Systemic Biomarkers Predictive of Anatomical and Functional Outcomes of Macular Edema Secondary to Retinal Vein Occlusion Following a Single Injection of Intravitreal Bevacizumab

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ABSTRACT

Introduction: Macular edema (ME) secondary to retinal vein occlusion (RVO) is a leading cause for visual impairment.

Objective: To identify the systemic biomarkers that influence the anatomical and functional outcomes of a single injection of intravitreal bevacizumab (IVB) for RVO related macular edema ME.

Methodology: A prospective interventional study was conducted on patients with treatment naïve RVO induced ME, from November 2019 to April 2021 after ethical approval. All participants underwent a complete systemic evaluation consisting of blood pressure measurement, blood sugar, glycosylated hemoglobin, hemoglobin, total and differential cell counts, lipid profile and renal function tests at baseline. IVB was administered for RVO induced ME. Anatomical outcome was measured as change in macular thickness from baseline to one month after treatment on optical coherence tomography and functional outcomes were improvement in visual acuity.

Result: Median best corrected visual acuity improved from 0.56±0.39 to 0.4±0.4 LogMAR ($p < 0.001$) with significant reduction in mean central retina thickness (CRT) from 609.9±216.5 µ to 337.6±168.2 µ ($p < 0.001$) at one month. On evaluating systemic parameters, longer duration of hypertension ($r = -0.2795$, $p = 0.037$), and those with higher eosinophil count ($r = -0.2595$, $p = 0.025$) were less likely to have a reduction in CRT. Higher HDL levels ($r = 0.2505$, $p = 0.031$) and better RBC counts ($r = 0.2732$, $p = 0.016$) were more likely to be predictive of a better reduction of CRT.

Conclusion: Patients with RVO related ME can experience visual improvement and reduction in edema at initiation of treatment. Systemic biomarkers correlating to those for cardiovascular morbidity influence outcomes of ME. Optimum management of these modifiable systemic biomarkers can enhance treatment outcomes.

Key words: Bevacizumab; eosinophil; hypertension; macular edema; retinal vein occlusion.

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INTRODUCTION

Retinal vein occlusion (RVO) is the second most common vascular disorder of the retina (Ip et al, 2018). It is broadly classified into central retinal vein occlusion (CRVO) and branched retinal vein occlusion (BRVO),(Ip et al, 2018). Systemic risk factors for RVO include hypertension, diabetes mellitus, hyperlipidemia, hyper-homocysteinemia and other disorders of coagulation. Metabolic syndrome (hypertension, diabetes mellitus and hyperlipidemia) is an important risk factor for RVO (Cho et al, 2019, Ip et al, 2018).

Acute vision loss in RVO is secondary to macular edema (ME) driven by vascular endothelial growth factor (VEGF). The gold standard for management of ME is intravitreal injection of anti-VEGF agents (bevacizumab, ranibizumab, or aflibercept) (Boyer et al, 2012, Brown et al, 2010, Campochiaro et al, 2010). Intravitreal bevacizumab (IVB) is commonly used as an off-label anti-VEGF agent for management of RVO related ME, primarily as it is the most economical of all the agents available. Outcomes have been comparable between ranibizumab and bevacizumab in management of RVO related ME (Wolf-Schnurrbusch et al, 2011). In SCORE 2 trial it was observed that intravitreal bevacizumab was noninferior to aflibercept in patients with ME secondary to central retinal vein occlusion, with respect to visual acuity after 6 months of treatment (Scott et al, 2017).

The management of ME secondary to RVO is well established, as are the systemic associations with RVO. There is paucity of literature on systemic biomarkers that can influence the response to treatment. The purpose of this study was to determine the systemic biomarkers that correlate to the anatomical and functional response to treatment with a single dose of bevacizumab injection. The anatomical response to treatment was determined by measuring various structural parameters on OCT, and functional response by change in visual acuity.

