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Type 3 Macular Neovascularization in Age-related Macular Degeneration

Baseline Predictors of 3-Year Macular Atrophy Development

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Purpose: To identify baseline OCT predictors of the 3-year macular atrophy (MA) development for type 3 (T3) macular neovascularization (MNV) secondary to neovascular age-related macular degeneration (nAMD) treated by anti-VEGF therapy.

Design: Multicenter, retrospective, longitudinal study.

Participants: We included patients with treatment-naive T3 MNV secondary to nAMD at baseline, treated with anti-VEGF during a 3-year follow-up.

Methods: Patients were identified from 6 retinal referral institutions: (1) San Raffaele University, Milan, Italy; (2) University of Genova, Genova, Italy; (3) Doheny Eye Institute, Los Angeles; (4) Stein Eye Institute, Los Angeles; (5) University of Paris Est, Creteil, France; and (6) Istituto di Ricovero e Cura a Carattere Scientifico Bietti Foundation, Rome, Italy. Several baseline predictors of 3-year MA area were analyzed based on structural OCT and demographics.

Main Outcome Measures: Multivariate analysis to identify baseline independent predictors of the 3-year MA development for T3 MNV secondary to nAMD treated by anti-VEGF therapy.

Results: We included 131 eyes of 131 patients (mean age, 80 ± 6 years; 81% females). Best-corrected visual acuity was 0.49 ± 0.40 logarithm of the minimum angle of resolution (logMAR) at the baseline and significantly decreased to 0.59 ± 0.43 logMAR at the end of 3-year follow-up ($P < 0.001$). Patients were treated with 11 ± 6 anti-VEGF injections and developed atrophy in 75% of cases (from 18% at the baseline). Eyes that developed 3-year MA were treated with a significantly lower number of injections compared with eyes without MA (9.9 ± 5.5 vs. 14.7 ± 7.2 injections, $P < 0.001$). The most relevant independent predictors at baseline of MA area at 3-year follow-up were: area of MA at baseline ($P < 0.001$), age-related macular degeneration phenotype (presence of reticular pseudodrusen) ($P = 0.017$), baseline presence of nascent geographic atrophy ($P = 0.008$), and the baseline presence of subretinal hyperreflective material ($P = 0.002$).

Conclusions: Macular atrophy development is a frequent complication of T3 MNV treated with anti-VEGF injections. Several factors could be considered baseline predictors of atrophy development during the anti-VEGF treatment.

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Age-related macular degeneration (AMD) is the main cause of visual decline in elderly White population.[1] The advanced stage of AMD is categorized into neovascular AMD (nAMD) or geographic atrophy (GA) based on the presence of macular neovascularization (MNV). Among nAMD subtypes, type 3 (T3) MNV is characterized by peculiar features in comparison to type 1 and type 2 MNV. Indeed, T3 MNV originates mainly from the deep capillary plexus of the retinal circulation, whereas type 1 and 2 MNV originate from the choriocapillaris of the choroidal circulation.[2–4] Despite that, T3 MNV represents a frequent scenario in clinical practice, accounting for >30% of nAMD cases in Whites.[5] Type 3 MNV is often a bilateral and aggressive form of MNV but a greater response in terms of best-corrected visual acuity (BCVA) improvement was reported after anti-VEGF injections in comparison to other subtypes of MNV.[6–10] However, long-term outcomes are usually poor due to the development of retinal pigment epithelium (RPE) and outer retinal atrophy.[9,10] For this reason, several groups suggested treating T3 MNV with a pro-re nata (PRN) or a treat-and-extend regimen to reduce the number

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of injections and the macular atrophy (MA) development.[10–12]

In recent years, thanks to the introduction in the clinical practice of high-resolution structural OCT and OCT angiography (OCTA), there was an increasing interest in the detection of biomarkers able to predict functional and anatomic outcomes in several maculopathies.[13–15] Our group reported baseline biomarkers that could predict the 3-year BCVA outcome in treatment-naive T3 MNV treated by anti-VEGF injections.[16] Furthermore, Forte et al[17] recently reported baseline biomarkers were able to predict the long-term development of fibrosis in T3 MNV treated by anti-VEGF injections. What is missing is information regarding the relationship between the baseline morphologic characteristics by means of structural OCT, the clinical features of the disease, and the long-term MA development of patients affected by T3 MNV. The aim of our study was to characterize baseline OCT predictors of the 3-year MA presence and area for T3 MNV secondary to nAMD treated by anti-VEGF therapy.

