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Imaging Biomarkers of 1-Year Activity in Type 1 Macular Neovascularization

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Purpose: The purpose of this study was to evaluate the predictive value of optical coherence tomography (OCT) and OCT angiography (OCTA) parameters at baseline on lesion's activity at the 1-year follow-up in type 1 macular neovascularizations (MNVs) treated with 1-year fixed regimen of intravitreal aflibercept injections (q8 IAIs).

Methods: All patients were imaged by structural OCT to evaluate central macular thickness (CMT), subretinal fluid (SRF), subretinal hyper-reflective material (SHRM), intraretinal fluid (IRF) and intraretinal hyper-reflective dots (HRDs), and by Swept-Source OCTA to measure baseline MNV area, perfusion density (PD), vessel length density (VLD), and vessel diameter index. At the end of q8 IAI, patients were classified in two groups: active-MNV (A-MNV) and inactive-MNV (I-MNV), considering the OCT signs of activity. Three binary logistic regression models were developed: (1) OCT-based, (2) OCTA-based, and (3) OCT/OCTA-based model.

Results: Thirty-one treatment-naïve type 1 MNVs were enrolled (13 A-MNV and 18 I-MNV). No differences were observed in baseline OCT and OCTA characteristics between A-MNV and I-MNV. Among the models developed, model 3 that combined OCT/OCTA parameters showed a performance of 87.5% and excellent sensitivity for A-MNV lesions (100%). By analyzing the model, the A-MNV group appears more likely to show at baseline SRF, greater CMT, wider MNV area, and lower PD and VLD compared to I-MNV.

Conclusions: Our study demonstrated that the combination of baseline OCT and OCTA parameters allowed to achieve a good models' performance in the prediction of MNV activity permitting to correctly classifying the active lesions at the end of follow-up period, with excellent sensitivity.

Translational Relevance: OCT/OCTA could integrate statistical models potentially useful for artificial intelligence.

Introduction

The current therapeutic approach to neovascular age-related macular degeneration (nAMD) is based on the use of anti-vascular endothelial growth factor (VEGF) drugs with the purpose to suppress macular neovascularization (MNV) activity and to consequently improve visual acuity (VA).[1] Currently, several anti-VEGF agents are available and different therapeutic strategies (i.e. monthly/bimonthly fixed regimen, treat and extend or pro re nata) can be chosen after considering debated baseline clinical features.[2–5]

In the type 1 MNV, the vessels are initially ingrowth from the choriocapillaris into and within the subretinal pigment epithelium (RPE) space, whereas in the type 2 MNV, the neovascular complex is located in the subretinal space, above the level of the RPE.[1] Different types of MNV showed different responses to anti-VEGF treatment,[6] in particular the regression of type 1 MNV after anti-VEGF appeared to be lower when compared to type 2 MNV.

Prognostic biomarkers are predictive factors that provide an indication as to the expected patient response to therapy.[2] The use of optical coherence tomography (OCT) has granted the identification of

imaging biomarkers of MNV activity, including the presence of subretinal fluid (SRF) and/or intraretinal fluid (IRF). The latter morphological signs may also have a prognostic role in terms of treatment response, in combination with other clinical and functional features that include patients' age, baseline VA, and early treatment response.[2,3,7–9]

OCT angiography (OCTA) has further increased our insights as this imaging technology allows for a qualitative and quantitative MNV blood flow analysis. Several studies have been conducted exploring multiple reproducible quantitative OCTA parameters, such as lesion's area, neovascular density, perfusion density (PD), fractal dimension (FD), vessel length density (VLD), lacunarity, vessel tortuosity, and vessel dispersion; and an intriguing scenario has been opened on the possible prognostic role that can be played by these parameters.[10–18]

However, the therapeutic regimen and drug chosen, the type of MNV, the device's acquisition algorithm, the use of nonstandardized qualitative evaluation, or a short follow-up period should be considered as drawbacks that can influence and confound the OCTA analysis.