METHODOLOGY

This prospective interventional study was approved by the institutional ethics committee and adhered to the tenets of the declaration of Helsinki. This single center study was conducted at the retina clinic of a tertiary eye care hospital in South India. Patients who presented to the retina clinic from November 2019 to April 2021 and were diagnosed to have treatment naive macular edema secondary to RVO were included in the study. Written informed consent was obtained from all participants for the off-label use of IVB as well as for study participation.

Basic demographic data collected included age, gender, occupation, and duration of symptoms. A detailed history of any systemic comorbidities including diabetes, hypertension, dyslipidemia, renal failure, stroke, or cardiovascular event was recorded. Those with a history of cardiovascular event or stroke were eligible to receive anti-VEGF injection only if a duration of more than six months had elapsed since the event, and after consultation and approval from treating physician. Systolic and diastolic blood pressure was measured by trained paramedical personnel. A complete hematological work-up that included blood sugar, glycosylated hemoglobin, hemoglobin, total and differential cell counts, lipid profile and renal function tests was done for all participants.

All participants underwent a complete ocular examination including recording of uncorrected visual acuity (UCVA) and best corrected visual acuity (BCVA), intraocular pressure measurement and anterior segment examination by slit lamp biomicroscopy. Fundus examination was done by slit lamp biomicroscopy using a 90D or 78D lens and indirect ophthalmoscopy with a 20D lens, by a fellowship trained vitreo-retinal surgeon. All the patients underwent enhanced depth optical coherence tomography (EDI-OCT) (Heidelberg Spectralis, Heidelberg Engineering, Germany) at baseline. All the patients with ME were treated with IVB (1.25mg in 0.05ml) under aseptic precautions. The ocular work-up was repeated at one month post injection visit. Although this study involves assessment of patient following a single injection, treatment was continued as per the standard treatment protocol for anti-VEGF injections. No serious ocular or systemic side effects secondary to bevacizumab were observed during the study period.

The EDI-OCT was analyzed by a single grader (ST). OCT features evaluated included central retinal thickness (CRT) pre & post injection, presence of subretinal fluid (SRF) and change in its height, presence of intraretinal fluid (IRF), hyperreflective foci (HRF), and sub foveal choroidal thickness (SFCT).

Primary outcome measure was correlation of reduction in central macular thickness with systemic biomarkers. Secondary outcome measures included visual improvement and change in OCT biomarkers like resolution of sub retinal fluid, reduction in IRF, and change in SFCT as well as HRF. For comparative analysis the eyes were subdivided into two subgroups- those with BRVO and those with CRVO. Eyes with hemi-central vein occlusion were included in the CRVO group, while those with tributary vein occlusion were included in the BRVO group.

Based on previous study by Brown et al (Brown et al., 2010) and considering mean ±SD difference of CRT to be 452.30±260.03 μ with 10% precision and 95% confidence interval, sample size was calculated to be 127 subjects to measure changes in CRT after a single intravitreal anti-VEGF injection.

Mean ±SD and frequency (percentage) was used to describe the summary data. Categorical variables (SRF and VR interface changes) were compared by Fisher's exact test/Chi-square test. Mean difference between pre and post treatment of the continuous variables (CRT, SRF changes, IRF changes, SFCT, and HRF changes) were compared by paired t test/Wilcoxon signed rank test. All the statistical analyses were performed by STATA 14.0 (Texas). p-value less than 0.05 was considered as statistically significant.

RESULT

The study included 127 participants, of whom 83 (65.4%) had BRVO and 44 (34.6%) had CRVO. The mean age of the patients was 58.8±11.8 years with a male preponderance (n = 78[61.4%]). Right eye was more commonly involved. The mean duration of defective vision was 8.3 ±10.9 weeks, with a majority of patients presenting with defective vision of one month to three months (entire cohort n = 57, 44.8%; CRVO n = 15, 34%; and BRVO n = 42, 50.6%) (Table 1).

Table 1: Demographic profile of patients receiving intravitreal bevacizumab for retinal vein occlusion.

