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Correlation Between Serum Vascular Endothelial Growth Factor-A (VEGF-A) Levels and Optical Coherence Tomography Angiography Parameters in Exudative Age-Related Macular Degeneration

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Abstract

Background and objective: Among inflammatory and angiogenic cytokines, VEGF-A has been recognized as a driver of increased vascular permeability in eyes with exudative age-related macular degeneration (ExARMD). The study aimed to evaluate the correlation between serum vascular endothelial growth factor-A (VEGF-A) levels and optical coherence tomography angiography (OCTA) parameters in ExARMD.

Methodology: In this prospective, single-arm, before-and-after interventional study, treatment-naïve eyes with ExARMD underwent assessment of best-corrected visual acuity (BCVA), central foveal thickness (CFT), subfoveal choroidal thickness (SFCT), and OCTA parameters, including foveal avascular zone (FAZ) and vessel density (VD) of different slabs of retina and choroid. The serum VEGF-A levels were measured with commercially supplied enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's protocol. Correlations between serum VEGF-A levels and ocular parameters were evaluated before and at one month after a single intravitreal injection of 0.5 mg/0.05 mL ranibizumab biosimilar.

Results: The study involved 36 eyes from 25 ExARMD patients, with a mean age of 63.9 ± 7.68 years. At baseline, the distance BCVA was LogMAR 1.1 ± 0.6 , CFT was 367.0 ± 237.1 (median: 294.0 (IQR: 219.5 to 395.0)) microns, SFCT was 262.9 ± 71.6 (median: 263.5 (IQR: 223.0 to 292.0)) microns, and serum VEGF-A levels were 221.1 (IQR: 130.0 to 355.7) pg/mL. Before treatment, VEGF-A levels correlated negatively with CFT (Rho = -0.236) and FAZ perimeter (Rho = -0.039) but positively with LogMAR BCVA ($r = 0.190$), SFCT ($r = 0.243$), FAZ area (Rho = 0.153), circularity ($r = 0.437$), and VD of most retino-choroidal layers. One month after treatment, the distance BCVA was LogMAR 0.8 ± 0.5 , CFT was 324.9 ± 208.0 (median: 284.0 (IQR: 183.5 to 426.5)) microns, SFCT was 240.4 ± 68.5 (median: 241.5 (IQR: 180.0 to 288.5)) microns, and serum VEGF-A levels were 207.2 (IQR: 106.3 to 423.9) pg/mL. The VEGF-A levels correlated negatively with FAZ area (Rho = -0.016), perimeter (Rho = -0.033), and circularity ($r = -0.170$) but positively with LogMAR BCVA ($r = 0.025$), CFT ($r = 0.032$), SFCT (Rho = 0.239), and VD of most retino-choroidal layers. None of the correlations were significant after applying Bonferroni correction.

Conclusion: In an exploratory unadjusted analysis, higher serum VEGF-A was associated with worse visual acuity (VA), increased SFCT, reduced FAZ perimeter, and increased VD of most retino-choroidal layers, though the association was weak. The correlation between serum VEGF-A levels and CFT, FAZ area, and circularity changed direction following treatment. After Bonferroni correction for multiple comparisons, none of these associations remained statistically significant.

Categories: Therapeutics, Ophthalmology, Healthcare Technology

Keywords: choroidal neovascular membrane, exudative age-related macular degeneration, optical coherence tomography, optical coherence tomography angiography, vascular endothelial growth factor A levels

Introduction

Exudative age-related macular degeneration (ExARMD) is characterized by abnormal choroidal neovascularization (CNV) that proliferates through defects in Bruch's membrane into the subretinal space, resulting in exudation, hemorrhage, fibrosis, and progressive central vision loss. The pathogenesis of ExARMD is mediated by several angiogenic and inflammatory cytokines, including vascular endothelial growth factor-A (VEGF-A), angiopoietin-2, placental growth factor (PIGF), and interleukin-8 (IL-8) [1,2,3]. Among these, VEGF-A is considered the principal mediator of pathological angiogenesis and vascular permeability. It is produced by multiple ocular cell types, including retinal pigment epithelial (RPE) cells, Müller cells, retinal ganglion cells, endothelial cells, and pericytes [4,5].

Optical coherence tomography angiography (OCTA) is a novel, non-invasive imaging modality that enables

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high-resolution two- and three-dimensional visualization of choroidal neovascular complexes in ExARMD. Its depth-resolving capability enables automated segmentation and visualization of the retinal and choroidal microvasculature at varying depths without dye injection. OCTA plays an important role in the evaluation of ExARMD by visualizing the vascularized network and studying flow pattern, location, and size of the lesion [6,7].

Intravitreal anti-VEGF agents remain the gold standard for managing neovascular age-related macular degeneration (nARMD) [8]. Unfortunately, treatment response varies, and not all patients respond adequately to them [3]. Although VEGF levels and OCTA parameters have been investigated separately in ExARMD [1,2,6,7,9], studies examining their relationship remain scarce.

In this study, we aimed to investigate the correlation between serum VEGF-A levels and OCTA-derived parameters in ExARMD. Although vitreous samples may more accurately reflect intraocular VEGF-A levels, blood sampling is more readily feasible and minimally invasive; therefore, serum samples were analyzed for VEGF-A levels. Elucidating the relationship between serum VEGF-A levels and ocular imaging biomarkers may provide insights into the role of VEGF-A in disease pathogenesis and progression. This may help address an important gap in the current understanding of ExARMD and facilitate the development of more personalized treatment strategies.

Materials And Methods

The Institutional Ethics Committee of Maulana Azad Medical College, New Delhi, India, approved the current study (Approval No. F.1/IEC/MAMC/MD/MS (92/04/2022/No. 290; dated August 29, 2022). All participants provided informed consent in accordance with the Declaration of Helsinki. Treatment-naïve Indian patients with ExARMD were prospectively recruited at the Department of Ophthalmology, Guru Nanak Eye Centre affiliated with Maulana Azad Medical College, New Delhi, India. The prospective, single-arm, before-and-after interventional study was conducted over a period of one year, from December 1, 2022, to December 31, 2023.