The aim of this study was to investigate the role of OCT and OCTA parameters at baseline as biomarkers of final lesion's activity, in treatment-naïve type 1 MNV eyes treated with a 1-year fixed regimen of intravitreal aflibercept injections (q8 IAI), integrating the information provided by these two different techniques, through a statistical model.

Methods

Study Participants

In this study, patients with treatment-naïve type 1 MNV treated with aflibercept and followed up for 1 year, between March 2017 and December 2019, were retrospectively included at the Department of Ophthalmology, IRCCS-Fondazione Bietti, Rome.

This observational study was approved by the Institutional Review Board of the IRCCS-Fondazione Bietti, and followed the tenets of the Declaration of Helsinki. Written informed consent was obtained from all participants.

Inclusion criteria were: 55 years of age or older, type 1 MNV treated with q8 IAI,[5] that consisted of 3 monthly injections followed by bimonthly injections, as per clinical practice for a total of 7 injections in the first year of treatment, a follow-up period of 1 year. The diagnosis of type 1 MNV was made on the basis of clinical and imaging evaluations.[19]

Patients performed a complete ophthalmological examination, which included the measurement of best corrected visual acuity (BCVA) using Early Treatment of Diabetic Retinopathy Study (ETDRS) visual charts, intraocular pressure (IOP), and dilated fundus examination. All patients were imaged by Spectral Domain (SD) OCT using Spectralis (Heidelberg Engineering, Heidelberg, Germany) and by Swept Source (SS) OCTA using the PLEXElite 9000 (Carl Zeiss Meditec Inc., Dublin, CA, USA) device. OCT and OCTA inclusion criteria were reported in "imaging protocol" section. Only one eye per patient has been included in the analysis.

Exclusion criteria were: history of anti-VEGF therapy, evidence of type 2 or type 3 MNV, evidence of polypoidal vasculopathy, macular edema secondary to other causes than nAMD, and significant lens opacity, graded above NO3 or NC3.[20] Poor quality images with a signal strength index (SSI) lower than six for the PLEXElite SS-OCTA or with significant motion artifacts (seen as large dark or grey lines on the enface angiograms) were also excluded.

Patients' charts were analyzed and BCVA, SD-OCT, and SS-OCTA parameters (see below) at baseline and their role as biomarker on lesion's activity 1 month after the end of q8 IAI, was investigated.

Imaging Protocol

SD-OCT images at baseline and at the end of follow-up by means of the Spectralis (Heidelberg Spectralis version 1.10.2.0; Heidelberg Engineering, Heidelberg, Germany) were analyzed. OCT raster scans were obtained in the macular region, with a volume scan of 20 degrees × 20 degrees (5.8 × 5.8 mm) containing 25 B-scans centered at the fovea. Individual B-scan had an average of 25 frames with 244 µm of distance between B-scans.

A macular map centered on the fovea for quantification of central macular thickness (CMT) that was automatically measured using instrument software and for qualitative evaluation of the presence of SRF, IRF, subretinal hyper-reflective material (SHRM), and hyper-reflective intraretinal dots (HRD) was acquired. All raster B-scan images were checked for errors in automatic segmentation and manual correction was made for all the identified segmentation errors.

Two expert readers (authors E.C. and M.P.) independently evaluated the morphological lesion activity and the interclass correlation coefficient (ICC) was calculated. In case of disagreement a third reader (author E.B.) assigned the final grade. SS-OCTA images were acquired at baseline visit using the SS-OCTA PLEXElite 9000 device, which uses a swept laser

source with a central wavelength of 1050 nm and a bandwidth of 100 nm.[21] This instrument has an axial resolution of approximately 5 µm and a lateral resolution estimated at approximately 14 µm. For each eye in the study, OCTA images were acquired using the 3 × 3 mm scan pattern and, based on the size of the MNV, only the MNV lesions that had been fully framed in the 3 × 3 scans acquired at the baseline visit were included in the analysis. As previously reported by our study group,[22] SS-OCTA RPE-RPE fit slabs provide an accurate and reproducible quantification of type 1 MNV lesions compared to choriocapillaris (CC) slabs and outer retina-choriocapillaris (ORCC) slabs. Two fully automated segmentation algorithms were used to the three-dimensional structural OCT data and applied to OCTA flow intensity with sum projection analyses, in order to obtain the RPE-RPE fit image which was visualized with a slab extended from the RPE to the RPE fit reference, the latter boundary corresponding to Bruch's membrane.[22]