		RVO ENTIRE COHORT (n = 127)	CRVO (n = 44)	BRVO (n = 83)
Age in years (Mean ±SD)		58.8 ±11.8	60 ±13	58.2 ±11.1
Gender n (%)	Male	78 (61.4)	25 (56.8)	53 (63.9)
	Female	49 (38.6)	19 (43.2)	30 (36.1)
Occupation n (%)	Physical	10 (7.9)	5 (11.4)	5 (6)
	Sedentary	117 (92.1)	39 (88.6)	78 (94)
RE n (%)		69 (52.8)	23 (52.3)	46 (55.4)
Defective vision duration in weeks Mean ±SD)		8.3 ±10.9	10.1 ±12.9	7.4 ±9.6

RVO- Retinal vein occlusion, CRVO- central retinal vein occlusion, BRVO- branch retinal vein occlusion, SD - standard deviation; RE - right eye

The mean UCVA improved from 0.78±0.36 LogMAR at baseline to 0.63±0.4 LogMAR (p <0.001) at one month after treatment. In those with CRVO the mean UCVA improved from 1±0.4 to 0.8±0.5 LogMAR (p = 0.007) while among those with BRVO the mean UCVA improved from 0.7±0.3 to 0.5±0.3 LogMAR (p <0.001). There was also a significant improvement in BCVA for the cohort from 0.56 ±0.39 at baseline to 0.4 ±0.4 LogMAR (p <0.001) at one month after treatment. Among CRVO patients, BCVA improved from 0.8±0.4 to 0.6±0.5 LogMAR (p = 0.001) while among BRVO patients, BCVA improved from 0.4±0.3 to 0.3±0.3 LogMAR (p <0.001) as shown in Figure 1. A lesser duration of defective vision was associated with more improvement in BCVA in the entire cohort (p = 0.2), CRVO (p = 0.31) and BRVO (p = 0.47), but the association was not statistically significant.

Patients with CRVO showed greater CRT at baseline (mean 700.0±271.4) than those with BRVO (mean 562.2±163.4). The entire cohort showed significant reduction in mean CRT from 609.9±216.5 µ at baseline to 337.6±168.2 µ (p <0.001) at one month after treatment as shown in Figure 2.