Methods

This was a multicenter retrospective longitudinal study including patients diagnosed with treatment-naive T3 MNV secondary to AMD treated with anti-VEGF therapy during a 3-year follow-up. Clinical data and multimodal imaging of patients presenting between January 2019 and December 2020 and followed until December 2023 were collected. Patients were captured from 6 retinal referred centers: (1) the Medical Retina and Imaging Unit of the Department of Ophthalmology, San Raffaele Scientific Institute in Milan, Italy; (2) the Eye Unit, Istituto di Ricovero e Cura a Carattere Scientifico Ospedale Policlinico San Martino, University of Genoa in Genoa, Italy; (3) the Doheny Eye Institute in Los Angeles, United States; (4) the Retinal Disorders and Ophthalmic Genetics Division, Stein Eye Institute, University of California in Los Angeles, United States; (5) the Istituto di Ricovero e Cura a Carattere Scientifico-Fondazione Bietti, Rome, Italy; and (6) the Department of Ophthalmology, Hospital Intercommunal de Creteil, University Paris Est Creteil in Creteil, France. All included patients signed a written informed consent that was previously approved by the local Ethics Committee or Institutional Review Board. The study followed the tenets set forth in the Declaration of Helsinki for research involving human subjects.

Inclusion criteria were: (1) patients aged >55 years old; (2) diagnosis of nAMD; (3) diagnosis of treatment-naive T3 MNV; and (4) 3-year anti-VEGF therapy using a rigorous PRN regimen. The diagnosis of nAMD was based on previously reported classification.[2] The diagnosis of T3 AMD was based on multimodal imaging assessment (including dye-based angiography or OCTA) following previously reported criteria.[2,18,19] For clinical practice, patients treated using a PRN regimen were evaluated every 4 to 8 weeks (based on the anti-VEGF drug) after 3 monthly consecutive anti-VEGF injections of loading phase. Patients were treated with any sign of exudation (presence of subretinal fluid [SRF], intraretinal fluid, subretinal hyperreflective material [SHRM], and hemorrhages).

Exclusion criteria were: (1) any previous retinal treatments (e.g., intravitreal injections, photodynamic therapy) in the macular area; (2) history of any other chorioretinal disorder; (3) inadequate fixation to permit high-quality imaging; (4) high refractive error (>+5.00 diopters (D) and <−6.00 D of sphere or 3D of cylinder); and (5) no adherence to the previously reported rigorous PRN regimen.

If both eyes of a patient were eligible, only 1 eye was included. The eye with a greater quality of imaging was chosen.

Clinical data and multimodal imaging were collected. For clinical practice, all patients were evaluated at the baseline and at 3-year follow-up with the assessment of distance BCVA using Snellen charts and converted to logarithm of the minimum angle of resolution (logMAR) for statistical evaluation, fundus examination, infrared reflectance images, short-wave fundus autofluorescence (FAF), and structural OCT. To confirm the diagnosis of T3 MNV, at the baseline, fluorescein or indocyanine angiography or OCTA was performed. For our clinical practice, dye angiographies were performed in cases of uncertain diagnosis with only structural OCT and OCTA. Infrared reflectance, FAF, structural OCT, and dye-based angiography were acquired using HRA2+OCT Spectralis (Heidelberg Engineering), whereas OCTA was acquired using PLEXElite 9000 (Carl Zeiss Meditec, Inc) or Optovue RTVue XR Avanti, Solix (Visionix International SAS, formerly Optovue).

The presence and the area of MA were evaluated at the baseline and at 3-year follow-up using structural OCT and FAF. Of note, the presence of MA was defined as a complete RPE and outer retinal atrophy (cRORA) on structural OCT in a nAMD eye.[20,21] In the case of MA presence, the area was measured at the baseline and 3-year follow-up on FAF images by 2 independent graders (R.S. and F.B.), and the mean area was used for statistical analysis.

OCT Grading

All structural OCT images at the baseline evaluated by 2 independent and trained readers (R.S. and F.B.) were masked to the MA outcomes. Eligible images were independently graded for several qualitative and quantitative features. In detail, the mentioned quantitative features were evaluated: size of MA on FAF (if present), central macular thickness (CMT), subfoveal choroidal thickness (ChT), ChT under T3 lesion (i.e., sublesion ChT), mean ChT, and neuroretinal thickness in the T3 location. Central macular thickness was recorded using the inbuilt Spectralis Software in the central 1-mm−diameter circle of the ETDRS, after evaluation of segmentation and eventually manual adjustment of errors. Choroidal thickness was measured as the distance between the Bruch's membrane and the sclerochoroidal interface in the subfoveal location (subfoveal ChT), under the T3 lesion (sublesion ChT), and as the mean among subfoveal, 500, and 1000 μm nasally and temporally to the fovea (mean ChT).[22] Neuroretinal thickness was measured as the distance between the inner limiting membrane and the interdigitation zone. All manual measurements were performed by 2 trained graders (R.S. and F.B.), and the mean values were used for statistical analyses.

The following qualitative OCT features were evaluated: AMD phenotype (presence of drusen, reticular pseudodrusen [RPD], or both), stage of T3 MNV,[19] presence of cRORA in the T3 MNV area, presence of cRORA elsewhere, presence of nascent GA,[23] localization of T3 MNV (subfoveal, parafoveal, perifoveal, or extrafoveal), presence of intraretinal hyperreflective foci (HRF) above the T3 lesion, intraretinal HRF elsewhere, presence of SRF, intraretinal fluid, SHRM, presence of pigment epithelium detachment (drusenoid or serous) above the T3 MNV, and number of T3 lesions.

