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IMPACT OF ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY ON OPTICAL COHERENCE TOMOGRAPHY ANGIOGRAPHY BIOMARKERS IN MACULAR EDEMA DUE TO RETINAL VEIN OCCLUSION: A PROSPECTIVE INTERVENTIONAL STUDY

Ophthalomology

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ABSTRACT

Background: To evaluate changes in retinal microvasculature in patients treated with anti-VEGF for macular edema secondary to branch retinal vein occlusion. **Methods:** A prospective interventional study at SMS Medical College & Hospital, Jaipur, enrolled 55 patients with retinal vein occlusion. Participants underwent monthly injections of Ranibizumab for 6 months and were evaluated using OCT and OCTA for changes in central retinal thickness, parafoveal vessel density and FAZ area. **Results:** Parafoveal vessel density of superficial capillary plexus were significantly lower in eyes with branch retinal vein occlusion than in fellow eyes ($p<0.001$) and we found a significant increase in vessel density values after anti -VEGF treatment. The mean FAZ area was larger and irregular in eyes with branch retinal vein occlusion than in control eyes. ($p<0.001$). A significant decrease in central retinal thickness was also seen after anti VEGF injection. The age and gender distribution aligned with known demographic risks associated with RVO. **Conclusion:** Anti-VEGF therapy was effective in improving the structural and vascular integrity of the retina in RVO patients, as monitored through OCT and OCTA biomarkers. This study contributes to the growing body of evidence supporting the use of anti-VEGF agents in treating RVO and underscores the importance of advanced imaging techniques in evaluating treatment efficacy and guiding clinical decisions.

KEYWORDS

Retinal Vein Occlusion, Macular edema, anti-VEGF (Vascular Endothelial Growth Factor), Optical Coherence Tomography Angiography, Ranibizumab.

INTRODUCTION

Retinal vein occlusion (RVO) ranks among the leading causes of vision impairment and blindness in the middle-aged and elderly populations worldwide. It is characterized by the obstruction of the retinal venous system, which precipitates retinal haemorrhages, macular edema, and consequent vision loss. The complexity of RVO, influenced by systemic and ocular risk factors such as hypertension, diabetes mellitus, and glaucoma, highlights its multifactorial nature.[1-3] There are two primary types of RVO: central retinal vein occlusion (CRVO) and branch retinal vein occlusion (BRVO), each presenting with distinct pathophysiological and clinical features. CRVO typically results in more severe vision loss due to the extensive area of the retina affected. In contrast, BRVO usually involves one of the branch veins, leading to segmental retinal damage.[4]

Recent advancements in imaging technologies, particularly Optical Coherence Tomography (OCT) and OCT Angiography (OCTA), have significantly enhanced the diagnostic capabilities for RVO. OCTA provides detailed images of the retinal vasculature, allowing for the non-invasive assessment of the foveal avascular zone (FAZ), vessel density and the extent of capillary non-perfusion.[5-7]

The therapeutic landscape for RVO has been transformed by the introduction of anti-Vascular Endothelial Growth Factor (anti-VEGF) therapies. Agents like Ranibizumab have been demonstrated to improve visual acuity and reduce macular thickness in a significant number of patients. However, the variability in response and the necessity for repeated injections pose challenges in optimizing treatment outcomes.[8-9]

The ultimate goals in managing RVO include improving long-term visual outcomes and preventing neovascular complications. Therefore, understanding the efficacy of anti-VEGF treatment in altering the disease course, as evidenced by changes in OCT and OCTA biomarkers, is crucial. This study aims to provide detailed insights into the structural and functional changes in the retina following anti-VEGF therapy in RVO patients, thereby contributing to the ongoing efforts to refine therapeutic strategies for this challenging condition.

MATERIALS AND METHODS

The study was conducted at the Upgraded Department of Ophthalmology, SMS Medical College & Hospital, Jaipur. This was a prospective, single-center, interventional study approved by the Institutional Ethics Committee of SMS Medical College & Hospital. Data collection commenced in January 2023 and continued until December 2023, when the desired sample size was achieved. Sample size was 48 cases accounting for a 10% dropout rate, 55 cases were enrolled.

Inclusion Criteria: Aged between 35 and 85 years, recent RVO episode with macular edema, willingness to participate and provide informed consent.