The subjects were diagnosed with ExARMD according to the definition of the International Classification System for Age-Related Maculopathy [10]. Participants were aged ≥ 50 years and had macular abnormalities, including hypopigmentation and/or hyperpigmentation of the RPE, neurosensory detachment (NSD), pigment epithelial detachment (PED), retinal hemorrhages, subretinal or sub-RPE neovascular membranes, or retinal fibrous scarring, in the absence of other retinal disorders. These macular changes were assessed using high-resolution digital color fundus photographs centered on the fovea, capturing an area of at least 6000 micrometers (approximately four disc diameters) in width. Additionally, optical coherence tomography (OCT) scans were examined to confirm these findings.

Patients with visual acuity (VA) worse than LogMAR 1.0 (equivalent to 6/60 or 20/200) were excluded from the study. Patients with significant ocular affections such as dense cataract or corneal opacity, glaucoma, optic nerve diseases, other chorio-retinal pathologies, particularly those affecting macular perfusion, previous vitrectomy, or a known risk of thromboembolic events were excluded.

All participants underwent a comprehensive ophthalmic examination, including monocular assessment of best-corrected visual acuity (BCVA) using Early Treatment Diabetic Retinopathy Study (ETDRS) charts [2,3,11]; intraocular pressure (IOP) measured by Goldmann applanation tonometry [12]; color vision (CV) using the Ishihara pseudoisochromatic plates and the Farnsworth D-15 test (Jutron Vision, Vadodara, Gujarat, India) [13,14]; and contrast sensitivity (CS) using the Pelli-Robson chart (<http://creativecommons.org/licenses/by/4.0/>) [15]. Following pupillary dilatation, color fundus photography and fundus fluorescein angiography (FFA) were performed. Spectral-domain optical coherence tomography (SD-OCT; RTVue, Optovue Inc., Fremont, CA) was performed over the central 30° retinal area centered on the fovea to assess central foveal thickness (CFT), NSD, PED, subfoveal choroidal thickness (SFCT), RPE abnormalities, and choroidal neovascular membrane (CNVM) characteristics.

The eye examination included an OCTA scan of the 3 × 3 mm macular region performed with a prototype OCTA system on a commercially available SD-OCT device (Optovue Inc., Fremont, CA). The OCTA software evaluated foveal avascular zone (FAZ) area, perimeter, circularity, and VD across six retino-choroidal layers: the superficial capillary plexus (SCP), deep capillary plexus (DCP), outer retina (OR), outer retinal choriocapillaris (ORCC), choriocapillaris (CC), and choroid (C). The CNVM was identified as a hyperreflective, tangled vascular network in the CC layer beneath the subretinal fluid (SRF). The FAZ area, perimeter, and circularity were measured. Using the ETDRS grid centered on the fovea, the foveal region was defined as the central 0.5-mm diameter circle, the parafoveal region as the annulus between the 0.5-mm and 1.5-mm rings, and the perifoveal region as the annulus between the 1.5-mm and 3.0-mm rings. The OCTA device acquired two volumetric scans at a rate of 85,000 A-scans per second, with each volume consisting of 304 × 304 A-scans and requiring approximately 3 seconds for acquisition. OCTA images were generated using the split-spectrum amplitude-decorrelation angiography (SSADA) algorithm. The scans having projection or motion artifacts, such as vessel doubling or edge duplication, were excluded. All images were taken at a signal strength index of 90% and a signal quality index of 4/5. All scans were graded by two independent, trained, and masked observers (PKS and DD), and readings were averaged.

The 3 mL venous blood samples were drawn from all subjects with minimal stasis, and the blood was collected in a red-cap vacutainer. After allowing the blood to clot at room temperature for 30 minutes, the sample was centrifuged at 3000 rpm for 15 minutes to remove the clot. The supernatant serum was separated and stored at -80°C until needed for the appropriate assays. After a single freeze-thaw cycle, all serum samples were analyzed during the same session using an enzyme-linked immunosorbent assay (ELISA) kit. The samples were assayed in duplicate with less than 15% coefficient of variation.

Serum VEGF-A levels were quantified using a quantitative sandwich ELISA according to the manufacturer's instructions (Human VEGF-A ELISA Kit; ELK Technology, Cat. No. ELK1129, Denver, USA). Briefly, a monoclonal antibody specific for VEGF-A was precoated onto the microplate wells. Standards and serum samples were added, allowing VEGF-A to bind to the immobilized antibody. After washing, an enzyme-linked polyclonal anti-VEGF-A antibody was added. The resulting color intensity, proportional to the concentration of VEGF-A in the sample, was measured spectrophotometrically. VEGF-A concentrations were determined from a standard curve generated using recombinant human VEGF-A standards and were expressed in pg/mL.

The intravitreal dose of 0.5 mg/0.05 mL ranibizumab biosimilar (RbB; Razumab; Intas, Ahmedabad, India) was administered using a 1.0 mL syringe with an integrated 30-gauge needle (1 mL tuberculin syringe; DispoVan, HMD, Haryana, India). All intravitreal injections were performed under sterile conditions, with the needle inserted 3.5-4.0 mm posterior to the limbus. After the needle was removed, a sterile cotton-tipped applicator was used to prevent reflux. Preoperatively and postoperatively, quinolone eye drops were instilled four times daily to prevent infection.

Following intravitreal anti-VEGF injection, IOP changes were assessed at one week, whereas changes in visual function, OCT, and OCTA parameters were evaluated at one month. Serum VEGF-A levels were measured again at one month after intravitreal injection. Throughout the follow-up period, patients were monitored for systemic adverse events and ocular complications, including anterior segment inflammation, vitritis, endophthalmitis, and retinal vasculitis.

