• Clinical Research •

Quantitative characterization of types 1 and 2 macular neovascularization in neovascular age-related macular degeneration with intravitreal conbercept: an analysis utilizing optical coherence tomography angiography

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Abstract

● **AIM:** To quantitatively assess central macular thickness (CMT), macular neovascularization (MNV) area, vascular tortuosity (VT), and vascular dispersion (VDisp) in neovascular age-related macular degeneration (nAMD), type 1 and type 2 MNV, by means of optical coherence tomography (OCT) and OCT angiography (OCTA) techniques.

● **METHODS:** In this retrospective and observational case series, patients were classified into type 1 or type 2 MNV groups. A comprehensive panel of OCT and OCTA metrics was evaluated, including CMT, MNV area, VT, and VDisp. All subjects underwent a standardized intravitreal conbercept (IVC) regimen [3+*pro re nata* (PRN)] with a 12-month follow-up. MNV area was obtained by manual measurements with OCTA software, and VT and VDisp were calculated by automated analysis with Image J software.

● **RESULTS:** A total of 101 participants were included, with 51 patients in the type 1 MNV group (mean age 67.32±9.12y) and 50 patients in the type 2 MNV group (mean age 64.74±5.21y). The mean number of IVC injections was 3.98±1.53 for type 1 MNV and 3.73±0.81 for type 2 MNV. Both subtypes exhibited significant improvements in visual acuity, accompanied by marked reductions in CMT and MNV area (P<0.05) at 12mo after treatment. In type 2 MNV, VT significantly decreased (P<0.05), whereas no significant change was observed in VT for type 1 MNV. VDisp did not significantly changed in either sybtypes. Moreover, in type 1 MNV, final best-corrected visual acuity (BCVA) using logMAR correlated positively with both pre- and post-treatment CMT, while in type 2 MNV, a significant positive correlation was found between the number of injections and final CMT.

● **CONCLUSION:** This study shows that conbercept treatment significantly improves visual acuity and macular structure in both type 1 and type 2 MNV with reductions in CMT and MNV area. The significant reduction in VT in type 2 MNV suggests its potential as a biomarker for disease activity. The findings imply the quantitative assessment useful for the stratification, prognostication, and personalized management of MNV in nAMD.

● **KEYWORDS:** macular neovascularization; age-related macular degeneration; optical coherence tomography angiography; conbercept; vessel tortuosity; vessel dispersion

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INTRODUCTION

Age-related macular degeneration (AMD) is the leading cause of severe, irreversible vision impairment in individuals over the age of 50 years old. The prevalence of AMD is influenced by ethnic and regional disparities. Global estimates indicate that the number of affected individuals will increase from approximately 196 million in 2020 to 288 million by 2040. In China, where the population accounts for nearly 18% of the world's total, prevalence rates vary geographically, with the highest rates reported in south-central regions (6.64% in 2000 and 6.74% in 2010)[1]. Macular neovascularization (MNV) is a key complication of advanced of AMD[2], which generally classified into three subtypes: type 1 MNV, characterized by neovascular growth beneath the retinal pigment epithelium (RPE), and type 2 MNV, which is marked by aberrant neovascular proliferation within the subretinal space due to the disruption of the Bruch's membrane-RPE complex[3]. While type 3 MNV refers to a downgrowth of vessels from the retinal circulation toward the outer retina[4].

Current diagnostic methods for MNV include fluorescein fundus angiography (FFA), indocyanine green angiography (ICGA), optical coherence tomography (OCT), and OCT angiography (OCTA). These imaging modalities play a crucial role in detecting and assessing MNV. By identifying key activity markers such as dye leakage observed on FFA/ICGA, the presence of intraretinal, subretinal, or sub-RPE fluid on OCT, and retinal hemorrhages evident during fundus examination[5]. The introduction of anti-vascular endothelial growth factor (anti-VEGF) therapy has transformed the clinical management of MNV, particularly in cases presenting with subretinal, intraretinal, or sub-RPE fluid, along with increased central macular thickness (CMT) as indicated on OCT[6-7]. Among available anti-VEGF agents, conbercept (KH902; Chengdu Kanghong Biotech Co, China), a recombinant fusion protein produced in a Chinese hamster ovary (CHO) cell expression system[8]. It has demonstrated both efficacy and safety in the treatment of AMD[9-10].