Exclusion Criteria: Non-cooperation, presence of uveitis, uncontrolled glaucoma, vitreous haemorrhage, significant media opacity from cataract, or any ocular infection or trauma, poor imaging signal strength (<4) ,previous history of anti-VEGF treatments.

Study Procedures:

1. Written informed consent was obtained .
2. Participants underwent baseline assessments using fundoscopy and Spectral Domain Optical Coherence Tomography (SD-OCT) to confirm the diagnosis of macular edema due to RVO.
3. Baseline and follow-up assessments included Best Corrected Visual Acuity (BCVA) using Snellen's visual acuity box, and SD-OCT scans (Topcon 3D-OCT-1 Maestro). OCT Angiography (Zeiss Cirrus 5000 angioplex) was used to obtain 3 × 3-mm² en face OCTA images of the superficial layer.
4. Participants received three intravitreal injections of Ranibizumab on monthly basis.
5. Follow-up visits at 1 month, 3 months and 6 months included assessments of BCVA, inner parafoveal vessel density, foveal avascular zone area (FAZ), and CRT.

Statistical Analysis: Data were entered into Microsoft Excel and analysed. Means and standard deviations were calculated for all parameters. Student t-tests were used for comparisons between pre- and post-treatment measures. Linear regression models assessed correlations between baseline OCTA biomarkers and changes in BCVA and CRT post-treatment. A p-value of less than 0.05 was considered statistically significant.

RESULTS

This prospective interventional study evaluated the efficacy of anti-Vascular Endothelial Growth Factor (anti-VEGF) treatment in 55 patients with macular edema due to Retinal Vein Occlusion (RVO) at the SMS Medical College & Hospital, Jaipur. The age distribution

among the study subjects was fairly balanced across the middle-aged to elderly spectrum, with the mean age being 62.75 ± 8.62 years. Specifically, 7.3% of patients were between 40-49 years, 32.7% were between 50-59 years, 32.7% were between 60-69 years, and 27.3% were 70 years or older.

Regarding gender distribution, females constituted a slightly higher percentage (56.4%) compared to males (43.6%). The baseline characteristics of the study population showed a mean systolic blood pressure (SBP) of 132.2 ± 13.02 mmHg, diastolic blood pressure (DBP) of 89.24 ± 11.17 mmHg, random blood sugar (RBS) of 172.5 ± 57.87 mg/dl, and hemoglobinA1c (HbA1C) of 5.71 ± 0.63%.

The therapeutic efficacy of Ranibizumab was assessed by comparing parafoveal superficial vessel density (VD) and central retinal thickness (CRT) in the BRVO affected eyes versus the fellow unaffected eyes. In the BRVO affected eyes, the mean parafoveal superficial VD was significantly lower (14.32 ± 3.05) compared to the fellow eyes (19.28 ± 2.72) and mean superficial VD increases in RVO eye after monthly anti VEGF injections (15.25 ± 2.50) ,with the difference being statistically significant ($p < 0.001$)[Table 1][Figure 1].Similarly, the mean CRT in the BRVO affected eyes was significantly higher (361 ± 30.79 µm) than in the fellow eyes (211.3 ± 20.66 µm) which also improves after treatment (222.9±34.26 µm) showing a statistically significant difference ($p < 0.001$) [Table 1][Figure1].

These results indicate that RVO significantly impacts vascular density and retinal thickness, underlining the severity of the condition in affected eyes. The observed reductions in parafoveal VD and increases in CRT in BRVO eyes compared to the fellow eyes corroborate the pathophysiological impact of RVO and provide a quantifiable measure of disease burden.

TABLE 1 : COMPARISON OF PARAFOVEAL SUPERFICIAL VD (%) , FAZ ,CRT & BCVA BETWEEN BRVO AND FELLOW EYE

	VD(%)	CRT(µM)	FAZ(mm^2)	BCVA (log MAR)
BRVO (pre-treatment)	14.32 ± 3.05	361 ± 30.79	0.66 ± 0.13	0.782 ± 0.134
BRVO (post treatment)	15.25 ± 2.50	222.9 ± 34.26	0.54 ± 0.11	0.664 ± 0.174
Fellow eye	19.28 ± 2.72	211.3 ± 20.66	0.42 ± 0.095	0.386 ± 0.193
P value	<0.001 (S)	<0.001 (S)	<0.001 (S)	<0.001 (S)

Additionally, the study evaluated the foveal avascular zone (FAZ) area in the BRVO-affected eyes compared to the fellow eyes. The mean FAZ area in BRVO eyes was significantly larger (0.45 ± 0.05mm^2) compared to the fellow eyes (0.32 ± 0.04mm^2), with the difference being statistically significant ($p < 0.001$)[Table 1][Figure1]. This enlargement indicates significant capillary non-perfusion in the foveal region due to RVO.