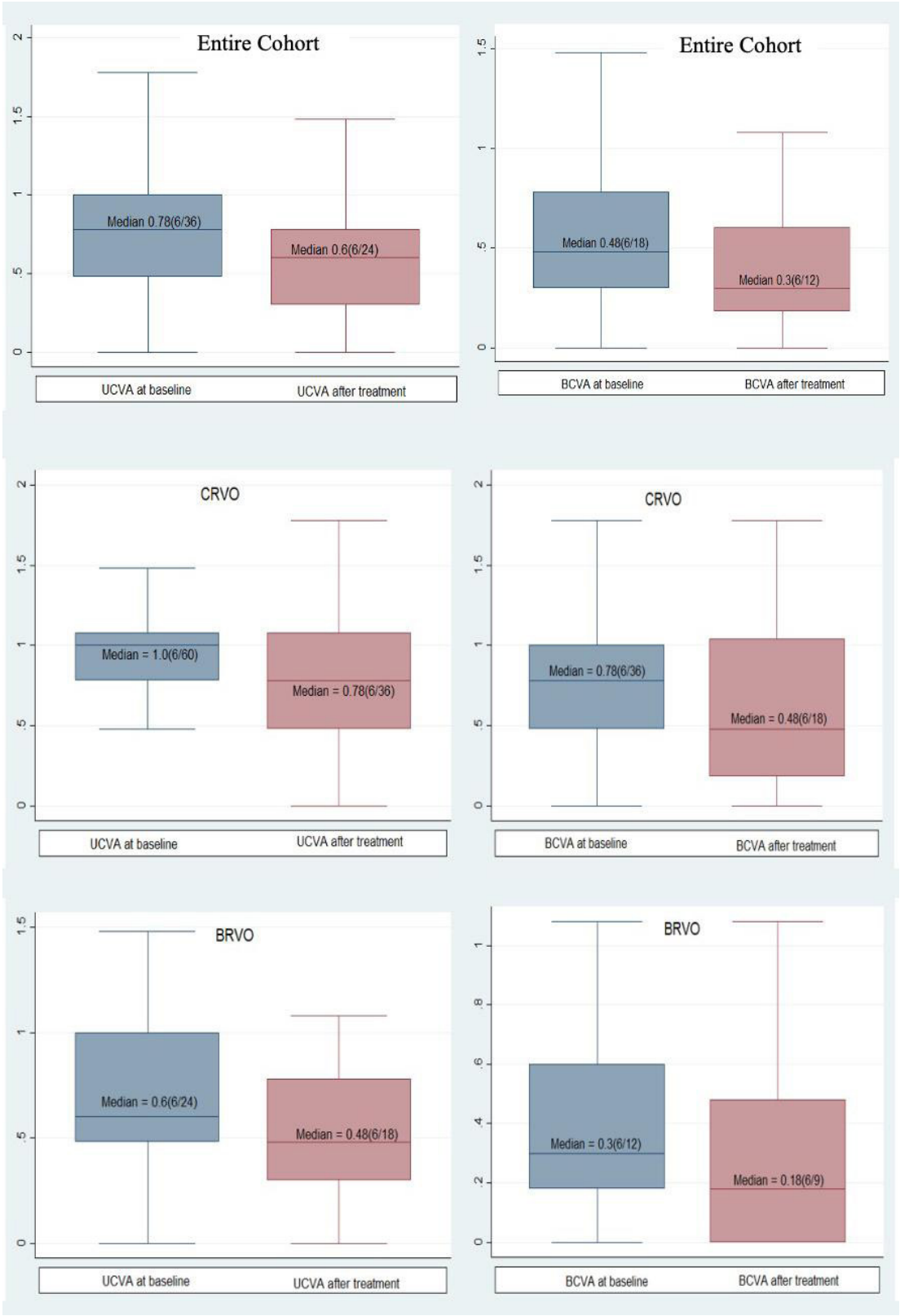

Figure 1: Box and Whisker plots of visual acuity pre and post treatment.