Sample size assessment

The sample size was calculated to reflect the study design and primary analytical endpoint: the bivariate correlation between serum VEGF-A levels and retinochoroidal OCTA parameters.

Using Fisher's Z transformation of the correlation coefficient, the sample size was calculated as follows:

$$N = \left[\frac{Z_{\alpha} + Z_{\beta}}{0.5 \ln \left(\frac{1+r}{1-r} \right)} \right]^2 + 3$$

With a two-tailed alpha of 0.05 ($Z_{\alpha} = 1.96$) and 80% statistical power ($Z_{\beta} = 0.84$), a sample size of 36 eyes provided adequate power to detect moderate-to-large correlation coefficients of r greater than or equal to 0.45 [16].

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY). The primary objective was to determine correlations between serum VEGF-A levels and OCTA parameters before and after intravitreal RbB injection. The secondary objectives were to evaluate correlations between serum VEGF-A levels and ocular and OCT-derived parameters over the same period. The Kolmogorov-Smirnov test was used to determine the normality of data. Data were summarized by the mean and standard deviation (SD) in the case of parametric data and median with interquartile range in the case of non-parametric data. The correlation was found using Pearson (r) and Spearman (Rho) correlation coefficients for parametric and non-parametric data, respectively. The correlation was considered significant only when the p -value was less than 0.05. To control the type 1 error in multiple comparisons, a Bonferroni correction was applied, and the adjusted significance threshold for p -values was calculated.

Results

Twenty-five patients with ExARMD were enrolled, including 20 (80%) males and 5 (20%) females. The mean age was 63.9 ± 7.68 years (range: 50-82 years). In 36 affected eyes, the VA was LogMAR 1.1 ± 0.6 (range: 0 to 1.8) (median VA was 1.0; IQR: 0.7 to 1.6), RE was -0.1 ± 1.8 (range: -4.5 to 4.5) (median RE: 0.1; IQR: -1.5 to 1.0), and BCVA was LogMAR 1.0 ± 0.6 (range: 0.0 to 1.8) (median BCVA: 1.0; IQR: 0.6 to 1.5). The IOP was 15.5 ± 2.6 (range: 10.2 to 20.6) mmHg (median IOP: 15.3; IQR: 14.6 to 17.3), and CS was 0.8 ± 0.6 (range: 0.1 to 1.9) (median: 0.5; IQR: 0.1 to 1.4).

On CV assessment with 1-21 Ishihara plates (IP), a score of 17.81 ± 7.20 (median score: 21; IQR: 21 to 21)

correctly identified plates was obtained at baseline, while examination on 22-25 plates gave a score of 3.19 ± 1.41 (median score: 4; IQR: 3 to 4) correctly read plates. The CFT was 367.0 ± 237.1 (median: 294.0; IQR: 219.5 to 395.0) microns, and SFCT was 262.9 ± 71.6 (median: 263.5; IQR: 223.0 to 292.0) microns. The number of NSD was 0.94 ± 0.71 (median: 1; IQR: 0.0 to 1). The height and width of NSD were 76.2 ± 141.0 (median: 28.0; IQR: 0.0 to 75.0) microns and 796.1 ± 1155.8 (median: 242.0; IQR: 0.0 to 1150.5) microns, respectively. The number of PED was 2.7 ± 3.9 (median: 1.5; IQR: 0.0 to 3.5). The height and width of PED were 84.4 ± 108.8 (median: 75.0; IQR: 0.0 to 105.5) microns and 386.5 ± 430.9 (median: 231.5; IQR: 0.0 to 713.0) microns, respectively.

Among 36 eyes, 18 (50%) had classic CNVM, while the other 18 (50%) had occult CNVM. The height and width of CNVM were 213.8 ± 262.4 (median: 44.0; IQR: 0.0 to 411.5) microns and 1229.5 ± 1550.7 (median: 266.0; IQR: 0.0 to 2297.0) microns, respectively. The FFA showed findings such as hyperfluorescence in the early phase that increased in size and intensity in the late phase, indicating scar, NSD, or CNVM; hyperfluorescence in the early phase that increased in intensity but not in size in the late phase, indicating PED; and stippled hyperfluorescence suggestive of RPE disturbance or atrophy.

The blood sample analysis at baseline showed that the serum VEGF-A levels were 323.2 ± 358.3 pg/mL (range: 31.3 to 1765.1) (median: 221.1; IQR: 130.0 to 355.7). Table 1 presents the correlation between serum VEGF-A levels and baseline ocular and OCT parameters.

S. No.	Parameter	Pearson Correlation Coefficient r	p-Value	Bonferroni-Adjusted p-Value	Spearman Correlation Coefficient Rho	p-Value	Bonferroni-Adjusted p-value
1.	VA (LogMAR)*	0.099	0.566	1.00	-0.147	0.393	1.00
2.	Refractive error*	0.108	0.532	1.00	0.201	0.239	1.00
3.	BCVA (LogMAR)*	0.190	0.268	1.00	-0.031	0.858	1.00
4.	Intraocular pressure	0.213	0.212	1.00	0.214	0.209	1.00
5.	Contrast sensitivity	-0.140	0.417	1.00	0.18	0.295	1.00
6.	Number of IP 1-21 read	-0.149	0.384	1.00	-0.024	0.889	1.00
7.	Number of IP 22-25 read	-0.101	0.557	1.00	0.25	0.141	1.00
8.	CFT	-0.173	0.312	1.00	-0.236	0.165	1.00
9.	SFCT*	0.243	0.153	1.00	0.093	0.591	1.00
10.	NSD number	-0.045	0.795	1.00	-0.234	0.17	1.00
11.	NSD height	-0.083	0.630	1.00	0.012	0.946	1.00
12.	NSD width	-0.086	0.617	1.00	-0.03	0.863	1.00
13.	PED number	-0.102	0.554	1.00	-0.036	0.833	1.00
14.	PED height	-0.022	0.900	1.00	-0.187	0.276	1.00
15.	PED width	0.040	0.819	1.00	-0.21	0.218	1.00
16.	CNVM height	-0.038	0.825	1.00	-0.251	0.14	1.00
17.	CNVM width	0.075	0.665	1.00	-0.251	0.139	1.00
18.	Number of HRF SCP	0.055	0.752	1.00	0.157	0.36	1.00
19.	Number of HRF in DCP	-0.109	0.526	1.00	-0.028	0.869	1.00
20.	Number of HRF in OR	0.185	0.281	1.00	0	0.998	1.00