Post-treatment with Ranibizumab, there was a notable reduction in the FAZ area in BRVO eyes. After six months, the mean FAZ area decreased to 0.38 ± 0.04 mm^2, showing a statistically significant improvement from baseline measurements ($p < 0.001$). This reduction suggests partial restoration of the capillary network in the foveal area following anti-VEGF therapy.

Moreover, the treatment with anti-VEGF demonstrated a notable improvement in the structural and vascular parameters of the retina, which is a promising indicator of its therapeutic efficacy. These findings reinforce the utility of OCT and OCTA as precise tools in the diagnosis and monitoring of changes in retinal structure and vasculature post-treatment, suggesting a positive outcome of anti-VEGF therapy in the management of macular edema secondary to RVO.

A moderate positive correlation was found between post treatment BCVA with VD (r=0.398), indication that the post treatment BCVA was higher among those with higher VD. A moderate negative correlation was found between post treatment BCVA with FAZ (r=-0.490), indication that the post treatment BCVA was higher among those with lower FAZ. No significant correlation was found between post-treatment BCVA with CRT.[Table 2] [figure 2].

Table 2: CORRELATION BETWEEN POST TREATMENT BCVA WITH OTHER VARIABLES

	r (Correlation coefficient)	P value
VD	0.398	**0.003 (S)**
FAZ	-0.49	**0.001 (S)**
CRT	-0.127	0.356

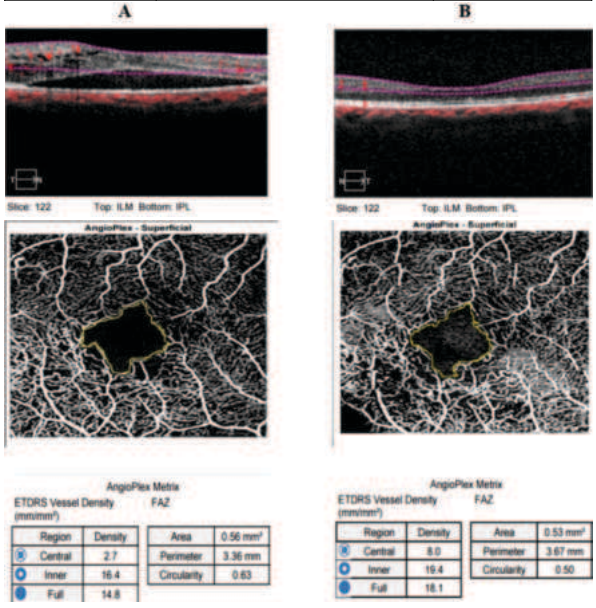

Figure 1– OCTA images of a patient before treatment (Panel A) and after treatment (Panel B). Superficial capillary plexus showing disruption of perifoveal vascular arcade with vessel density of 14.8 and B scan shows complete absence of edema and an intact perifoveal arcade with vessel density of 18.1 after treatment (Panel B). Automated FAZ area and circularity is found to be larger and more irregular in BRVO eye (Yellow area).