SD-OCT Parameters

SD-OCT parameters evaluated at baseline and at the end follow-up were mean CMT, the presence of SRF, IRF, SHRM, and HRD. At the end of 1-year q8 IAI we evaluated the OCT signs of lesion's activity,[23] considering as being inactive (i.e. no tomographic signs of lesion activity) a lesion that showed the absence of any kind of intraretinal or subretinal fluid with or without the pigment epithelium detachment (PED).[23] On the basis of the OCT signs of lesion's activity at the end of q8 IAI, we subdivided the study population in two groups: the active MNV (A-MNV) group and the inactive MNV (I-MNV) group.

OCTA Parameters and Analysis

The OCTA parameters evaluated at baseline were the MNV area, the PD, the VLD, and vessel diameter index (VDI). OCTA enface images (RPE-RPE fit) were opened in image analysis ImageJ software (National Institutes of Health; http://imagej.nih.gov/ij/).[24]

An experienced grader (author E.C.) visualized and delineated the border of the MNV lesions to measure the MNV area. In a previous study, we found an excellent inter-reader agreement in the MNV area calculated in RPE-RPEfit slabs (ICC = 0.989), for this reason, we did not assess it in the present study.[22]

Furthermore, these images were used to binarize and skeletonize the MNV lesion, with Phansalkar method (radius 15 pixel),[11,25,26] to investigate the MNV PD, VLD, and VDI, respectively.[26]

PD defines the ratio of the area occupied by the vessels divided by the total area; VLD is the total vessel length divided by the total number of pixels in the analyzed skeletonized image; and VDI measures the average vessel caliber by dividing the area in the binarized area by that in the skeletonized area.[26]

Statistics

Statistical evaluation was performed using SPSS (IBM SPSS Statistics version 25). Continuous variables, including age, BCVA ETDRS letters score, and instrument parameters were expressed as mean ± standard deviations (SDs), whereas categorical variables were expressed as frequencies.

The ICC was calculated to estimate the absolute agreement between the two expert readers grading on OCT signs of lesion's activity measurement. In general, ICC values less than 0.5 are indicative of poor reliability, values between 0.5 and 0.75 indicate moderate reliability, values between 0.75 and 0.9 indicate good reliability, and values greater than 0.9 indicate excellent reliability.[27]

The normal data distribution was tested using the one-sample Kolmogorov–Smirnov test. The independent sample *t*-test and the Mann–Whitney test were used to compare the parameter values between the two groups. A χ^2 test or a Fisher exact test two sides as appropriate, was performed to investigate the relationship between the groups and the clinical categorical variables. The dependent sample *t*-test and the Wilcoxon signed-rank test were used to compare SD-OCT parameters changes over time in the study groups.

A binary logistic regression model was applied using the OCT and OCTA variables as explanatory independent variables (i.e. predictors) to classify the lesion's activity (A-MNV) and the lesion's inactivity (I-MNV) cases (i.e. the categorical dependent variable). A threshold of 0.35 was chosen. The variance inflation factor (VIF), which assesses how much the variance of an estimated regression coefficient increases if the predictors are correlated, was used to assess multicollinearity, only variables with a VIF > 1 and VIF < 10 were considered as covariates.