Beyond qualitative assessments, the incorporation of quantitative indicators are increasingly recognized for their role in accurately identifying and monitoring of MNV progression. OCTA as a non-invasive technique, enables detailed visualization of retinal and choroidal microvasculature[11], and provides morphological biomarkers for evaluating neovascular activity[12-18]. The prognosis of AMD treatment varies widely, numerous studies have investigated MNV characteristics, including lesion area, vessel density, and the presence of intraretinal and subretinal fluid. However, vessel density measurements often yield inconsistent results due to variations in imaging equipment, with some systems relying on automated analyses. While CMT is a well-established biomarker, with clear conclusions drawn for type 1 and type2 MNV, research on Vascular tortuosity (VT) and vascular dispersion (VDisp) remains limited[19-20]. VT and VDisp are two important metrics used in the OCTA technique to assess MNV activity. VT reflects the complexity of the vascular network, whereas VDisp may be indicative of the spatial distribution of vessel growth. The aim of this study was to further understand the pathological characteristics of MNV in neovascular AMD (nAMD) by using these quantitative indicators.

PARTICIPANTS AND METHODS

Ethical Approval The study was conducted at Shandong Eye Hospital in China, between October 2018 and December 2022. All procedures adhered to the Declaration of Helsinki and were approved by the Institutional Review Board of Shandong Eye Hospital (Approval No.202101-1). Informed consent was obtained from all participants.

Participants This retrospective, observational case series included a follow-up period of 12 to 24mo and compared two groups: 51 patients with type 1 MNV and 50 patients with type 2 MNV. The type 1 MNV group comprised 32 males (63%), while in the type 2 MNV group included 33 males (66%). Each participant contributed one eye to the study. Due to the rarity of type 3 MNV, patients with this subtype were not included.

Patients were eligible for inclusion if they met the following criteria: 1) Patients diagnosed with primary type 1 MNV and type 2 MNV associated with AMD[12]; 2) Patients who has intravitreal conbercept (IVC) injections; 3) Patients has been followed up for a minimum of 12mo after their initial visit; 4) Patients with nAMD who were primed and previously treated with anti-VEGF therapy were included in this study. Previously treated patients were required to have not received any treatment for at least 3mo after the end of treatment.

Patients were excluded if they met any of the following conditions: 1) presence of significant refractive interstitial opacity compromising multimodal imaging quality; 2) co-existing ocular or systemic diseases that could lead to vision loss or MVN-like symptoms, including polypoidal choroidal vasculopathy (PCV), pathologic myopia, and glaucoma; 3) patients with a history of intraocular surgery; 4) cases with

significant pigment epithelial detachment (PED; PED>250 μm) were excluded to avoid impact on OCTA image quality.

Ophthalmologic Examination Each participant underwent a comprehensive ophthalmologic examination conducted by an experienced physician. This included measurements of best-corrected visual acuity (BCVA) using logMAR chart, intraocular pressure (IOP) assessment, slit-lamp biomicroscopy of the anterior and posterior segments, and color fundus photography. Additionally, spectral-domain OCT (SD-OCT) and OCTA images were acquired using the Heidelberg Spectralis HRA+OCT system (Heidelberg Engineering, Heidelberg, Germany). Using Heidelberg Spectralis HRA+OCT with the macula as the center of the scan, 40 000 A-scans were acquired and 12 B-scans were acquired per examination. Automatic registration tool (ART) value set to ≥12 to ensure image quality. All cross-sectional OCTA scans obtained during each examination were reviewed, and the B-scans showing the largest areas of MNV lesions were selected for analysis. The CMT and MNV area were manually measured using the built-in virtual caliper function in the OCTA software. All OCTA images were evaluated by quality control software, excluding images with a resolution of less than 10 dB. Segmentation results were independently assessed by two experienced ophthalmologists and manually corrected where necessary. Correction methods included manual adjustment of vessels that were segmented incorrectly.

Quantitative parameters, including VT[21-22] and VDisp[23], were extracted from processed OCTA images using Image J software (https://imagej.net/Fiji/Downloads). The original images were converted to 8-bit grayscale using Fiji software, and the "skeletonization" plugin was used to skeletonize the binarized image. VT was calculated using the "Analyze Skeleton" tool, while the "Directionality" tool was applied to determine VDisp.