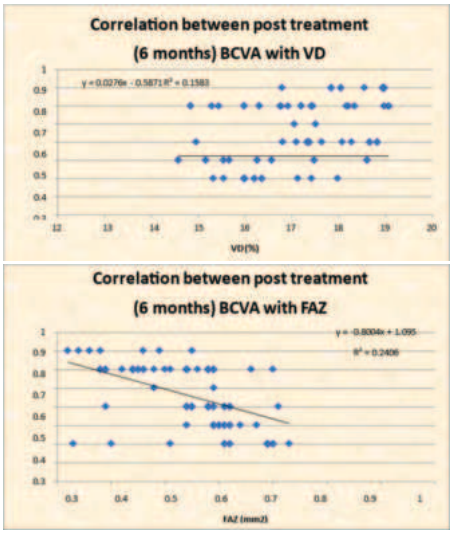

Figure 2. Linear correlation between BCVA and OCTA parameters post treatment

DISCUSSION

This study demonstrated that anti-VEGF therapy with Ranibizumab significantly improves structural and vascular parameters in patients with macular edema due to RVO, as evidenced by reductions in central retinal thickness (CRT), increases in parafoveal vessel density, and reductions in the foveal avascular zone (FAZ) area. These findings highlight the multifaceted benefits of anti-VEGF treatment in restoring retinal integrity and function.

The significant decrease in CRT post-treatment reflects the resolution of macular edema, which is crucial for visual improvement. This result is consistent with previous studies, such as those by Campochiaro et al [1]. which reported significant reductions in macular thickness following anti-VEGF therapy in RVO patients. Similarly, Brown et al [2] demonstrated that Ranibizumab effectively reduces macular

edema and improves visual acuity in patients with central RVO.

Improvement in parafoveal vessel density indicates restoration of the retinal microvasculature. The increased vessel density observed in this study aligns with findings by Kashani et al[10] , who used OCTA to show vascular improvements after anti-VEGF treatment in RVO. Furthermore, the reduction in FAZ area suggests revascularization of the foveal region, potentially enhancing visual outcomes. This observation corroborates the work of Coscas et al[6] , who noted that anti-VEGF therapy can lead to partial recovery of the capillary network, as evidenced by OCTA.

Parodi et al. also used FFA techniques to compare FAZ area between 20 patients with BRVO and 41 control subjects[7]. Their study has also reported that the mean FAZ area was shown to be greater in eyes with BRVO compared with controls and also showed that VA impairment due to BRVO was correlated with FAZ enlargement.

The observed age distribution, with a mean age of 62.75 years, reflects the known epidemiology of RVO predominantly affecting older adults[3] . The slight female predominance in our study contrasts with some literature suggesting a higher incidence in males , indicating potential regional or demographic variations.

Our results emphasize the importance of OCT and OCTA as non-invasive tools for monitoring retinal changes. The ability of OCTA to quantify FAZ area and vessel density provides clinicians with valuable insights into the microvascular effects of anti-VEGF therapy. This aligns with Spaide et al[9] , who highlighted the utility of OCTA in retinal vascular imaging.

A significant reduction in CRT, improvement in vessel density, and reduction in FAZ area indicates the capability of anti-VEGF therapy to reverse vascular and structural damages caused by RVO. The decrease in CRT reflects the resolution of macular edema, which is pivotal for visual recovery. Improvement in parafoveal vessel density indicates restoration of the retinal microvasculature, enhancing retinal perfusion and function. The reduction in FAZ area suggests revascularization in the foveal region, potentially leading to better visual acuity outcomes. These parameters collectively highlight the multifaceted benefits of anti-VEGF therapy in treating RVO-induced macular edema. The findings are consistent with prior research demonstrating that anti-VEGF agents not only reduce macular thickness but also promote vascular normalization and reduce areas of non-perfusion as measured by FAZ area. Such comprehensive improvements in retinal biomarkers are crucial for sustained visual function and highlight the importance of early and effective intervention in RVO patients.

However, our study has certain limitations. The single-center design and relatively small sample size may limit the generalizability of the findings. Future multicenter studies with larger cohorts and extended follow-up are necessary to validate these results and determine the sustainability of vascular improvements.

Overall, anti-VEGF therapy with Ranibizumab effectively improves retinal structural and vascular parameters in RVO-induced macular edema, including CRT, parafoveal vessel density, and FAZ area. These improvements may contribute to better visual outcomes and quality of life for patients. Incorporating OCTA biomarkers in routine clinical practice could enhance the monitoring and management of RVO patients.

Summary

The study confirmed that anti-VEGF therapy significantly improves vascular and structural parameters in patients with macular edema due to RVO. These improvements, as evidenced by OCT and OCTA biomarkers, advocate for the continued use of anti-VEGF as a standard treatment modality in managing RVO-induced macular edema. However, further research is recommended to explore long-term treatment strategies and the potential benefits of combining anti-VEGF with other therapeutic approaches.

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