To evaluate the developed models, we measured the complexity by the Akaike Information Criterion (AIC) and the Bayesian Information Criteria (BIC), whereas the accuracy of estimated probability was measured by the Brier's Score.[14] The model performance to distinguish between active and inactive groups was measured by the receiver operating characteristic (ROC) analysis with the area under the curve (AUC). Lower values of AIC, BIC, and Brier's Score indicate a better goodness

Table 1. Demographic, Clinical, and Optical Coherence Tomography (OCT) Parameter Differences Between Groups

		A-MNV Group $N = 13$	I-MNV Group $N = 18$	*t*-Test/Mann Whitney *U* Test, *P* Value
Baseline	Age	75.54 ± 7.13	79.67 ± 5.94	0.102
	BCVA	66.08 ± 11.38	66.11 ± 12.24	0.747
	CMT (µm)	400.15 ± 144.15	353.67 ± 51.87	0.216
				Chi Square/Exact Fisher Test, *P* Value
	SRF (%)	84.6	68.8	0.410
	SHRM (%)	61.5	81.3	0.406
	IRF (%)	46.2	62.5	0.379
	HRD (%)	46.2	56.3	0.588
				t-Test/Mann Whitney *U* Test, *P* Value
Follow-up	BCVA	68.08 ± 20.97[§,a]	73.83 ± 7.91[§g]	<0.001[*]
	CMT (µm)	312.38 ± 94.17[§,b]	253.50 ± 36.99[§h]	<0.001[*]
				Chi Square/Exact Fisher Test, *P* Value
	SRF (%)	76.92[§c]	0	<0.001[*]
	SHRM (%)	7.69[§d]	0	<0.001[*]
	IRF (%)	46.15[§e]	0	<0.001[*]
	HRD (%)	23.07[§f]	22.22[§g]	1.000

[*]Significant value.

[§]Paired samples *t*-test/Wilcoxon Signed Ranks Test = *P* value baseline versus follow-up in A-MNV group; a = 0.41, b = 0.055, McNemar test c =1.000, d = 0.016, e = 1.000, f = 0.500.

[§]Paired samples *t*-test/Wilcoxon Signed Ranks Test = *P* value baseline versus follow-up in the I-MNV group; g < 0.001, McNemar test h = 1.000.

A-MNV, active macular neovascularization; I-MNV, inactive macular neovascularization; SRF, subretinal fluid; SHRM, subretinal hyper-reflective material; IRF, intraretinal fluid; HRD, hyper-reflective intraretinal dots.

of fit, whereas higher AUC values indicate better discriminative ability.

Statistically significant differences were set at *P* value (*P*) < 0.05 for all the tests performed.

Results

Thirty-one treatment-naïve type 1 MNV eyes (23 women and 8 men) were enrolled. Mean ± SD patients' age was 78.0 ± 6.7 years (range = 63–90 years). Mean ± SD baseline BCVA was 66.0 ± 11.7 ETDRS letters (20/50 Snellen equivalent, with a range from 20/25 to 20/320). Mean ± SD baseline CMT was 373.2 ± 102.1 µm, as determined on the macular map.

Thirteen out of 31 patients were classified in the A-MNV group (41.93%) and 18 of the patients were classified in the I-MNV group (58.06%), according on OCT signs of lesion's activity.

The baseline OCT and OCTA parameters (CMT, SRF, IRF, SHRM, HRD, MNV area, PD, VLD, and VDI) of A-MNV and I-MNV groups were reported in Tables 1 and 2.

When comparing the baseline OCT and OCTA parameters between the A-MNV and I-MNV groups no statistically significant differences were found (see Tables 1 and 2).

An absolute agreement, ICC = 1, was found between two readers (authors M.P. and E.C.) for the morphological lesion activity, at the end of q8 IAI.

A high degree of reliability was found between readers grading and OCT signs of lesion's activity measurement. The average measure ICC was 0.793 with a 95% confidence interval from 0.556 to 0.902 ($F(30, 30) = 5.431$, $P < 0.001$).