The following clinical features were also recorded: presence of hemorrhage at the baseline, fellow eye status (i.e., intermediate AMD, GA, nAMD), number of injections received, and administrated anti-VEGF drug.

Statistical Analysis

A sample size of 131 eyes has a >80% power to identify significant predictors among ≤14 possible predictors, with an α error of 0.05.

Statistical analyses were carried out using Statistical Package for the Social Sciences (SPSS) software (ver. 29.0.1.0; SPSS, Inc). Normal distribution of continuous variables was tested using Kolmogorov−Smirnov test. Continuous variables were reported as means ± standard deviation. Categorical variables were reported as counts and percentages. Student paired *t* test was performed to compare mean BCVA and MA area between baseline and 3-year follow-up. Comparisons of quantitative variables between groups of eyes with and without MA at 3-year follow-up were performed using Student *t* test for independent samples and using chi-square test or Fisher exact test for qualitative variables. The agreement between individual measurements from both readers was performed using the intraclass correlation coefficient (95% confidence interval).

Univariate and multivariate analyses served to identify risk factors associated with the MA development and area after 3-year follow-up. The MA development was defined as presence of cRORA using structural OCT at 3-year follow-up examination. The MA area was detected at 3-year follow-up using FAF. A linear regression model was performed. Factors included in the multivariate model needed a *P* value <0.2 in the univariate analysis.

The chosen level of statistical significance was $P < 0.05$ for all analyses.

Results

Among 153 eyes diagnosed with treatment-naive T3 MNV, 131 eyes of 131 patients (mean age, 80 ± 6 years; 106 females [81%]) fulfilled the inclusion/exclusion criteria and were included in the study. Of note, 22 of 162 eyes (14%) (mean age, 80 ± 5 years; $P = 0.429$) were excluded because they dropped out before the 3-year follow-up.

All included patients were White. Sixty-seven eyes (51%) were pseudophakic and 64 eyes (49%) were phakic. At the baseline, 10 eyes were classified as stage 1 T3 MNV, 66 as stage 2, and 55 as stage 3 by OCT.[19] Most cases were affected by concomitant drusen and RPD (93 of 131 cases, 71%), followed by only RPD (24 of 131 cases, 18%), and only drusen (14 of 131 cases, 11%). Only 18% of eyes (24 of 131) showed cRORA at the baseline, and the mean MA area was 0.23 ± 0.55 mm^2. The fellow eye was affected by nAMD in 72 of 131 eyes (55%), whereas 59 of 131 eyes (45%) were affected by GA.

At the baseline, mean BCVA was about 20/63 Snellen equivalent (0.49 ± 0.40 logMAR), and no significant difference was disclosed compared with 22 dropped-out eyes (0.48 ± 0.30 logMAR, $P = 0.440$). Mean CMT was 374 ± 124 μm, neuroretinal thickness was 338 ± 76 μm, subfoveal ChT was 171 ± 74 μm, sublesion ChT was 167 ± 73 μm, and mean ChT was 165 ± 66 μm. There was excellent interobserver variability between readers for all measurements (intraclass correlation coefficient, >0.9). All demographics and main clinical features are reported in the Table 1.

At 3-year follow-up, BCVA significantly decreased to about 20/80 Snellen equivalent (0.59 ± 0.43 logMAR, $P < 0.001$) from 20/63 Snellen equivalent (0.49 ± 0.40 logMAR). At the baseline, 83 eyes (63%) were treated with ranibizumab, 40 eyes (31%) by aflibercept, and 8 eyes (6%) by bevacizumab. During the follow-up, patients were treated with a mean of 11 ± 6 injections. At the end of the follow-up, 75% of eyes (98 of 131) showed cRORA using structural OCT. The mean MA area significantly increased to 2.70 ± 2.88 mm^2 ($P < 0.001$) (Fig 1).

No significant correlation was identified between the number of injections and MA area at the 3-year follow-up ($P = 0.140$). However, 98 eyes that displayed MA after 3-year follow-up were treated with a significantly lower number of injections in comparison to 33 eyes without MA after 3-year follow-up (mean number of injections of 9.9 ± 5.5. vs. 14.7 ± 7.2, respectively, $P < 0.001$) (Fig 2).

Baseline Structural OCT Biomarkers and Clinical Factors Associated with Presence/Absence of MA at 3-Year Follow-up

The baseline clinical and structural OCT parameters (age, baseline BCVA, CMT, subfoveal ChT, sublesion ChT, mean ChT, neuroretinal thickness above the T3 lesion, AMD phenotype, T3 MNV stage, presence of hemorrhage, presence of nascent GA, presence of HRF elsewhere, number of exudative T3 lesions, presence of SRF, presence of SHRM, and presence of pigment epithelium detachment below the T3 MNV) associated with and without MA at 3-year follow-up are reported in Table 2. Of note, the baseline features significantly associated with MA at 3-year follow-up were as follows: age ($P < 0.001$), presence of nascent GA ($P < 0.001$), presence of HRF elsewhere ($P < 0.001$), and presence of pigment epithelium detachment (i.e., stage 3 disease) ($P = 0.037$) (Table 2).