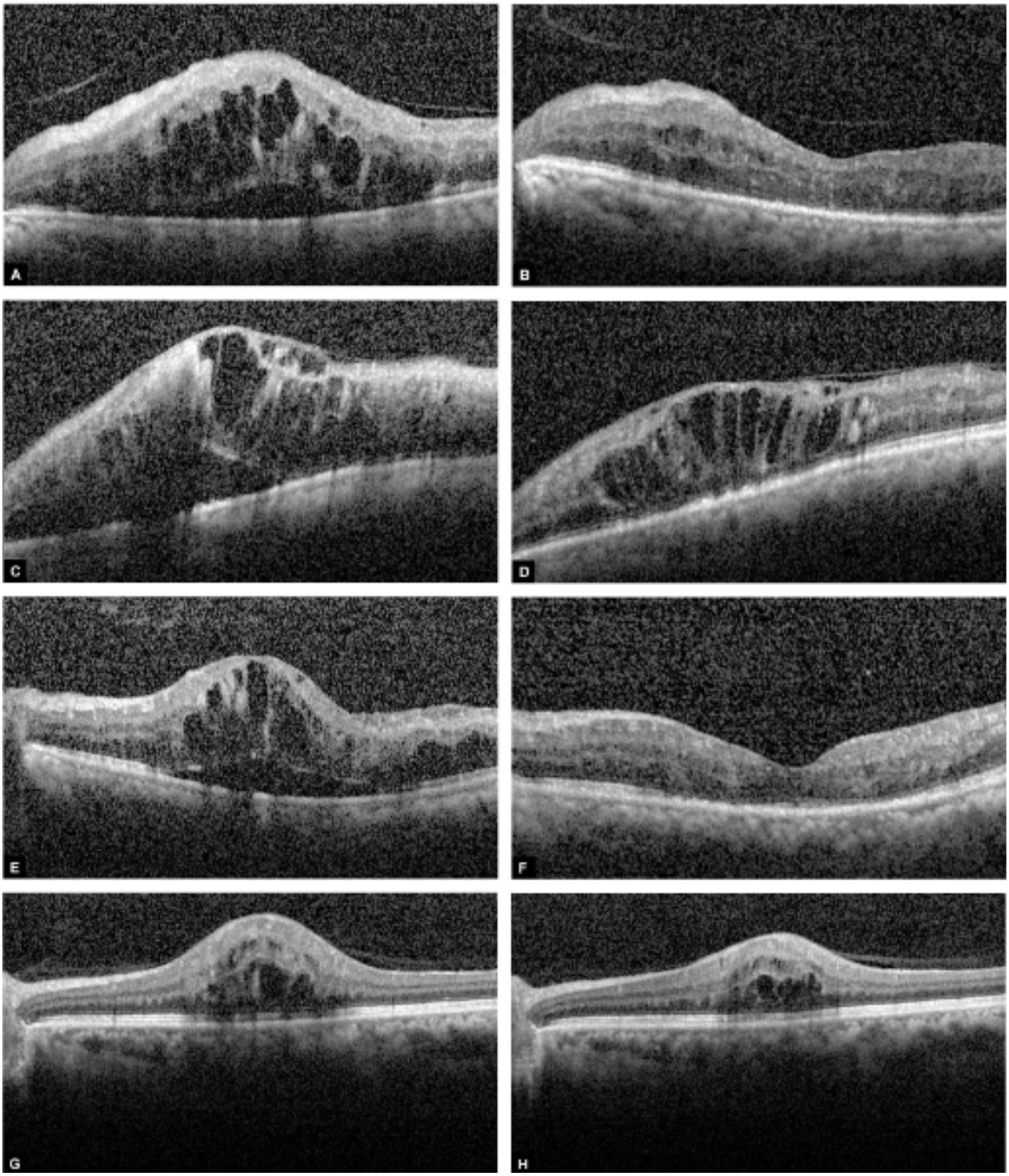

Figure 2: Enhanced depth optical coherence tomography images pretreatment (left column) and post treatment (right column).

A significant reduction in SRF height and sub foveal choroidal thickness (SFCT) was also noted (Table 2). Out of 127 patients, SRF was seen in 47 (37%) cases at baseline and had resolved in 30 (23.6%, p <0.001) post injection. There was a significant reduction in IRF from 100 (78.7%) cases with IRF at baseline to 35 (27.6%, p <0.001) post injection. Hyperreflective spots (HRF) were noted to reduce in 26 (20.4%) cases post treatment (p <0.001). There was statistically significant correlation of CRT reduction with improvement in BCVA in those with BRVO (p = 0.0004) and thereby also in the entire cohort (p = 0.0003), but not in those with CRVO (p = 0.216).

The cohort had 56 (44%) participants with hypertension for a mean of 6 ±5.5 years, 40 (31.5%) with diabetes for a mean duration of 6.7 ±5.2 years. Cardiac illness was present in 9(7%), dyslipidemia in 4 (3%), and three (2.4%) others had other systemic illnesses (jaw carcinoma -1, hypothyroidism 2). On correlation of response to treatment with systemic parameters, shown in Table 3 patients with longer duration of hypertension (spearman rank correlation r = -0.2795, p = 0.037), and those with higher eosinophil count (r =-0.2595, p = 0.025) were less likely to have a reduction in CRT. On the other hand, those who had higher HDL levels (r = 0.2505, p = 0.031) and better RBC counts (r = 0.2732, p = 0.016) were more likely to experience CRT reduction.

Table 2: Optical coherence tomography biomarkers at baseline and following treatment with intravitreal bevacizumab.