Treatment Protocol All patients received IVC injection following a [3+ *pro re nata* (PRN)] regimen (0.5 mg/0.05 mL; Chengdu Kanghong, Chengdu, China), with the need for additional injections determined by disease progression. OCT and OCTA imaging were performed within one week prior to the intravitreal injection, and follow-up examinations were conducted monthly throughout the study period, with relevant indicators measured at baseline and at the last follow-up visit. PRN retreatment was initiated if any of the following conditions were met: a decline in visual acuity by more than three lines, the presence of new retinal hemorrhages detected during fundoscopic examination, or the identification of subretinal, intraretinal, or sub-RPE fluid accumulation on OCT, along with an increase in CMT. Treatment was discontinued after three consecutive months of stability, defined as the absence of intraretinal and subretinal fluid on OCT.

Data Analysis Statistical analysis was conducted using SPSS software (version 27.0, SPSS Inc., Chicago, IL, USA). Categorical variables were reported as absolute values, while continuous variables were expressed as mean±standard deviation (SD). The Wilcoxon Mann-Whitney test was applied to compare differences in continuous variables, while Spearman correlation analysis was used to assess relationships between key indicators. A P-value<0.05 was considered statistically significant for all analyses.

RESULTS

A total of 101 participants meeting the predefined inclusion criteria, were enrolled in this study, including 51 patients with type 1 MNV and 50 patients with type 2 MNV. The mean age of the type 1 MNV was 67.32±9.12y, while that of the type 2 MNV was 64.74±5.21y, with an overall range of 51 to 87y. The mean number of anti-VEGF injections administered throughout the study period was 3.98±1.53 for type 1 MNV and 3.73±0.81 for type 2 MNV. A detailed summary of clinical and demographic characteristics is provided in Table 1.

Following conbercept treatment, patients with type 1 MNV demonstrated a significant improvement in mean BCVA (logMAR) improved from 0.67±0.42 at baseline to 0.54±0.41 (P<0.001). Simultaneously, the mean CMT decreased from 369.20±179.10 μm at baseline to 304.75±161.12 μm (P<0.001), while the mean MNV area reduced from 1.73±2.37 to 1.44±1.94 mm² (P=0.019). OCTA image reconstruction revealed a mean decrease in VT from 11.01±2.86 to 10.41±3.18 (P=0.267), and VDisp decreased from 8.60±3.83 to 8.42±4.63 (P=0.423), though neither change was statistically different. A compilation of clinical and OCTA parameters for type 1 MNV before and after anti-VEGF treatment is presented in Table 2.

In the type 2 MNV cohort, a significant improvement in mean BCVA (logMAR) was observed, improved from a baseline score of 0.59±0.40 to 0.23±0.23 (P<0.001). Concurrently, the mean CMT showed a significant reduction from 304.12±108.11 to 192.12±56.56 μm (P<0.001), and the mean MNV area decreased from 0.74±0.79 mm^2 to 0.44±0.51 mm^2 (P<0.001). OCTA image analysis further revealed a notable decrease in mean VT from 14.59±3.64 to 9.60±3.73 (P<0.001), suggesting a reduction in vascular complexity. In contrast, mean VDisp increased from 9.64±9.02 to 11.28±8.78 (P=0.197). A detailed summary of the clinical and OCTA parameters for type 2 MNV before and after anti-VEGF treatment is outlined in Table 2.

Comparative analysis revealed that the mean final BCVA and CMT were significantly higher in the type 1 MNV group compared to the type 2 MNV group (P<0.001). Additionally, both baseline and final MNV area measurements were significantly larger in type 1 MNV than that in type 2 MNV (P=0.004 and P<0.001, respectively). However, the mean baseline VT was significantly lower in type 1 MNV compared

Table 1 Demographic and clinical characteristics of enrolled patients *n* (%)

Variable	Type 1 MNV (*n*=51)	Type 2 MNV (*n*=50)	*P*
Gender			0.733
Male	32 (63)	33 (66)	
Female	19 (37)	17 (34)	
Age (y), mean±SD	67.32±9.12	64.74±5.21	0.116
Total number of anti-VEGF injections, mean±SD	3.98±1.53	3.73±0.81	0.327
Hypertension	18 (35)	17 (33)	0.767
Diabetes mellitus	7 (14)	6 (12)	0.835
Cardiovascular disease	6 (12)	5 (10)	0.750

VEGF: Vascular endothelial growth factor; SD: Standard deviation; MNV: Macular neovascularization.

to type 2 MNV (P<0.001). A detailed summary of the clinical and OCTA parameters for both MNV subtypes before and after anti-VEGF treatment is provided in Table 2.