Baseline Structural OCT Predictors Analysis for MA Area at 3-Year Follow-up

All eyes displayed HRF and intraretinal fluid at baseline, and thus, they were excluded from the univariate analysis. All other features were analyzed in the univariate analysis and reported in Table 3. Of note, only the following baseline features were significantly correlated with the area of atrophy at 3-year follow-up: area of MA ($P < 0.001$), T3 MNV stage ($P = 0.015$), presence of cRORA elsewhere ($P < 0.001$), and presence of nascent GA ($P = 0.008$) (Table 3).

All features showing a $P < 0.2$ in the univariate analyses were included in the multivariate model (Table 4). Of all included features, area of MA at the baseline ($\beta = 0.478$; $P < 0.001$), AMD phenotype ($\beta = 0.201$; $P = 0.017$) at baseline, presence of baseline nascent GA ($\beta = -0.224$; $P = 0.008$), and presence of baseline SHRM ($\beta = 0.285$; $P = 0.002$) were independently associated with MA area at the 3-year follow-up, and thus considered independent predictors. Analyzing the AMD phenotype, eyes with only RPD displayed a 3-year MA area of 4.44 ± 4.16 mm^2 versus an MA area of 2.69 ± 2.63 mm^2 for the mixed

Table 1. Demographics and Main Clinical Features of the Study Population at the Baseline

	Overall
Number of eyes (patients)	131 (131)
Sex, n (%)	
Male	25 (19)
Female	106 (81)
Age (yrs), mean ± SD	80 ± 6
Baseline BCVA (logMAR), mean ± SD	0.49 ± 0.40
CMT (μm), mean ± SD	374 ± 124
Subfoveal ChT (μm), mean ± SD	171 ± 74
Sublesion ChT (μm), mean ± SD	167 ± 73
Mean ChT (μm), mean ± SD	165 ± 66
Neuroretinal thickness above T3 lesion (μm), mean ± SD	338 ± 76
AMD phenotype, n (%)	
Drusen	24 (18)
RPD	14 (11)
Both drusen and RPD	93 (71)
T3 MNV stage, n (%)	
Stage 1	10 (8)
Stage 2	55 (42)
Stage 3	66 (50)
Presence of hemorrhage, n (%)	
Yes	77 (59)
No	54 (41)
Presence cRORA under the T3 lesion, n (%)	
Yes	20 (15)
No	111 (85)
Presence cRORA elsewhere, n (%)	
Yes	24 (18)
No	107 (82)
Presence of nascent GA, n (%)	
Yes	49 (37)
No	82 (63)
Presence of HRF above the T3 lesion, n (%)	
Yes	131 (100)
No	0 (0)
Presence of HRF elsewhere, n (%)	
Yes	107 (82)
No	24 (18)
Number of exudative T3 lesions, n (%)	
1 lesion	119 (91)
2 lesions	12 (9)
Presence SRF, n (%)	
Yes	69 (53)
No	62 (47)
Presence IRF, n (%)	
Yes	131 (100)
No	0 (0)
Presence SHRM, n (%)	
Yes	60 (46)
No	71 (54)
Presence PED, n (%)	
Yes	119 (91)
No	12 (9)

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; ChT = choroidal thickness; CMT = central macular thickness; cRORA = complete retinal pigment epithelium and outer retinal atrophy; GA = geographic atrophy; HRF = hyperreflective foci; IRF = intraretinal fluid; logMAR = logarithm of the minimum angle of resolution; MNV = macular neovascularization; PED = pigment epithelium detachment; RPD = reticular pseudodrusen; SD = standard deviation; SHRM = subretinal hyperreflective material; SRF = subretinal fluid; T3 = type 3.

phenotype (both drusen and RPD) and an MA area of 1.77 ± 2.42 mm^2 for the only drusen phenotype (Fig 3). Furthermore, eyes with baseline nascent GA displayed a 3-year MA area significantly greater than eyes without (3.53 ± 3.17 mm^2 vs. 1.99 ± 2.41 mm^2, respectively) (Fig 3).

Discussion

In this study, we report that MA development, defined as cRORA on OCT, is a common complication during the treatment of T3 MNV (75% of cases at 3-year follow-up) and that the baseline independent predictors of MA area after 3 years of anti-VEGF therapy are the baseline area of MA, presence of RPD, presence of nascent GA, and presence of SHRM.