TABLE 1: Correlation of serum VEGF-A levels with ocular and optical coherence tomography features at the pre-treatment stage

p-value < 0.05 was considered statistically significant; * indicates parametric data; the Pearson correlation coefficient (r) was used for parametric data, and the Spearman correlation coefficient (Rho) was used for non-parametric data.

LogMAR: Logarithm of the Minimum Angle of Resolution; VA: Visual acuity; BCVA: Best corrected visual acuity; IP: Ishihara plates; CFT: Central foveal thickness; SFCT: Subfoveal choroidal thickness; NSD: Neurosensory detachment; PED: Pigment epithelial detachment; CNVM: Choroidal neovascular membrane; HRF: Hyperreflective foci; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; OR: Outer retina.

Among all study variables, only LogMAR VA, LogMAR BCVA, RE, and SFCT were normally distributed. Therefore, Pearson's correlation analysis was performed on these variables, and all showed a positive correlation with serum VEGF-A. For the remaining variables, Spearman's rank correlation coefficient was used to assess the relation with serum VEGF-A levels. Correlation analysis demonstrated a negative correlation between serum VEGF-A levels and CFT, NSD number and width, PED number, height and width, CNVM height and width, and the number of HRF in the DCP. Positive correlations were observed with LogMAR VA, LogMAR BCVA, RE, IOP, CS, SFCT, NSD height, and the number of HRF (hyperreflective foci) in the SCP, whereas no correlation was observed with the number of HRF in the OR. Serum VEGF-A levels

showed a negative correlation with the number of correctly identified IP 1-21, whereas a positive correlation was observed with the number of correctly identified IP 22-25. The IP 22-25 are used to examine red-green color defects. However, none of these correlations reached statistical significance.

Among OCTA parameters, the FAZ area was 0.10 ± 0.12 (median: 0.03; IQR: 0.02 to 0.14) mm^2 , FAZ perimeter was 1.49 ± 0.96 (median: 0.86; IQR: 0.82 to 2.36) mm, and circularity was 0.45 ± 0.12 (median: 0.46; IQR: 0.36 to 0.53). The VD in SCP whole was 18.6 ± 15.8 (median: 18.5; IQR: 3.5 to 30.5), DCP whole was 4.5 ± 6.9 (median: 1.0; IQR: 0.0 to 7.5), OR whole was 5.2 ± 6.7 (median: 2.5; IQR: 0.0 to 8.0), ORCC whole was 31.2 ± 15.4 (median: 34.0; IQR: 20.0 to 42.5), CC whole was 14.3 ± 12.8 (median: 10.5; IQR: 4.0 to 20.5), and choroid whole was 23.5 ± 15.6 (median: 23.0; IQR: 11.5 to 35.5). Table 2 presents the correlation between serum VEGF-A levels and baseline OCTA parameters.

S. No.	Parameter	Pearson Correlation Coefficient r	p value	Bonferroni-Adjusted p-Value	Spearman Correlation Coefficient Rho	p-Value	Bonferroni-Adjusted p-Value
1.	FAZ area	-0.037	0.832	1.00	0.153	0.373	1.00
2.	FAZ perimeter	-0.105	0.541	1.00	-0.039	0.822	1.00
3.	FAZ circularity*	0.437	0.008**	0.376	0.221	0.196	1.00
4.	SCP foveal VD	0.089	0.606	1.00	0.041	0.814	1.00
5.	SCP parafoveal VD*	0.061	0.723	1.00	0.138	0.421	1.00
6.	SCP perifoveal VD*	0.032	0.851	1.00	0.133	0.438	1.00
7.	SCP whole VD*	0.013	0.941	1.00	0.067	0.698	1.00
8.	DCP foveal VD	0.229	0.180	1.00	-0.109	0.527	1.00
9.	DCP parafoveal VD	0.166	0.335	1.00	0.048	0.783	1.00
10.	DCP perifoveal VD	0.126	0.465	1.00	0.051	0.767	1.00
11.	DCP whole VD	0.197	0.249	1.00	-0.109	0.526	1.00
12.	OR foveal VD	0.241	0.157	1.00	-0.019	0.914	1.00
13.	OR parafoveal VD	0.196	0.252	1.00	0.062	0.721	1.00
14.	OR perifoveal VD	-0.024	0.891	1.00	-0.075	0.663	1.00
15.	OR whole VD	0.142	0.408	1.00	0.046	0.79	1.00
16.	ORCC foveal VD*	0.166	0.333	1.00	0.265	0.119	1.00
17.	ORCC parafoveal VD*	0.205	0.230	1.00	0.219	0.199	1.00
18.	ORCC perifoveal VD*	0.082	0.635	1.00	0.09	0.602	1.00
19.	ORCC whole VD*	0.175	0.307	1.00	0.228	0.181	1.00
20.	CC foveal VD	-0.004	0.872	1.00	0.12	0.487	1.00
21.	CC parafoveal VD	0.028	0.872	1.00	0.049	0.777	1.00
22.	CC perifoveal VD	0.088	0.609	1.00	0.088	0.608	1.00

23.	CC whole VD*	0.059	0.732	1.00	0.064	0.71	1.00
24.	Choroid foveal VD	0.040	0.817	1.00	0.2	0.243	1.00
25.	Choroid parafoveal VD*	0.101	0.556	1.00	0.228	0.181	1.00
26.	Choroid perifoveal VD*	0.107	0.535	1.00	0.151	0.379	1.00
27.	Choroid whole VD*	0.076	0.661	1.00	0.179	0.296	1.00

TABLE 2: Correlation of serum VEGF-A levels with optical coherence tomography angiography features at the pre-treatment stage

p-value < 0.05 was considered statistically significant; * indicates parametric data; ** indicates statistical significance before adjusted analysis; the Pearson correlation coefficient (r) was used for parametric data, and the Spearman correlation coefficient (Rho) was used for non-parametric data.