Furthermore, in type 1 MNV, a significant positive correlation was observed between final BCVA (logMAR) and both pre- and post-treatment CMT. Similarly, baseline BCVA (logMAR) was significantly correlated with baseline CMT (Figure 1). In type 2 MNV, a significant positive correlation was found between the number of IVC and final CMT in type 2 MNV (Figure 2). Representative multimodal imaging examples are depicted in Figures 3 and 4.

DISCUSSION

In this study, we conducted a comprehensive evaluation of 51 eyes with type 1 MNV and 50 eyes with type 2 MNV that underwent IVC therapy. Our findings demonstrate that intravitreal injections of conbercept effectively reduced MNV activity, leading to a reduction of CMT and MNV area. Additionally, treatment resulted in a significant improvement in BCVA with no serious ocular complications, aligning with previous studies that have demonstrated the efficacy of conbercept in the treatment of MNV[10,24]. While traditional assessments of MNV activity have relied on qualitative imaging findings, such as dye leakage on FFA/ICGA and fluid accumulation on OCT, our study sought to enhance the precision of disease monitoring through quantitative analysis using OCTA. By incorporating objective parameters such as MNV area, VT, and VDisp, this study provides a more detailed characterization of MNV dynamics and the response to conbercept treatment[14,25].

Our analysis revealed that anti-VEGF therapy led to a significant reduction in MNV area in both type 1 and type 2 MNV. Additionally, a significant decrease in VT was observed specifically in type 2 MNV, whereas no significant change was noted in type 1 MNV. VT, defined as the ratio of the actual path length to the shortest possible straight-line distance, serves as an indicator of vascular network complexity and perfusion efficiency. The observed decline in VT following suggests a reduction in vascular complexity and perfusion, consistent with the findings of Faatz *et al*[26], who reported a post-treatment decrease in total MNV vessel length and the number of individual vascular segments post-treatment. A predictive model developed by Coscas *et al*[27], utilizing quantitative OCTA parameters, demonstrated a strong correlation between MNV area and MNV activity, incorporating metrics such as blood flow area, vascular density, and fractal dimension. This model successfully distinguished between active and remission phases of neovascular AMD. Furthermore, Arrigo *et al*[19] identified that type 1 MNV secondary to AMD could be stratified into subgroups with divergent clinical outcomes based on VT, where lower VT was associated with more

Table 2 Clinical and OCTA features of type 1 and type 2 MNV at baseline and last follow-up after treatment with intravitreal injections of conbercept

Variable	Type 1 MNV	Type 2 MNV	P^1
BCVA (logMAR)			
Baseline	0.67±0.42	0.59±0.40	0.326
Last follow-up	0.54±0.41	0.23±0.23	<0.001[c]
P^2	<0.001[c]	<0.001[c]	
CMT (μm)			
Baseline	369.20±179.10	304.12±108.11	0.164
Last follow-up	304.75±161.12	192.12±56.56	<0.001[c]
P^2	<0.001[c]	<0.001[c]	
MNV area (mm²)			
Baseline	1.73±2.37	0.74±0.79	0.004[b]
Last follow-up	1.44±1.94	0.44±0.51	<0.001[c]
P^2	0.019[a]	<0.001[c]	
MNV VT			
Baseline	11.01±2.86	14.59±3.64	<0.001[c]
Last follow-up	10.41±3.18	9.60±3.73	0.431
P^2	0.267	<0.001[c]	
MNV VDisp			
Baseline	8.60±3.83	9.64±9.02	0.449
Last follow-up	8.42±4.63	11.28±8.78	0.390
P^2	0.423	0.197	

[1]Comparison between groups; [2]Comparison within group. OCTA: Optical coherence tomography angiography; MNV: Macular neovascularization; BCVA: Best corrected visual acuity; CMT: Central macular thickness; VT: Vessel tortuosity; VDisp: Vessel dispersion. [a]P<0.05; [b]P<0.01; [c]P<0.001.