OCT parameters		Entire cohort Mean ±SD	p-value	CRVO Mean ±SD	p-value	BRVO Mean ±SD	p-value
CRT (μm)	Baseline	609.9±216.5	<0.001	700±0271.4)	<0.001	562.2±163.4	<0.001
	Post Rx	337.6±168.2		385.8±234.3		312.1±113.1	
SRF height (μm)	Baseline	237±184.5	0.002	288.8±254.6		210.3±132.8	
	Post Rx	115.9±120.6		68.2±33.5		135.8±138.9	
SFCT (μm)	Baseline	304.9±49.5	<0.001	313.2±51.2		300.5±48.3	
	Post Rx	276.5±45.2		280.8±52.9		274.1±40.7	

OCT- optical coherence tomography; SD -standard deviation; CRVO- central retinal vein occlusion, BRVO- branch retinal vein occlusion CRT- central retinal thickness; Rx -treatment; SRF-subretinal fluid; SFCT - sub foveal choroidal thickness

Table 3: Correlation of systemic parameters with Central Retinal Thickness reduction following treatment with intravitreal bevacizumab.

	Mean (SD)	Median (IQR)	Min - Max	Spearman rank Correlation	
				Correlation with CRT reduction	P-value
Hypertension duration (years)	6.0±5.5	4.5(1.5 - 10)	1 – 20	-0.2795	0.0370
Diabetes duration (years)	6.7±5.2	6(2 - 10)	1 – 24	-0.0970	0.5517
FBS (mgs%)	106.1±28.1	99(87 - 119)	65 – 256	-0.0841	0.398
RBS (mgs%)	127.4±38.0	118(102 - 146)	72 – 263	-0.1039	0.335
PPBS (mgs%)	168.9±46.3	162(137 - 194)	90 – 367	-0.0150	0.8949
Hba1c (%)	6.5±1.2	6.1(5.8 – 6.7)	5.1 – 10.6	0.1018	0.3817
Systolic BP (mmHg)	139.4±16.6	140(130 - 150)	100 – 180	-0.1260	0.158
Diastolic BP (mmHg)	82.3± 8.0	80(80 - 90)	60 – 100	0.0457	0.610
Eosinophil (%)	4.7±4.5	4(3 - 5)	0 – 30	-0.2595	0.025
RBC count (million cells/cu mm)	4.4± 0.7	4.4(3.9 – 4.9)	3.2 – 6.4	0.2732	0.016
Basophil (%)	0.1± 0.4	0(0 - 0)	0 – 3	-0.0635	0.586
Neutrophil (%)	61.8± 7.0	62(56 - 66)	47 – 76.5	0.0877	0.455
Monocyte (%)	3.4± 2.5	3(2 - 5)	0 – 10	-0.0658	0.575
Lymphocyte (%)	30.0± 6.8	29(26 - 35)	16 – 44	0.1130	0.334
Platelet count (lakh cells/ cu mm)	2.6± 0.6	2.7(2.3 – 2.9)	1.3 – 4.2	-0.1049	0.371
Blood Urea (mgs%)	27.0± 10.5	26(19 - 32)	13.3 – 77	0.1926	0.0810
Serum creatinine (mgs%)	1.0± 0.74	0.9(0.8 – 1.1)	0.6 – 6.9	0.1317	0.2352
Total Cholesterol (mgs%)	186.1± 35.2	184(163 - 208)	113 – 277	0.1097	0.3490
LDL (mgs%)	114.0± 28.6	110(95 - 127)	53 – 205	0.0048	0.9678
Serum TGL (mgs%)	138.3± 54.4	130.5(105 - 158)	63 – 356	0.1558	0.1849
VLDL (mgs%)	27.4± 10.8	25.5(20 – 31.5)	13 – 71	0.0731	0.542
HDL (mgs%)	42.3± 11.4	42(34 - 48)	20 – 84	0.2505	0.031
Cholesterol/HDL ratio	4.6± 1.2	4.4(3.7 - 5)	2.4 – 9.2	-0.1862	0.1121
LDL/HDL ratio	2.9± 1.1	2.7(2.2 – 3.2)	1 – 7.1	-0.2175	0.0645

FBS-fasting blood glucose; RBS-random blood glucose; PPBS-post prandial blood glucose; BP-blood pressure; RBC-red blood cells; LDL-low-density lipoprotein; TGL-triglyceride, VLDL-very low-density lipoprotein; HDL- high-density lipoprotein

Bold indicates values of statistical significance.