Macular atrophy, along with fibrosis, are important adverse complications of nAMD, significantly limiting the visual gain obtained by anti-VEGF therapy. The rate of MA development increases with the follow-up duration. Sadda et al[21] reported that MA occurred in 29.4% of cases at the end of 2-year follow-up in the HARBOR study patients. A similar percentage of MA development was reported in the IVAN study after 24 months (29.7%).[24] On the other hand, the CATT study reported a lower percentage of MA development (18.3%).[25] However, this difference could be due to the different definitions and imaging modalities used for the MA definition. Studies with long follow-up showed that the MA rate dramatically increased during that time. The MANEX study reported that 51% and 45% of nAMD eyes were affected by MA after 4 years of treatment with anti-VEGF after a treat-and-extend or PRN regimen, respectively.[26] The SEVEN-UP studies showed that 98% of cases were affected by MA after 7 years of anti-VEGF treatment.[27]

The presence of T3 MNV is associated with an increased risk of MA development.[28,29] Our data confirmed that the development of MA is a very common complication in T3 MNV. Although the rate of MA at baseline (18%) may be underestimated due to the presence of MNV that can mask the identification of atrophy, there was a dramatic increase in the rate of eyes with MA after 3-year of anti-VEGF treatment (75%). This could be due to different features affecting T3 MNV eyes in comparison to type 1 and 2 forms. Type 3 MNV are associated with severe choroidal thinning and choriocapillaris flow impairment, which are independent risk factors for RPE and outer retinal atrophy.[14,30,31] Choroidal thinning and choriocapillaris impairment cause retinal hypoperfusion and ischemia, leading to atrophy development.[32] Furthermore, T3 MNV are frequently associated with the RPD presence. Reticular pseudodrusen together with basal laminar deposits are well-known risk factors for GA development.[33–35] In our series, we also showed that the presence of RPD at baseline is an independent predictor of MA area after 3-year treatment with anti-VEGF. At 3-year follow-up, eyes with RPD showed an MA size of 4.44 mm^2 in comparison to 2.69 mm^2 in eyes with mixed phenotype (both drusen and RPD)

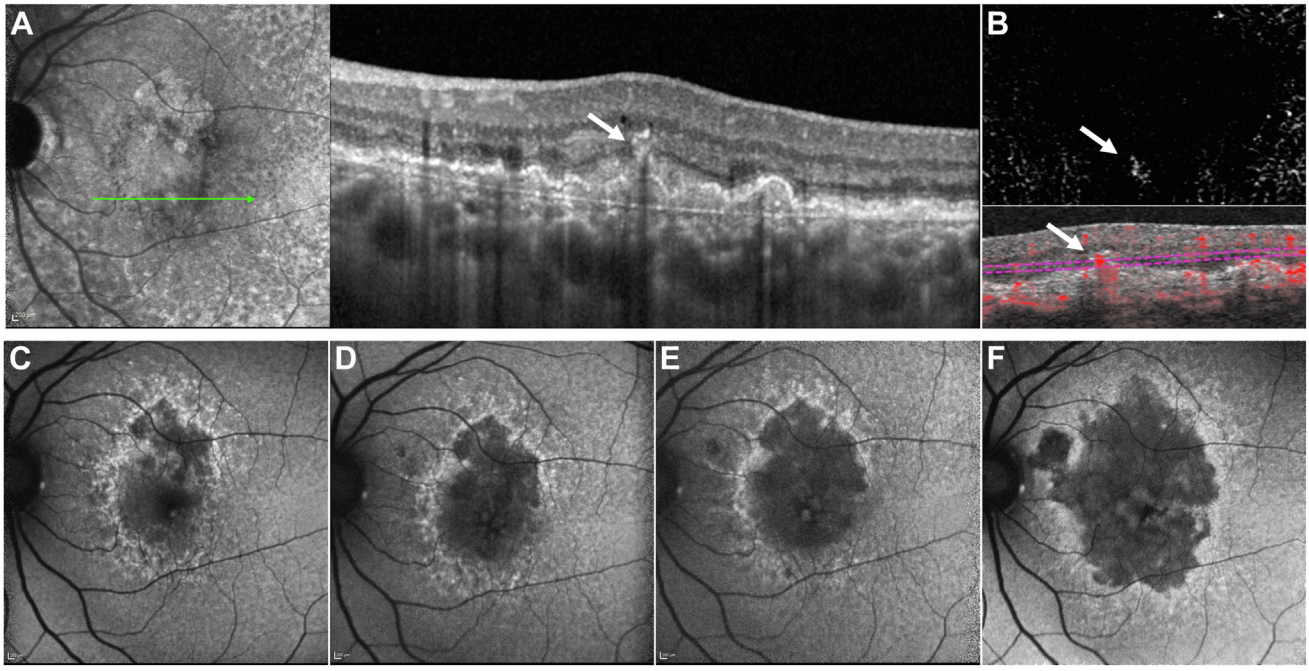

Figure 1. Progression of macular atrophy during the 3-year follow-up of an 84-year-old patient affected by treatment-naive active type 3 macular neovascularization (MNV) at the baseline. **A,** Combined indocyanine green angiography and structural horizontal OCT passing through the lesions showing presence of a type 3 MNV (white arrow) with signs of exudation (i.e., small intraretinal cystic spaces and thickening of the neuroretina). **B,** OCT angiography confirmed the presence of flow inside the lesion (white arrows). Short-wave fundus autofluorescence images showing the progression of the atrophic area starting from (**C**) the baseline, (**D**) at 1-year follow-up, (**E**) at 2-year follow-up, and (**F**) at 3-year follow-up.

and 1.77 mm^2 in eyes with only drusen. These data confirmed the crucial role of RPD not only in the development of atrophy, but also in the fast progression of the lesion. Other baseline factors independently associated with the MA area after 3 years of anti-VEGF treatment were the presence of nascent GA and SHRM. Nascent GA is an OCT sign first described by Wu et al[29] in 2014 as a precursor of drusen-associated atrophy development after a mean of 11 months. However, recently nascent GA was also reported as a precursor of T3 MNV development in patients affected for intermediate AMD.[36] For these reasons, nascent GA in intermediate AMD stages may represent a precursor for progression to either late stage of AMD (nAMD and GA). Our series suggested that nascent GA should also be considered a precursor of MA development in patients affected by T3 MNV.