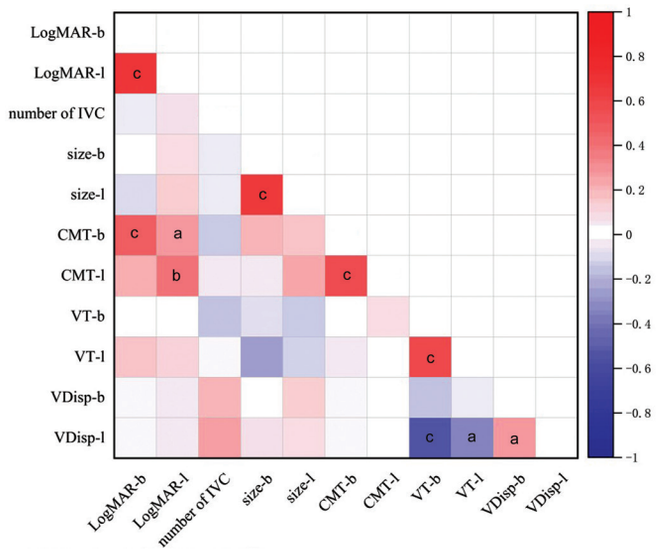

Figure 1 Heatmap illustrated the correlation between 11 variables of type 1 MNV The color scale ranges from blue (negative correlation) to red (positive correlation), with darker shades indicating stronger correlations. In type 1 MNV, a significant positive correlation was observed between final BCVA (logMAR) and both pre- and post-treatment CMT. Similarly, baseline BCVA (logMAR) was significantly correlated with baseline CMT. IVC: Intravitreal conbercept; CMT: Central macular thickness; VT: Vessel tortuosity; VDisp: Vessel dispersion; b: Baseline; l: Last follow-up; MNV: Macular neovascularization; BCVA: Best-corrected visual acuity. [a]*P*<0.05; [b]*P*<0.01, [c]*P*<0.001.

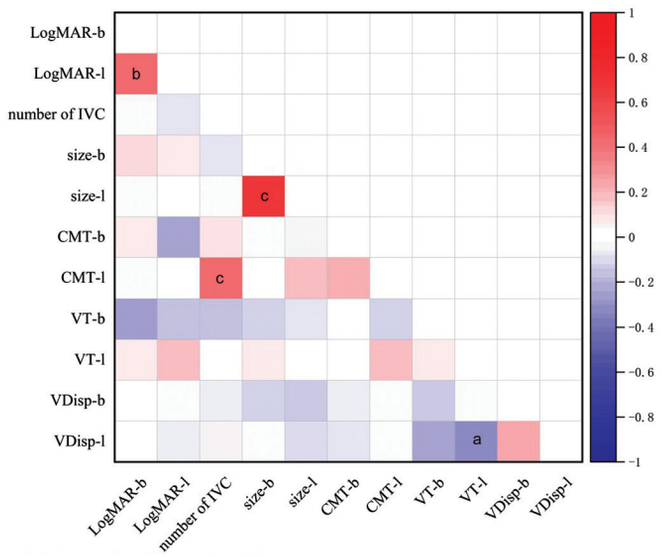

Figure 2 Heatmap illustrated the correlation between 11 variables of type 2 MNV The color scale ranges from blue (negative correlation) to red (positive correlation), with darker shades indicating stronger correlations. In type 2 MNV, a significant positive correlation was found between the number of IVC and final CMT. IVC: Intravitreal conbercept; CMT: Central macular thickness; VT: Vessel tortuosity; VDisp; Vessel dispersion; b: baseline; l: Last follow-up; MNV: Macular neovascularization. [a]*P*<0.05; [b]*P*<0.01, [c]*P*<0.001.

favorable visual outcomes and fewer signs of extraretinal degenerative changes. Conversely, higher VT has been linked to increased vascular complexity, which may predispose patients to a greater risk of subretinal fibrosis and atrophy.In our study, the significant reduction in VT observed in type 2 MNV post-treatment correlated with the superior outcomes achieved in this group compared to type 1 MNV. The absence of a statistically significant change in VT in type 1 MNV may reflect the intrinsically lower activity of this subtype, rendering it less responsive to anti-VEGF therapy.