FAZ: Foveal avascular zone; SCP: Superficial capillary plexus; VD: Vessel density; DCP: Deep capillary plexus; OR: Outer retina; ORCC: Outer retinal chorio-capillaries; CC: Chorio-capillaries.

The following variables were normally distributed: FAZ circularity; SCP parafoveal, perifoveal, and whole VD; ORCC foveal, parafoveal, perifoveal, and whole VD; CC whole VD; and choroidal parafoveal, perifoveal, and whole VD. Therefore, Pearson's correlation analysis was performed for these variables, whereas Spearman's rank correlation analysis was used for the remaining variables. Correlation analysis demonstrated a trend toward a negative correlation between serum VEGF-A levels and FAZ perimeter, and positive correlations with FAZ area, FAZ circularity, and VD in most retinal and choroidal layers. However, none of these correlations were statistically significant.

Correlation analysis showed no significant associations between serum VEGF-A levels and any clinical, OCT, or OCTA parameters after adjustment for multiple comparisons using the Bonferroni method (47 comparisons; adjusted significance threshold: $p < 0.00106$). Although FAZ circularity showed a moderate positive Pearson correlation with serum VEGF-A levels ($r = 0.437$, unadjusted; $p = 0.008$), this association was no longer statistically significant after Bonferroni correction (adjusted $p = 0.376$). All remaining Pearson and Spearman correlation coefficients were weak and non-significant (p -value = 1) following adjustment.

At the post-treatment evaluation, the VA improved to 0.9 ± 0.5 LogMAR (range: 0.0-1.8), with a median of 1.0 LogMAR (IQR: 0.5-1.5). The RE changed to -0.2 ± 1.9 diopters (range: -5.5 to 5.0), with a median of -0.1 diopters (IQR: -1.4 to 1.0), indicating a slight myopic shift. The BCVA also improved to 0.8 ± 0.5 LogMAR (range: 0.0-1.8), with a median of 0.8 LogMAR (IQR: 0.4-1.2). The IOP remained essentially unchanged at 15.5 ± 2.6 mmHg (range: 10.2-20.6), with a median of 15.3 mmHg (IQR: 14.6-17.3). Similarly, the CS showed improvement at 0.9 ± 0.6 (range: 0.1-2.0), with a median of 1.0 (IQR: 0.4-1.5).

On CV assessment with 1-21 IP, a score of 16.92 ± 7.5 (median score: 21; IQR: 17 to 21) correctly identified plates was obtained after treatment, while examination on 22-25 plates gave a score of 3.389 ± 1.32 (median score: 4; IQR: 4 to 4) correctly read plates.

Following treatment, the CFT reduced to 324.9 ± 208.0 (median: 284.0; IQR: 183.5 to 426.5) microns, and SFCT reduced to 240.4 ± 68.5 (median: 241.5; IQR: 180.0 to 288.5) microns. The number of NSD also decreased to 0.58 ± 0.91 (median: 0; IQR: 0 to 1). The height and width of NSD reduced to 54.7 ± 95.7 (median: 0.0; IQR: 0.0 to 90.5) microns and 722.1 ± 1068.7 (median: 0.0; IQR: 0.0 to 1323.5) microns, respectively.

The number of PEDs decreased to 1.89 ± 2.50 , with a median of 1.0 (IQR: 0.0-3.75). The height and width of PED reduced to 51.8 ± 64.4 (median: 30.5; IQR: 0.0 to 88.0) microns and 282.2 ± 365.4 (median: 113.0; IQR: 0.0 to 483.25) microns, respectively.

There was no change in the type of CNVM following treatment. At the post-treatment evaluation, 18 eyes (50%) continued to have classic CNVM, while seven (19.44%) eyes continued to have occult CNVM. The remaining 11 (30.55%) eyes with occult CNVM at baseline demonstrated regression of the CNVM, which was replaced by scar tissue. In eyes with regressed CNVM, FFA showed absent or markedly reduced vascular leakage and scar tissue formation; OCT showed resolution of subretinal and/or intraretinal fluid with collapse of the fibrovascular PED, while OCTA demonstrated shrinkage of the neovascular network and

reduced VD parameters. Thus, anti-VEGF therapy did not alter the angiographic subtype of CNVM in eyes with persistent neovascularization. The mean CNVM height and width decreased to 164.3 ± 216.9 microns (median: 37.5 microns; IQR: 0.0-302.0 microns) and 1118.4 ± 1409.9 microns (median: 128.0 microns; IQR: 0.0-2390.0 microns), respectively.

At one month following treatment, analysis of the blood samples demonstrated that the serum VEGF-A levels were 347.5 ± 426.3 pg/mL (range: 31.3-2000.0 pg/mL), with a median of 207.2 pg/mL (IQR: 106.3-423.9 pg/mL). Table 3 presents the correlation between serum VEGF-A levels and post-treatment ocular and OCT features.