Model's Results

We used a binary logistic regression model including OCT and OCTA baseline parameters as predictive variables able to differentiate between A-MNV and I-MNV groups. We developed three models. In the first five-parameters model (model 1 OCT-based) we explored the combination of SD-OCT parameters (CMT, SRF, IRF, HRD, and SHRM) as predictive factors for final lesion activity. The model 1 showed an AIC of 46.067, a BIC of 54.270, and a Brier's score of 0.405.

In a second model (model 2 OCTA-based) we explored the combination of three SS-OCTA

Table 2. Optical Coherence Tomography Angiography (OCTA) Parameter Differences Between Groups

Baseline OCTA Parameters	A-MNV Group (Mean ± SD)	I-MNV Group (Mean ± SD)	*t*-Test/Mann Whitney *U* Test, *P* Value
RPE-RPE fit MNV lesion size (area mm^2)	0.775 ± 0.470	0.521 ± 0.476	0.069
RPE-RPE fit MNV VDI	7.805 ± 1.032	8.319 ± 2.516	0.966
RPE-RPE fit MNV VLD	8.314 ± 1.779	8.427 ± 2.016	0.933
RPE-RPE fit MNV PD	63.826 ± 10.391	67.259 ± 13.661	0.467

*Significant value.

A-MNV, active macular neovascularization; I-MNV group, inactive macular neovascularization; RPE-RPE fit MNV, macular neovascularization in RPE-RPE fit Optical Coherence Tomography Angiography slab; VDI, vessel diameter index; VLD, vessel length density; PD, perfusion density.

Table 3. Models' Comparing Analysis

	AIC	BIC	Brier's Score
Model 1 OCT (IRF + HRD + SRF + SHRM + CMT)	46.067	54.270	0.405
Model 2 OCTA (RPE-RPE fit MNV Area + PD + VLD)	45.915	**51.520**	**0.379**
Model 3 OCT + OCTA (IRF + HRD + SRF + SHRM + CMT + RPE-RPE fit MNV Area + PD + VLD)	**45.876**	57.866	0.455

AIC, Akaike Information Criterion; BIC, Bayesian Information Criteria; IRF, intraretinal fluid; HRD, hyper-reflective intraretinal dots; SRF, subretinal fluid; SHRM, subretinal hyper-reflective material; CMT, central macular thickness; RPE-RPE fit, Optical Coherence Tomography Angiography slab; MNV, macular neovascularization; PD, perfusion density; VLD, vessel length density.

Table 4. Models' Performance Analysis

Target Sensitivity >> Active Lesion Specificity >> Inactive Lesion	AUC (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)	AUC *P* Value (Level of Model's Significance)
Model 1 (OCT)	70.4% (50.7–85.8)	84.6% (54.6–98.1)	56.2% (29.9–80.2)	0.013*
Model 2 (OCTA)	65.2% (46.0–81.3)	69.2% (38.6–90.9)	61.1% (35.7–82.7)	0.088
Model 3 (OCT + OCTA)	87.5% (69.5–96.9)	100% (73.5–100)	75% (47.6–92.7)	<0.001*

*Significant value.

AUC, area under curve; CI, confidence interval.

parameters (RPE-RPE fit MNV area, PD, and VLD), excluding the VDI for a potential collinearity problem (VIF > 10), as showed in Table 3. The model 2 showed an AIC of 45.915, a BIC of 51.520, and a Brier's score of 0.379.

A third model has been developed, combining the OCT parameters, explored in the model 1, with the OCTA parameters of the model 2. This model 3 (OCT/OCTA-based) showed an AIC of 45.876, a BIC of 57.866, and a Brier's score of 0.455.

The Table 4 reports the models' performance analysis; the sensitivity was related to the detection of A-MNV group (target characteristic), the specificity to the I-MNV group. In the model 3, an excellent sensitivity (100%) was achieved and the specificity also increased up to 75%. The models 1 and 3 showed a significant AUC ($P = 0.013$ for model 1 and $P < 0.001$ for model 3), in the model 2, the AUC was not statistically significant $P = 0.088$.