The presence of SHRM in T3 MNV may represent different lesion types including fibrin or hemorrhage.[37] The presence of SHRM was previously associated with the development of fibrovascular scarring which may be a

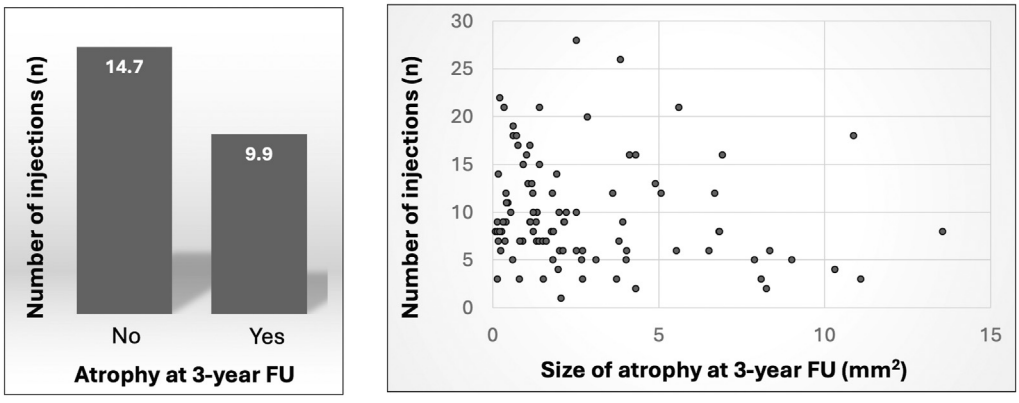

Figure 2. Association between number of injections and macular atrophy. Histograms (on the left) showing that number of injections was lower in patients that developed macular atrophy at the end of 3-year follow-up (FU; $P < 0.001$). Boxplot (on the right) showing the lack of association between the number of injections and the macular atrophy size at 3-year FU ($P = 0.140$).

Table 2. Baseline Clinical Features of Eyes With and Without MA After 3-Year Follow-Up

	Presence of 3-Year MA (n = 98)	Absence of 3-Year MA (n = 33)	*P* Value
Age (yrs), mean ± SD	79 ± 6	83 ± 6	<0.001*
Baseline BCVA (logMAR), mean ± SD	0.47 ± 0.40	0.55 ± 0.41	0.292
CMT (μm), mean ± SD	371 ± 116	384 ± 147	0.596
Subfoveal ChT (μm), mean ± SD	172 ± 71	170 ± 81	0.906
Sublesion ChT (μm), mean ± SD	168 ± 72	164 ± 75	0.779
Mean ChT (μm), mean ± SD	166 ± 66	160 ± 68	0.663
Neuroretinal thickness above T3 lesion (μm), mean ± SD	337 ± 80	338 ± 64	0.938
AMD phenotype, n (%)			0.374
Drusen	16 (16)	8 (24)	
RPD	9 (9)	5 (15)	
Both drusen and RPD	73 (75)	20 (61)	
T3 MNV stage, n (%)			0.823
Stage 1	8 (8)	2 (6)	
Stage 2	42 (43)	13 (39)	
Stage 3	48 (49)	18 (55)	
Presence of hemorrhage, n (%)			0.068
Yes	53 (54)	24 (73)	
No	45 (46)	9 (27)	
Presence of nascent GA, n (%)			<0.001*
Yes	45 (46)	4 (12)	
No	53 (54)	29 (88)	
Presence of HRF elsewhere, n (%)			<0.001*
Yes	92 (94)	15 (45)	
No	6 (6)	18 (55)	
Number of exudative T3 lesions, n (%)			1.000
1 lesion	89 (91)	30 (91)	
2 lesions	9 (9)	3 (9)	
Presence SRF, n (%)			0.163
Yes	48 (49)	21 (64)	
No	50 (51)	12 (36)	
Presence SHRM, n (%)			0.068
Yes	40 (41)	20 (61)	
No	58 (59)	13 (39)	
Presence PED, n (%)			0.037*
Yes	86 (88)	33 (100)	
No	12 (12)	0 (0)	

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; ChT = choroidal thickness; CMT = central macular thickness; GA = geographic atrophy; HRF = hyperreflective foci; logMAR = logarithm of the minimum angle of resolution; MA = macular atrophy; MNV = macular neovascularization; PED = pigment epithelium detachment; RPD = reticular pseudodrusen; SD = standard deviation; SHRM = subretinal hyperreflective material; SRF = subretinal fluid; T3 = type 3.
*Statistically significant result.

pathway to MA development.[38] Furthermore, nonexudative SHRM was recently reported as a biomarker of atrophy development in the absence of MNV.[39]

Finally, presence of HRF was also associated with the development of MA even if no correlation with the MA area was disclosed. Hyperreflective foci are a well-established risk factor of GA development but also a biomarker of nAMD conversion (especially T3 MNV).[2,39] With nascent T3 development HRF are located contiguous with T3 MNV development;[2] in our series, however, HRF outside the T3 lesions were correlated with MA development. Thus, a precise localization of HRF is of relevance to predict long-term anatomic outcomes.