S. No.	Parameter	Pearson Correlation Coefficient r	p-Value	Bonferroni-Adjusted p-Value	Spearman Correlation Coefficient Rho	p-Value	Bonferroni-Adjusted p-Value
1.	VA (LogMAR)*	0.042	0.807	1.00	0.031	0.855	1.00
2.	Refractive error*	-0.041	0.812	1.00	-0.092	0.595	1.00
3.	BCVA (LogMAR)*	0.025	0.883	1.00	0.036	0.833	1.00
4.	Intraocular pressure	-0.129	0.452	1.00	0.009	0.959	1.00
5.	Contrast sensitivity*	-0.036	0.833	1.00	-0.041	0.813	1.00
6.	Number of IP 1-21 read	0.186	0.277	1.00	0.107	0.534	1.00
7.	Number of IP 22-25 read	0.156	0.363	1.00	0.181	0.291	1.00
8.	CFT*	0.032	0.853	1.00	-0.084	0.625	1.00
9.	SFCT	0.174	0.310	1.00	0.239	0.161	1.00
10.	NSD number	-0.061	0.723	1.00	0.051	0.768	1.00
11.	NSD height	0.053	0.758	1.00	0.129	0.454	1.00
12.	NSD width	-0.015	0.930	1.00	0.071	0.679	1.00
13.	PED number	0.096	0.578	1.00	0.209	0.222	1.00
14.	PED height	0.014	0.936	1.00	0.195	0.254	1.00
15.	PED width	0.068	0.694	1.00	0.21	0.218	1.00
16.	CNVM height	0.006	0.973	1.00	-0.082	0.633	1.00
17.	CNVM width	0.008	0.965	1.00	-0.088	0.608	1.00
18.	Number of HRF SCP	0.016	0.925	1.00	0.132	0.444	1.00
19.	Number of HRF in DCP	0.137	0.426	1.00	-0.021	0.902	1.00
20.	Number of HRF in OR	0.154	0.369	1.00	0.143	0.404	1.00

TABLE 3: Correlation of serum VEGF-A levels with ocular and optical coherence tomography features at the post-treatment stage

p-value < 0.05 was considered statistically significant; * indicates parametric data; the Pearson correlation coefficient (r) was used for parametric data, and the Spearman correlation coefficient (Rho) was used for non-parametric data.

LogMAR: Logarithm of the Minimum Angle of Resolution; VA: Visual acuity; BCVA: Best-corrected visual acuity; IP: Ishihara plates; CFT: Central foveal thickness; SFCT: Subfoveal choroidal thickness; NSD: Neurosensory detachment; PED: Pigment epithelial detachment; CNVM: Choroidal neovascular membrane; HRF: Hyperreflective foci; SCP: Superficial capillary plexus; DCP: Deep capillary plexus; OR: Outer retina.

Among the variables, only LogMAR VA, LogMAR BCVA, RE, CS, and CFT were normally distributed, and Pearson correlation analysis was performed on these variables. For the remaining variables, the Spearman correlation coefficient was calculated. Correlation analysis demonstrated a trend toward a negative correlation between serum VEGF-A levels and RE, CS, CNVM height and width, and the number of HRF in the DCP. In contrast, positive correlations were observed with LogMAR VA, LogMAR BCVA, IOP, color perception (CP) assessed using IP 1-21 and 22-25, CFT, SFCT, the number, height, and width of NSD and PED, and the number of HRF in the SCP and OR. None of the correlations were significant after applying Bonferroni correction.

Among OCTA parameters, the mean FAZ area was 0.15 ± 0.23 (median: 0.05; IQR: 0.03 to 0.19) mm², FAZ perimeter was 1.76 ± 1.39 (median: 1.23; IQR: 0.92 to 1.92) mm, and circularity was 0.40 ± 0.13 (median: 0.37; IQR: 0.29 to 0.51). The mean vessel density (VD) reduced in different layers, and the mean VD in SCP whole was 14.3 ± 14.1 (median: 9.0; IQR: 4.5 to 26.0), DCP whole was 3.9 ± 6.4 (median: 1.0; IQR: 0.0 to 5.0), OR whole was 3.6 ± 5.2 (median: 1.0; IQR: 0.0 to 4.5), ORCC whole was 29.9 ± 15.0 (median: 32.0; IQR: 18.5 to 42.5), CC whole was 13.5 ± 14.3 (median: 8.0; IQR: 3.0 to 19.0), and choroid whole was 22.9 ± 17.2 (median: 19.0; IQR: 8.5 to 36.0). The correlation between post-treatment serum VEGF-A levels and OCTA features is shown in Table 4.

S. No.	Parameter	Pearson Correlation Coefficient r	p-Value	Bonferroni-Adjusted p-Value	Spearman Correlation Coefficient Rho	p-Value	Bonferroni-Adjusted p-Value
1.	FAZ area	0.012	0.943	1.00	-0.016	0.928	1.00
2.	FAZ perimeter	0.057	0.742	1.00	-0.033	0.846	1.00
3.	FAZ circularity*	-0.170	0.322	1.00	-0.179	0.296	1.00
4.	SCP foveal VD	0.134	0.435	1.00	0.214	0.21	1.00
5.	SCP parafoveal VD	0.239	0.161	1.00	0.13	0.452	1.00
6.	SCP perifoveal VD	0.199	0.245	1.00	0.117	0.499	1.00
7.	SCP whole VD	0.216	0.206	1.00	0.098	0.571	1.00
8.	DCP foveal VD	0.173	0.314	1.00	0.063	0.717	1.00
9.	DCP parafoveal VD	0.152	0.376	1.00	0.145	0.398	1.00
10.	DCP perifoveal VD	0.106	0.537	1.00	0.065	0.706	1.00
11.	DCP whole VD	0.142	0.407	1.00	0.063	0.714	1.00
12.	OR foveal VD	0.334	0.046**	1.00	0.075	0.663	1.00
13.	OR parafoveal VD	0.082	0.636	1.00	-0.045	0.795	1.00
14.	OR perifoveal VD	0.207	0.227	1.00	-0.069	0.687	1.00
15.	OR whole VD	0.175	0.306	1.00	-0.057	0.743	1.00
16.	ORCC foveal VD*	0.020	0.910	1.00	0.103	0.55	1.00
17.	ORCC parafoveal VD*	0.008	0.964	1.00	0.082	0.633	1.00
18.	ORCC perifoveal VD*	0.221	0.196	1.00	0.077	0.654	1.00
19.	ORCC whole VD*	0.106	0.539	1.00	0.119	0.491	1.00
20.	CC foveal VD	-0.104	0.545	1.00	-0.019	0.914	1.00
21.	CC parafoveal VD	-0.012	0.943	1.00	0.125	0.474	1.00
22.	CC perifoveal VD	0.158	0.358	1.00	0.15	0.381	1.00
23.	CC whole VD	-0.024	0.887	1.00	0.069	0.69	1.00
24.	Choroid foveal VD	0.021	0.905	1.00	0.032	0.853	1.00