DISCUSSION

In this study analyzing the systemic biomarkers for the response of macular edema secondary to retinal vein occlusion, the participants experienced significant visual improvement following initiation of treatment. CRT was greater in patients with CRVO, but both subgroups show reduction in macular edema following intervention. The reduction in CRT was accompanied by significant resolution of SRF and a reduction in IRF. Those with longer duration of hypertension and elevated eosinophil counts had lesser possibility of reduction in CRT, while higher HDL levels and better RBC counts correlated to better possibility of reduction in CRT. The reduction in CRT corresponded to an improvement in vision, which was statistically significant for those with BRVO.

Duration of visual loss has been shown to be an independent factor contribution to visual outcomes. The patients in this study presented with an average duration of defective vision of 8.3±10.9 weeks, with the majority presenting between 1-3 months. There were significant visual gains in the entire cohort with treatment, similar to outcomes from previous trials (Boyer et al, 2012, Brown et al, 2010, Campochiaro et al, 2010, Holz et al, 2013). While we found that a shorter duration of symptoms correlated to better BCVA gains, this was not statistically significant. In the BRAVO trial, 65% of patients had a duration of symptoms of ≤ 3months, while 69% in CRUISE had a duration of symptoms of ≤ 3 months (Brown et al, 2010, Campochiaro et al, 2010). Earlier treatment with anti-VEGF can result in quantitatively larger visual acuity gains. While ongoing treatment results are sustained and improving visual outcomes, the major improvement occurs on administration of the first dose of injection (Boyer et al, 2012, Brown et al, 2010, Holz et al, 2013, Honda et al, 2014). IVB has also shown to have immediate improvement in vision with first dose, seen at 4-6 weeks following treatment, similar to our results (Abegg et al, 2008, Honda et al, 2014, Manayath et al, 2009).

The cohort also had an improvement in various biomarkers on OCT. An overall reduction in CRT was noted from baseline for the entire cohort as well as both the subgroups. This finding has been seen in all previous studies on anti-VEGF use for RVO related ME (Abegg et al, 2008, Boyer et al, 2012, Brown et al, 2010, Campochiaro et al, 2010, Holz et al, 2013, Honda et al, 2014, Manayath et al, 2009, Scott et al, 2017, Wolf-Schnurrbusch et al, 2011). The maximum reduction in CRT is noted following the first injection, with further reduction and stabilization noted with ongoing injections. SRF, which is accumulation of fluid between neurosensory retina and retinal pigment epithelium, has been characteristic OCT finding in RVO. In our study, significant change in SRF was observed after treatment ($p < 0.001$). Cinal et al also showed effective reduction in SRF, with complete resolution in 16 of 19 cases following IVB in patients with CRVO (Cinal et al, 2011). The mean SFCT showed a statistically significant reduction to 276.5(±45.2) μ ($p<0.001$) at 1 month after treatment in our cohort. This was concurrent with a study by Hall et al which showed significant decrease in SFCT from 282μ to 227μ following multiple intravitreal bevacizumab at 6 month follow up (Hall et al, 2019). SFCT has been noted to be increased in patients with diabetes mellitus, and

to increase with worsening of stage of diabetic retinopathy as well as with the development of diabetic macular edema (Regatieri et al, 2012). VEGF which is produced by RPE cells has a tropic role on the choroidal vasculature (Maharaj and D'Amore, 2007). It has been hypothesized that an increase in VEGF levels can cause dilatation of choroidal vasculature, increase choroidal permeability resulting in an increased choroidal thickness in patients with diabetic retinopathy. A similar effect of VEGF on the choroid in patients with RVO, followed by a reduction of VEGF levels following IVB could account for reduction of SFCT in patients in our cohort. Significant reduction in IRF, as well as HRF was noted post treatment in our cohort. HRF were noted to reduce in 26(20.4%) cases post treatment ($p<0.001$). This finding was comparable to those in a study by Kang et al. where eyes with BRVO showed significant reduction in mean HRF along with a corresponding improvement in visual acuity (Kang et al, 2014).