There are 3 potential pathways involved in MA development in patients with nAMD treated with anti-VEGF: The natural progression of the atrophy related to the dry form of the AMD, the possible regression of the MNV due to the anti-VEGF therapy, and the suppression of the VEGF levels due to the therapy itself. To date, evidence suggests that there is not a straightforward link between anti-VEGF injections exposure and MA development. Several studies showed that there is no association between the enlargement of MA and the number of injections received.[29,40] Our study confirmed the lack of association between the number of injections and the area of MA. However, in our series, eyes with MA after 3 years of treatment showed a significantly lower number of injections in comparison to eyes without MA (9.9 ± 5.5. vs. 14.7 ± 7.2, $P < 0.001$). This may relate to the MA development itself. Indeed, eyes with MA are characterized by loss of RPE cells and thus lower VEGF levels, leading to a lower angiogenic drive and reduced need for anti-VEGF treatment. A parallel concept may explain the absence of

Table 3. Univariate Analysis for Predictors of MA Area at 3-Year Follow-Up (n = 98)

	MA Area	P Value
Quantitative variables		
Age	$r = -0.032$	0.752
Baseline BCVA	$r = 0.022$	0.827
CMT	$r = -0.131$	0.199
Subfoveal ChT	$r = -0.015$	0.887
Sublesion ChT	$r = -0.041$	0.687
Mean ChT	$r = -0.075$	0.465
Neuroretinal thickness above T3 lesion	$r = -0.100$	0.325
Area of MA	$r = 0.561$	<0.001*
Qualitative variables		
AMD phenotype		0.083
Drusen	1.77 ± 2.42	
RPD	4.44 ± 4.16	
Both drusen and RPD	2.69 ± 2.73	
T3 MNV stage		0.015*
Stage 1	5.38 ± 4.97	
Stage 2	2.73 ± 2.95	
Stage 3	2.23 ± 2.09	
Presence of hemorrhage		0.800
Yes	2.63 ± 2.55	
No	2.78 ± 3.24	
Presence cRORA under the T3 lesion		0.923
Yes	2.66 ± 2.70	
No	2.72 ± 2.99	
Presence cRORA elsewhere		<0.001*
Yes	4.62 ± 3.73	
No	2.04 ± 2.19	
Presence of nascent GA		0.008*
Yes	3.53 ± 3.17	
No	1.99 ± 2.41	
Presence of HRF elsewhere		0.495
Yes	2.65 ± 2.85	
No	3.48 ± 3.40	
Number of exudative T3 lesions		0.215
1 lesion	2.81 ± 2.98	
2 lesions	1.56 ± 1.08	
Presence SRF		0.171
Yes	2.29 ± 2.28	
No	3.09 ± 3.33	
Presence SHRM		0.119
Yes	3.29 ± 3.25	
No	2.32 ± 2.51	
Presence PED		0.080
Yes	2.51 ± 2.80	
No	4.06 ± 3.18	

AMD = age-related macular degeneration; BCVA = best-corrected visual acuity; ChT = choroidal thickness; CMT = central macular thickness; cRORA = complete retinal pigment epithelium and outer retinal atrophy; GA = geographic atrophy; HRF = hyperreflective foci; MA = macular atrophy; MNV = macular neovascularization; PED = pigment epithelium detachment; r = correlation coefficient (Pearson); RPD = reticular pseudodrusen; SHRM = subretinal hyperreflective material; SRF = subretinal fluid; T3 = type 3.
*Statistically significant result.

Table 4. Results of Stepwise Multiple Regression Analysis of the Association Between MA Area at 3-Year Follow-Up and Baseline Predictors (n = 98)

	Final MA Area as Dependent Variable	
	Standardized β Coefficient (SE)	P *Value*
CMT	−0.114 (0.002)	0.242
Area of MA	0.478 (0.436)	<0.001*
AMD phenotype	0.201 (0.473)	0.017*
Type 3 MNV stage	−0.028 (0.523)	0.808
Presence of cRORA elsewhere	0.047 (0.633)	0.628
Presence of nascent GA	0.224 (0.471)	0.008*
Presence of SRF	−0.008 (0.658)	0.947
Presence of SHRM	0.285 (0.513)	0.002*
Presence of PED	−0.134 (0.752)	0.122

AMD = age-related macular degeneration; CMT = central macular thickness; cRORA = complete retinal pigment epithelium and outer retinal atrophy; GA = geographic atrophy; MA = macular atrophy; MNV = macular neovascularization; PED = pigment epithelium detachment; SE = standard error; SHRM = subretinal hyperreflective material; SRF = subretinal fluid.
*Statistically significant result.