25.	Choroid parafoveal VD	-0.018	0.917	1.00	0.133	0.439	1.00
26.	Choroid perifoveal VD*	0.249	0.142	1.00	0.235	0.169	1.00
27.	Choroid whole VD*	0.182	0.289	1.00	0.213	0.213	1.00

TABLE 4: Correlation of serum VEGF-A levels with optical coherence tomography angiography features at the post-treatment stage

p-value < 0.05 was considered statistically significant; * indicates parametric data; ** indicates statistical significance before adjusted analysis; the Pearson correlation coefficient (r) was used for parametric data, and the Spearman correlation coefficient (Rho) was used for non-parametric data.

FAZ: Foveal avascular zone; SCP: Superficial capillary plexus; VD: Vessel density; DCP: Deep capillary plexus; OR: Outer retina; ORCC: Outer retinal chorio-capillaries; CC: Chorio-capillaries.

The variables were normally distributed: FAZ circularity; ORCC foveal, parafoveal, perifoveal and whole; and the choroid perifoveal and whole VD. Therefore, Pearson's correlation analysis was performed for these variables, whereas Spearman's rank correlation analysis was used for the remaining variables. Correlation analysis demonstrated a trend whereby higher VEGF levels were negatively correlated with FAZ area, perimeter, and circularity. It positively correlated with VD in most retinal layers, except the OR parafoveal, perifoveal, and whole VD, and CC foveal VD. None of the correlations were significant after applying Bonferroni correction.

At post-treatment, no significant correlations were observed between serum VEGF-A levels and any of the clinical, OCT, or OCTA parameters after Bonferroni correction (47 comparisons; adjusted significance threshold, $p < 0.00106$). The strongest unadjusted association was observed between serum VEGF-A levels and OR foveal VD (Pearson's $r = 0.334$, unadjusted $p = 0.046$); however, this association did not remain significant after correction for multiple testing (adjusted $p = 1.000$). Overall, none of the evaluated structural, functional, or OCTA parameters demonstrated a statistically significant correlation with serum VEGF-A levels after correction for multiple comparisons.

Discussion

Clinical biomarkers of oxidative stress and chronic inflammation that contribute to fluid leakage are important for assessing disease presentation and progression and for guiding treatment decisions. These biomarkers include parameters from ophthalmic examination, OCT, and OCTA, as well as levels of circulating cytokines such as VEGF-A. VEGF-A is the key mediator in the pathogenesis of nARMD, and intravitreal anti-VEGF therapy is the most widely practiced therapy for its management [9]. However, prolonged and intensive anti-VEGF treatment may compromise the retinal and choroidal blood supply, potentially contributing to retino-choroidal atrophy [6,17]. Understanding the relationship between serum VEGF-A levels and disease severity may therefore provide valuable insights into the disease's pathophysiology and facilitate the development of individualized treatment strategies.

Although OCT provides high-resolution structural imaging of the retina and choroid, OCTA offers additional qualitative and quantitative assessment of the retinal and choroidal microvasculature at different depths. The relationship between OCTA-derived parameters and serum VEGF-A levels has been infrequently investigated in ExARMD. Therefore, in the present study, we evaluated correlations among ocular biomarkers, including OCTA-derived parameters and serum VEGF-A levels, to investigate the association of VEGF-A with FAZ characteristics and VD in the retina and choroid. We further reassessed these correlations following treatment to determine whether anti-VEGF therapy modifies the relationship between ocular imaging biomarkers and serum VEGF-A levels.

As VEGF165 is the predominant and biologically most active isoform of VEGF-A, Haas et al. quantified serum VEGF165 levels using ELISA and found these to be 531.89 pg/mL in predominantly classic CNV, 324.53 pg/mL in minimally classic CNV, 375.93 pg/mL in occult CNV, and 289.30 pg/mL in retinal angiomatous proliferation [1]. Similarly, Moshtaghion et al. demonstrated significantly higher tear VEGF levels in 29 patients with ExARMD (124.9 pg/mL) compared with healthy controls (36.46 pg/mL; $p < 0.001$) [18]. Baharivand et al. reported a significant correlation between vitreous and serum VEGF levels [19]. So we measured serum VEGF-A levels in our subjects. In the present study, the baseline serum VEGF-A levels were 323.2 ± 358.3 pg/mL, with values ranging from 31.3 to 1765.1 pg/mL. As the data were not normally distributed, the median serum VEGF-A level was also calculated and was 221.1 pg/mL (interquartile range (IQR): 130.0-355.7 pg/mL).

Todoroki et al. reported that aqueous humor VEGF-A levels increased from 0.16 ± 1.15 to 1.16 ± 5.71 pg/ μ L following a switch from aflibercept to faricimab [8]. In contrast, Nonogaki et al. found that the mean aqueous humor VEGF-A concentration decreased from 160.35 ± 63.56 pg/mL at baseline to below the lower limit of detection in all eyes after faricimab administration [2]. Gu et al. found that serum VEGF concentrations decreased from 323.64 to 311.79 pg/mL ($p > 0.05$) in ARMD patients at one month following a single intravitreal injection of ranibizumab (0.5 mg) [20]. In the present study, the mean serum VEGF-A level was 347.5 ± 426.3 pg/mL at one month following RbB treatment, with values ranging from 31.3 to 2000.0 pg/mL. As the data were not normally distributed, the median serum VEGF-A level was also calculated and was 207.2 pg/mL (interquartile range (IQR): 106.3-423.9 pg/mL), and the post-treatment median was lower than the baseline level of 221.1 pg/mL.