Our findings also indicate that VDisp remained largely unchanged following treatment. While previous studies have primarily focused on baseline VDisp measurements, fewer have explored pre- and post-treatment comparisons, limiting insights into its dynamic response to therapy. VDisp, reflects the spatial distribution and complexity of the vascular network above the RPE, may serve as an indicator of vascular expansion within a broader neovascular space. The lack of significant change in VDisp observed in our study could be attributed to the intrinsic structural complexity of the neovascular network, where any potential alterations induced by anti-VEGF therapy may be subtle and difficult to detect statistically.

In terms of treatment outcomes, patients with type 2 MNV in our study typically demonstrated significant visual improvement after three anti-VEGF injections. In contrast, type 1 MNV, despite exhibiting lower baseline neovascular activity, was found to be more resistant to suppression[25]. This differential response to treatment between the two subtypes underscores necessity for tailored therapeutic strategies and highlights the importance of identifying subtype-specific biomarkers to optimize disease monitoring and treatment efficacy.

In our study, a significant positive correlation was observed in type 1 MNV, between final BCVA (logMAR) and both pre- and post-treatment CMT. This implies that an increase in CMT, suggesting that greater macular thickness, either at baseline or after treatment, was associated with better visual outcomes. Özen and Koçak Altıntaş's[18] study found that, in type 2 MNV, there was a significant positive correlation between the number of drug injections and final CMT, a finding that aligns with our results. This further supports the notion that CMT and treatment burden may serve as key indicators of disease progression and therapeutic response in different MNV subtypes.

The present study provides a comprehensive evaluation of the efficacy of conbercept in the treatment of type 1 and type 2 MNV associated with nAMD. The findings indicate that conbercept therapy significantly improves visual acuity improvements in both subtypes, with substantial reductions in CMT and MNV area. Notably, type 2 MNV exhibited a significant decrease in VT following treatment, suggesting that

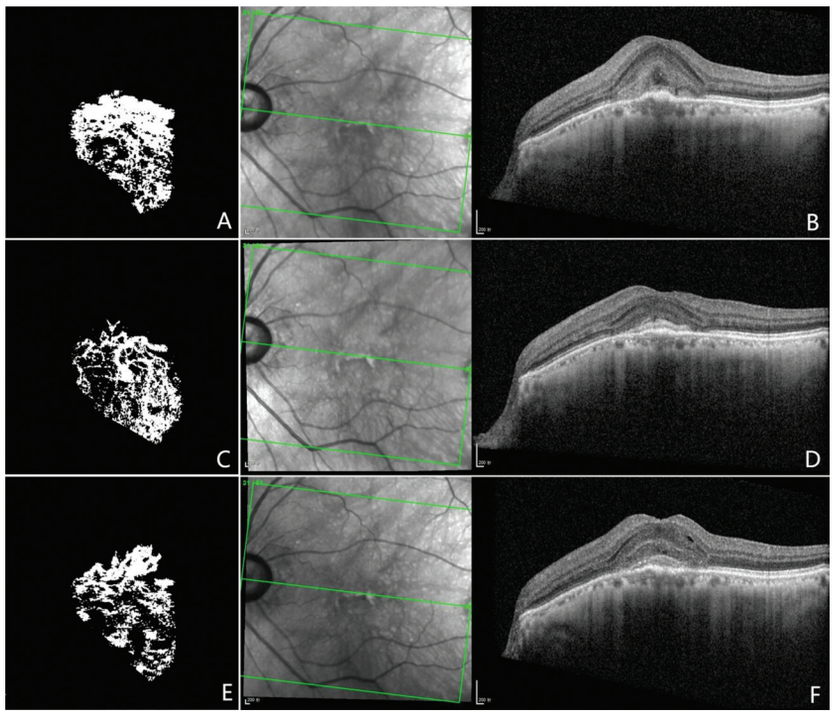

Figure 3 Multimodal imaging of a 74-year-old woman with type 1 MNV in the left eye Following three anti-VEGF treatments over a 12-month follow-up period, the patient's BCVA (logMAR) improved from 1.00 to 0.82. Reconstructed OCTA images (A, C, E) show a slight regression of MNV from pre-treatment levels. SD-OCT images (B, D, F) reveal no significant changes. VEGF: Vascular endothelial growth factors; BCVA: Best corrected visual acuity; OCTA: Optical coherence tomography angiography; MNV: Macular neovascularization; SD-OCT: Spectral-domain optical coherence tomography.