fluid in eyes with more advanced atrophy and the correlation of end point SRF with better visual prognosis in eyes with nAMD.[41,42]

However, we cannot exclude that the lower number of injections, and thus a suboptimal dosing regimen, was the cause of atrophy development. Indeed, a suboptimal PRN regimen could lead to greater fluctuation of CMT, which was previously associated with a greater probability of MA development.[43]

Limitations of the study include the retrospective nature of the analysis and the relatively small sample size. Due to the retrospective nature and the clinical setting of the study, 14% of patients dropped out during the 3-year follow-up and they were not included in our study cohort. For this reason, we do not know if identified biomarkers apply to all T3 patients. However, baseline features of dropped-out patients and included patients were not different. Furthermore, this is one of the largest T3 series in the literature and all patients were strictly followed for a 3-year follow-up. Another limitation was due to the PRN regimen and different anti-VEGF agents administrated during the treatment. Even if rigorous, the presence of a control group treated by a pro-active regimen could be of interest to confirm our results. However, the comparison between the efficacy of these 2 different regimens fell outside our aim.

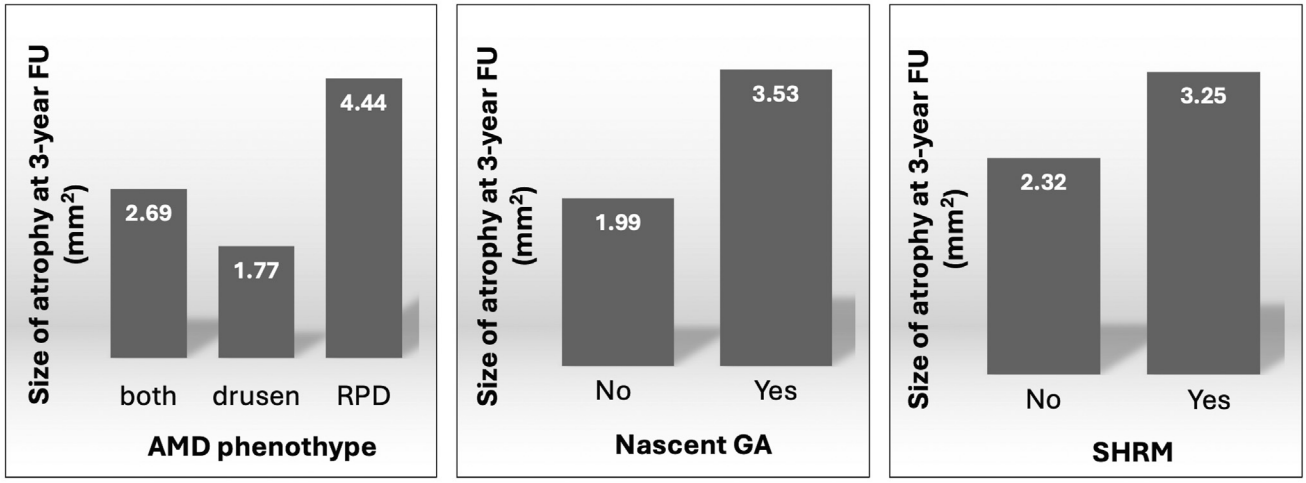

Figure 3. Associations between macular atrophy size and significant predictors. Histograms showing the association between macular atrophy size with age-related macular degeneration (AMD) phenotype (graph on the left), presence of nascent geographic atrophy (GA; graph in the middle), and presence of subretinal hyperreflective material (SHRM; graph on the right). FU = follow-up; RPD = reticular pseudodrusen.

In conclusion, we identified structural OCT features associated with the development of MA after 3-year treatment with anti-VEGF injections in treatment-naive T3 MNV. Of note, the presence of RPD, nascent GA, and SHRM at baseline were the most significant independent predictors of MA area. Current findings may be employed to identify less favorable T3 patterns and to better characterize the prognosis of patients with nAMD.

Footnotes and Disclosures

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No animals were used in this study.

Author Contributions:

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Analysis and interpretation: Sacconi, Forte, Beretta, Iannuzzi, Polito, Nicolò, Parravano, Souied, Sarraf, Sadda, Bandello, Querques.

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Abbreviations and Acronyms:
AMD = age-related macular degeneration; **BCVA** = best-corrected visual acuity; **ChT** = choroidal thickness; **CMT** = central macular thickness; **cRORA** = complete retinal pigment epithelium and outer retinal atrophy; **FAF** = fundus autofluorescence; **GA** = geographic atrophy; **HRF** = hyperreflective foci; **logMAR** = logarithm of the minimum angle of resolution; **MA** = macular atrophy; **MNV** = macular neovascularization; **nAMD** = neovascular age-related macular degeneration; **OCTA** = OCT angiography; **PRN** = pro-re nata; **RPD** = reticular pseudodrusen; **RPE** = retinal pigment epithelium; **SHRM** = subretinal hyperreflective material; **SRF** = subretinal fluid; **T3** = type 3.

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