The OCTA features have been investigated relatively infrequently in ExARMD. Faatz et al. reported a significant reduction in the CNV size at the RPE, OR, CC, and choroidal levels following anti-VEGF therapy [7]. In another study evaluating CC in areas of regenerated fundus autofluorescence after RPE tears, OCTA showed variable flow density patterns, including unchanged, increased, and decreased flow signals [9]. While investigating OCTA-derived NV parameters as predictors of frequent recurrence in nARMD, Choi et al. found that, among NV area, NV density, total NV length, junction density, mean lacunarity, and largest vessel diameter, only endpoint density was a significant predictor [6].

Mottet et al. used laser Doppler flowmetry (LDF) to evaluate changes in subfoveal choroidal blood flow following the first intravitreal ranibizumab injection in patients with newly diagnosed nARMD. They observed a reduction in choroidal blood flow velocity as early as seven days after treatment, suggesting that anti-VEGF therapy may induce vasoconstriction of the large choroidal vessels [21]. We also found that VD in most retino-choroidal layers, including the choroid, decreased following intravitreal RbB.

The studies evaluating VEGF levels in ExARMD have primarily assessed treatment response using BCVA and structural OCT parameters, such as CFT and SFCT [2,8]. To the best of our knowledge, the relationship between VEGF levels and OCTA-derived parameters has rarely been systematically investigated.

After anti-VEGF, all visual functions, including VA, CS, and CP on IP 22-25, improved; the RE increased with a slight myopic shift, while CP assessed on IP 1-21 decreased. We found a negative correlation of serum VEGF-A levels with HRF in DCP and CNVM height and width, while a positive correlation was observed with LogMAR VA, LogMAR BCVA, IOP, CP on IP 22-25, SFCT, NSD height, and HRF in SCP at both before and after treatment. So, an increase in VEGF-A led to an increase in IOP, SFCT, NSD height, and HRF in SCP and better CP on IP 22-25, while this led to reduced VA, CNVM height and width, and HRF in DCP. The relationships between serum VEGF-A levels and RE, CS, CP on IP 1-21, CFT, NSD number and width, and PED number, height, and width reversed following treatment.

Following treatment, the OCTA parameters showed deterioration. There was an increase in FAZ area and perimeter and a reduction in FAZ circularity and VD in all retinal and choroidal layers. We found a negative correlation between serum VEGF-A and FAZ perimeter, while a positive correlation was found with VD in most retino-choroidal layers. The direction of the correlation between serum VEGF-A levels and FAZ area and circularity changed following treatment. These findings suggest that one of the two - either ocular features or serum VEGF-A - tends to be influenced by additional factors [3].

The major strength of the study was its prospective design and inclusion of only treatment-naïve eyes with ExARMD. However, the study has several limitations. First, the sample size was relatively small. As withholding standard-of-care anti-VEGF therapy in treatment-naïve ExARMD patients presents ethical constraints, an untreated parallel control arm was not feasible. The lack of an untreated or sham-control arm and a before-and-after interventional design limits direct attribution of the structural and functional changes solely to therapeutic efficacy. Second, because the primary objective was exploratory characterization of ophthalmic parameters in relation to cytokine levels, 36 eyes derived from 25 patients were analyzed as independent units, introducing potential clustered correlation, which is an acknowledged limitation of standard bivariate Pearson and Spearman correlation testing. Third, the sample size provided statistical power primarily for moderate-to-large bivariate correlations, and after strict Bonferroni correction for multiple testing, no significant association was observed. Fourth, the single-dose regimen with a one-month follow-up precludes evaluation of long-term real-world anti-VEGF outcomes. Finally, serum samples were collected because blood testing is minimally invasive, though vitreous VEGF-A concentrations may more accurately reflect the intraocular angiogenic milieu and disease activity, and this factor may also dampen correlation strength. Furthermore, the OCTA device used in this study acquired only 3×3 mm macular scans, whereas ExARMD subjects have reduced central vision and poor fixation, which may have introduced motion and fixation-related artefacts. Additionally, the presence of CNVM and large PEDs might have introduced segmentation errors and pressure effects, leading to incorrect VD measurements across different layers. The authors intend to publish additional, distinct findings derived from the same research project in separate publications.

Conclusions

This exploratory study involves evaluating the relationship between OCTA-derived parameters and serum

VEGF-A levels in ExARMD across two evaluation points, that is, before and after treatment with anti-VEGF therapy. Higher serum VEGF-A levels were associated with poorer VA, more NSD height, smaller CNVM height and width, fewer HRF in the DCP, higher IOP, better CP on IP 22–25, greater SFCT, and a greater number of HRF in the SCP at both occasions. The positive association between serum VEGF-A levels and CP on IP 22–25 suggests that red-green color perception was not adversely affected at the serum VEGF-A levels observed in this cohort (median: 221.1 pg/mL at baseline and 207.2 pg/mL after treatment). Among the OCTA-derived parameters, higher serum VEGF-A levels were associated with a smaller FAZ perimeter and higher VD in most retinal and choroidal layers at both time points. However, as none of the observed correlations reached statistical significance, our findings indicate that circulating serum VEGF-A is not a reliable surrogate biomarker for localized retino-choroidal microvascular alterations in ExARMD. Future prospective studies with larger cohorts and intraocular cytokine sampling are warranted to validate these relationships. Further generalized estimating equations or multilevel mixed-effects regression models may be employed to formally account for inter-eye dependencies.

Additional Information

Author Contributions

All authors have reviewed the final version to be published and agreed to be accountable for all aspects of the work.

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Disclosures

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