Combining SD-OCT and OCTA parameters a significant improvement of models' performance was observed.

By the analysis of these results, the A-MNV group is more likely to show at baseline the presence of SRF, greater CMT, wider area of MNV on OCTA scans, and lower PD and VLD compared to I-MNV.

Discussion

In this study, we aimed to evaluate the prognostic value of baseline OCT and OCTA parameters on final lesion's activity, in treatment-naïve patients with type 1 MNV after 1-year q8 IAI, by using a statistical model that allowed a comprehensive evaluation of these parameters.

We found that the combination of baseline OCT and OCTA parameters allowed to achieve a good

models' performance in the prediction of MNV activity enabling to correctly classify the active lesions at the end of the follow-up period, with excellent sensitivity.

Coscas et al.[28] recently published a predictive model for treatment decisions, based on the combination of four-qualitative OCTA parameters: tiny branching vessels, peripheral anastomotic arcades, loops, and CC hypointense halo, with a positive predictive value of 87.9%. In their model, these OCTA parameters appeared to predict the lesion activity, enabling to guide the re-treatment decision.

The same group reported another interesting predictive model based on quantitative OCTA parameters, identifying in the lesion area, VD, and FD, three variables useful to distinguish between nAMD active and in remission. The authors showed that there are measurable characteristics of blood flow on OCTA, as area of lesion and FD, that appeared to be more likely associated with exudative structural signs.[14]

Starting from these results, we aimed to understand if any baseline morphological parameters could predict the response to anti-VEGF treatment for type 1 MNV, showing a prognostic role.

Despite that no differences were found in OCT and OCTA parameters between the A-MNV and I-MNV groups at baseline, the use of logistic regression models allowed to consider morphological findings that could predict the disease activity at the end of the therapeutic period.

Our logistic regression model 1, that combined only the OCT parameters (CMT, SRF, IRF, HRD, and SHRM), showed a good performance (AUC = 70.4%), and enabled to detect the MNV lesion activity in 84.6% (sensitivity). Differently, the model 2, that combined only OCTA parameters (RPE-RPE fit MNV area, PD, and VLD), did not show a statistically significant performance (AUC = 65.2%).

Interestingly, when we added the OCTA parameters to OCT ones in model 1 (model 3), including the MNV area, the PD, and VLD, the model's performance improved (AUC = 87.5%), and achieved an excellent sensitivity (100%) in identifying baseline parameters that could predict lesion activity after treatment. Therefore, the combination of OCT and OCTA parameters guarantees to achieve the best performance in distinguishing active and inactive MNV.

By the analysis of the results provided by these models, the A-MNV group is more likely to show at baseline the presence of SRF, greater CMT, wider area on OCTA scans, and lower PD and VLD compared to the I-MNV group.

In previous studies, the role of each OCT parameter was explored in terms of impact on final VA and for lesion's activity.[2,3,7–9]

SRF was identified as a strong prognostic factor in many studies.

It has been reported that MNV lesions with a greater baseline SRF required more injections with an increase in retreatment frequency.[2,3,7–9] Our results agreed with these, as in our model, the presence of baseline SRF was one of the factors that could predict the persistence of lesion's activity (A-MNV), requiring further treatment at the end of 1-year of q8 IAI therapy.

The role of CMT as biomarker of disease activity in nAMD has been widely debated.

CMT could represent a useful quantitative parameter that expresses the degree of retinal thickening, influenced by the presence of retinal fluid, even if it is not able to provide detailed information about the characteristics of the fluid.[29]

Likely to the SRF, a great CMT was found as a predictive factor of lesion activity at the end of q8 IAI treatment.

In addition to the OCT parameters discussed since here, in the model 3, we analyzed the contribution of any OCTA characteristics.

OCTA provides both quantitative and qualitative information on type 1 MNV, appearing as a reproducible way to evaluate its characteristics.