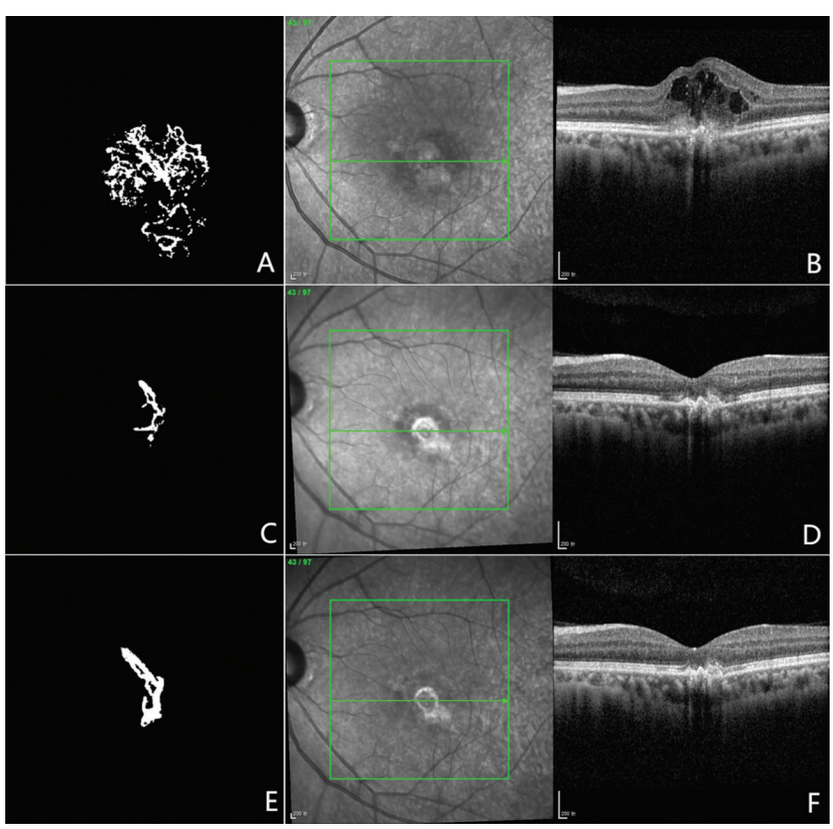

Figure 4 Multimodal imaging of a 52-year-old woman with type 2 MNV in the left eye After three anti-VEGF treatments over a 12-month period, the patient's BCVA (logMAR) improved significantly from 0.92 to 0.22. OCTA images (A, C, E) demonstrate a dramatic resolution of MNV. SD-OCT images V (B, D, F) show a clear reduction in intraretinal fluid. VEGF: Vascular endothelial growth factors; BCVA: Best corrected visual acuity; OCTA: Optical coherence tomography angiography; MNV: Macular neovascularization; SD-OCT: Spectral-domain optical coherence tomography.

VT may serve as a potential biomarker for monitoring disease activity in this subtype. Furthermore, our results reinforce the utility of OCTA as a non-invasive imaging modality capable of providing detailed insights into retinal and choroidal microvasculature, facilitating quantitative disease assessment. The differential response to conbercept treatment between type 1 and type 2 MNV highlights the clinical importance of MNV subtype classification. While type 2 MNV exhibited a more pronounced therapeutic response to treatment, type 1 MNV, despite its lower baseline neovascular activity, was found to be less responsive to anti-VEGF therapy. These findings emphasize the need for personalized treatment strategies tailored to the specific characteristics of each MNV subtype, potentially optimizing therapeutic outcomes in patients with nAMD.

The study also acknowledges certain inherent limitations including the potential for minor errors in OCTA measurements and the lack of dynamic observations over the follow-up period. Future research should aim to address these limitations by incorporating longitudinal data and refining OCTA analysis techniques to enhance measurement accuracy and disease monitoring.

In summary, our investigation offers valuable insights the efficacy of conbercept in MNV treatment, demonstrating its effectiveness in reducing MNV activity and improving visual outcomes. Additionally, the identification of potential biomarkers, such as VT for type 2 MNV, represents a significant contribution to the field. Leveraging OCT and OCTA-based quantitative parameters to predict nAMD prognosis offer distinct advantages, equipping clinicians with additional tools for personalized treatment planning and optimized disease management.

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