In this study there was a significant correlation between changes in CRT and improvement in BCVA following treatment, for eyes with BRVO and the entire cohort. This was found to be concurrent with the study by Kim et al, which showed that improvement in BCVA correlated significantly with decrease in CRT in the BRVO subgroup in their study (Kim et al, 2015). This correlation was not significant for eyes with CRVO, as also observed by Manayath et al (Manayath et al, 2009).

The commonest associated systemic comorbidity in our cohort was hypertension, seen in 56 (44%) participants, followed by 40(31.5%) with diabetes. A similar preponderance of hypertension and diabetes amongst patients with RVO has been noted in previous studies (Cinal et al, 2011, Honda et al, 2014). A previous metanalysis showed concurrent results with any form of RVO attributable to hypertension in 48% cases, hyperlipidemia in 20% and diabetes in 5% (O'Mahoney, 2008). An association between CRT change at baseline with systolic blood pressure was demonstrated in a study by Kim et al (Kim et al, 2015). Dodson et al also found increased recurrence of retinal vein occlusion was associated with hypertension, hyperlipidemia, and low HDL levels (Dodson et al, 1985). In our cohort longer duration of hypertension was found to be associated with lower possibility of reduction in CRT, possibly indicating long standing atherosclerotic damage to vasculature. Patients with higher HDL levels ($r = 0.2505$, $p = 0.031$) showed better possibility of reduction in CRT in our study. The protective role of HDL in cardiovascular diseases is long established (Gordon et al, 1977). HDL has been shown to exhibit numerous atheroprotective functions including efflux of cellular cholesterol, reduction of cell death, decreased vasoconstriction, reduction of inflammatory biomarkers and thereby reducing oxidative stress, reduced platelet aggregation and improved glucose metabolism (Kontush, 2014). This protective function of HDL can be contributory to better response to anti-VEGF therapy, making regularization of lipid levels more crucial in patients with RVO.

In this study, higher eosinophil count was associated with the possibility of poorer reduction of CRT ($r =-0.2595$, $p = 0.025$). Eosinophils have been shown to play a role in thrombus growth in coronary artery disease (Sakai et al, 2009). A significant association is demonstrated

between higher absolute eosinophil counts and prevalence coronary artery disease, multiple vessel disease and chronic occlusions in a study by Verdoia et al. They conclude higher eosinophil counts to be associated with cardiovascular risk factors and lower levels of HDL (Verdoia et al, 2015). Leukocyte subtypes, mainly eosinophils have been shown to produce cytotoxic and prothrombotic mediators, that produce reactive oxygen species resulting in endothelial damage, platelet activation and fibroblast collagen release, thereby modulating atherosclerosis progression (Chihara et al, 1995, Fauci et al, 1982).

Limitations of the study are that this is a single center study, with data from a subset of population that has presented to a tertiary eye care center, that may introduce inherent biases. The study recruited only patients receiving bevacizumab, and no other anti-VEGF drugs.

This study highlights that systemic parameters can be used as prognostic indicators to response following treatment by intravitreal bevacizumab in patients with macular edema following RVO. Higher HDL levels along with high RBC count can be considered as good prognostic factors whereas longer duration of hypertension as well as higher eosinophil count can be considered as bad prognostic factors. The systemic associations in this study correlate to known cardiovascular risk factors. A systematic review has shown there is an association between RVO and risk for mortality of 34.7%, for stroke of 6.5% and myocardial infarction of 3.9-5.7% (Woo et al, 2016). Optimizing systemic control can improve anatomical and visual outcomes, prevent recurrence of RVO and reduce mortality.

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