New Delhi, India: Jaypee Brothers Medical Publishers (P) Ltd., Ch. 28.

Verma L, Thulasidas M, Purohit A, et al., (2021). Clinical efficacy and safety of Razumab® (CESAR) study: Our experience with the world's first biosimilar Ranibizumab. *Indian Journal of Ophthalmology*; 69 (2): 347-351. DOI: [10.4103/ijo.IJO\\_2516\\_20](https://doi.org/10.4103/ijo.IJO_2516_20)

Vujosevic S, Toma C, Villani E, et al., (2020). Diabetic macular oedema with neuroretinal detachment: OCT and OCT-angiography biomarkers of treatment response to anti-VEGF and steroids. *Acta Diabetologica*; 57(3): 287-296. DOI: [10.1007/s00592-019-01424-4](https://doi.org/10.1007/s00592-019-01424-4).

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