Greater area, low PD, and VDL at baseline, analyzed with OCT parameters, are likely to be associated with the MNV activity.

In our model, the OCTA lesion area is likely to be associated to the MNV activity after 1 year of treatment. In particular, a greater lesion could be predictive of persistence of activity in the long term follow up.[8,30] Recently, Kim et al.[6] reported different OCTA responses to anti-VEGF treatment in type 1 and type 2 neovascularization with no significant changes in lesion area in type 1 in comparison with a great reduction in type 2 MNV. Vascular density showed no significant changes for both groups after treatment and showed no association with the change in lesion size. This absence of change in type 1 MNV lesion size and vessel density after treatment could be due to a vascular remodeling characterized by a pruning process responsible for possible reopening or new sprouting of the vessels.[6,31]

The quantitative OCTA parameters PD and the VLD are representative of the index of neovascular degree inside the lesion. Our results suggest to hypothesize that neovascular lesions with greater area and with low blood flow inside are less responsive to anti-VEGF treatment and associated to a persistent activity after 1-year treatment.

It has been demonstrated that anti-VEGF agents show anti-permeability and anti-angiogenesis properties, especially on capillary MNV who are highly

responsive to anti-VEGF therapy. In contrast, MNV lesions with high arterialization and low new vascular sprouts could be characterized by worse response to treatment.[6,32,33]

In particular, the treatment response appeared to be related to the vessel maturity.[6,34]

A vascular pattern with a disorganized morphology, with tiny capillaries and loops, is suggestive for immature MNV, a vascular pattern subject to arterialization, with thicker, dilated vascular trunks and absence of tiny ramifications, is suggestive for a mature neovascular lesion.[31]

Although conceptually interesting, to accurately classify vessels into mature versus immature types by using OCTA appears to be difficult.

Miere et al. reported an exudation on SD-OCT in mature MNV patterns in 36.4% of the cases, suggesting that, even when the tiny ramifications corresponding to newformed capillaries disappear, mature, large vascular trunks within MNV may generate exudative features on SD-OCT.[31]

The analysis of our results agrees with these even if our objective was not to describe the vascular remodeling during anti-VEGF treatment but to explore if the vascular organization inside the lesion at baseline could influence the morphological outcome in response to anti-VEGF treatment.

The limitation of our study is mainly represented by the small simple size, due to the strict inclusion criteria for our population and the retrospective nature of our analysis. In particular, we included a homogeneous population of type 1 MNV treated with the same therapeutic strategy (q8 IAI) in order to eliminate the confounding factors as the number of injections or the type of drug used. Our statistical model 3 highlighted the importance to integrate the information provided by different devices to obtain a clinically useful analysis.

Further analysis, including a higher number of patients, are needed to validate our results as the statistical model explored in our study could be potentially useful for the artificial intelligence in the construction of a strong predictive model for MNV lesions.

In conclusion, in this study, we analyzed the predictive value of baseline OCT and OCTA parameters in treatment-naïve type 1 MNV treated with q8 IAI, using statistical logistic regression models. By the analysis of the model, the presence of SRF, great CMT, large MNV area, and low PD and VLD represent predictive biomarkers for lesion's activity after 1-year treatment in type 1 MNV.

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Data Availability: The data used to support the findings of this study are available from the corresponding author upon request.

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E.C. was responsible for study design, data acquisition, analysis, and interpretation, drafting and revision of the manuscript, and the preparation of the tables. M.P. was responsible for the concept and study design, data analysis and interpretation, supervision, drafting, revision, and final approval of the manuscript. D.G. was responsible for the statistics, data analysis and interpretation, and preparation of the tables. E.B. was responsible for the study design, methods, data interpretation, and revision of the manuscript. R.S. was responsible for data interpretation, and revision of the manuscript. G.Q. was responsible for the concept and study design, data interpretation, supervision, and revision and final approval of the manuscript.

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