A 5-Year Longitudinal Study of Macular Atrophy

Um Estudo Longitudinal de 5 Anos de Atrofia Macular

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ABSTRACT

INTRODUCTION: Macular atrophy (MA) is one of the late stages of age-related macular degeneration (AMD) and leads to irreversible loss of visual function. During the past years, efforts have been made towards a more detailed comprehension of the characteristics of MA, and a panel of retina specialists has recently established a new classification system to describe atrophy in the context of neovascular AMD, by the CONAN group. Furthermore, recent publications have focused on investigating the progression of MA, as well as the factors that might influence MA growth rates, particularly anti-VEGF injections.

METHODS: This was a retrospective analysis of patients with treatment-naïve neovascular AMD between 2016 and 2021. During the study period, patients underwent neovascular AMD treatment with either ranibizumab or aflibercept. A complete ophthalmologic examination was performed, including ETDRS best-corrected visual acuity (BCVA), biomicroscopy and dilated fundoscopy. Multimodal imaging included macular spectral-domain optical coherence tomography, ultra-widefield fundus photograph and autofluorescence, fluorescein angiography and optical coherence tomography angiography (OCT-A) at baseline, 1 and 5 years. The main outcome was the characterization of the MA type, graded according to the CONAN criteria based on multimodal imaging.

RESULTS: Fourty-five eyes from 45 patients (13 male patients) were included. Mean age at baseline was 76.60±5.66 years. Patients received a total mean of 12.95±7.44 intravitreal injections of either ranibizumab or aflibercept. All patients developed at least one type of MA at 5 years and the most prevalent was incomplete outer retinal atrophy (iORA; 81.6%). Eyes receiving more anti-VEGF injections developed less complete retinal pigment epithelium (RPE) and outer retinal atrophy (cRORA; p=0.05) and lost fewer letters at 5 years (p=0.018). The only significant predictor of cRORA at 5 years was complete outer retinal atrophy (cORA; p=0.024).

CONCLUSION: A new grading system for MA has enabled ophthalmologists a more objective and detailed characterization of the late stages of AMD. In our study, the only significant predictor of cRORA at 5 years was cORA at baseline. Number of anti-VEGF injections was protective against the development of cRORA and visual acuity loss. More studies are needed to establish the clinical and anatomical findings that can influence and foretell the disease prognosis.

KEYWORDS: Aflibercept; Macula Lutea; Macular Degeneration/drug therapy; Ranibizumab.

RESUMO

INTRODUÇÃO: A atrofia macular (MA) é um dos estágios finais da degeneração macular relacionada à idade (DMRI) e leva à perda irreversível da função visual. Nos últimos anos, esforços têm sido feitos no sentido de uma compreensão mais detalhada das características da MA, e um painel de especialistas em retina estabeleceu recentemente um novo sistema de classificação para descrever a atrofia no contexto da DMRI neovascular, pelo grupo CONAN. Além disso, publicações recentes têm se concentrado na investigação da progressão da MA, bem como nos fatores que podem influenciar as taxas de crescimento da MA, particularmente as injeções de anti-VEGF.

MÉTODOS: Esta foi uma análise retrospectiva de pacientes com DMRI neovascular sem tratamento prévio entre 2016 e 2021. Durante o período do estudo, os pacientes foram submetidos a tratamento com DMRI neovascular com ranibizumab ou aflibercept. Um exame oftalmológico completo foi realizado, incluindo a acuidade visual corrigida (BCVA), biomicroscopia e fundoscopia sob midríase. A imagem multimodal incluiu tomografia de coerência óptica de domínio espectral macular, fotografia de fundo ocular, autofluorescência, angiografia com fluoresceína e angiografia por tomografia de coerência óptica (OCT-A) no início do estudo, 1 e 5 anos. O principal objetivo foi a caracterização do tipo de AM, classificado de acordo com os critérios do CONAN com base em imagens multimodais.

RESULTADOS: Quarenta e cinco olhos de 45 doentes (13 doentes do sexo masculino) foram incluídos. A idade média no início do estudo foi de 76,60 ± 5,66 anos. Os doentes receberam uma média total de 12,95 ± 7,44 injeções intravítreas de ranibizumab ou aflibercept.Todos os doentes desenvolveram pelo menos um tipo de MA em 5 anos e o mais prevalente foi atrofia retiniana externa incompleta (iORA; 81,6%). Os olhos que receberam mais injeções de anti-VEGF desenvolveram menos atrofia da retina externa e do epitélio pigmentar da retina (cRORA; $p = 0,05$) e perderam menos letras em 5 anos ($p = 0,018$). O único preditor significativo de cRORA em 5 anos foi a atrofia retiniana externa completa (cORA; $p = 0,024$).

CONCLUSÃO: Um novo sistema de classificação para MA permitiu aos oftalmologistas uma caracterização mais objetiva e detalhada dos estágios finais da DMRI. Neste estudo, o único preditor significativo de cRORA em 5 anos foi cORA no início do estudo. O número de injeções de anti-VEGF foi protetor contra o desenvolvimento de cRORA e a perda de acuidade visual. Mais estudos são necessários para analisar os achados clínicos e anatómicos que podem influenciar e predizer o prognóstico da doença.

PALAVRAS-CHAVE: Aflibercept; Degenerescência Macular/tratamento farmacológico; Macula Lutea; Ranibizumab.

INTRODUCTION

Macular atrophy (MA) is one of the late stages of age-related macular degeneration (AMD) and leads to irreversible loss of visual function. During the past years, efforts have been made towards a more detailed comprehension of the characteristics of macular atrophy, and a panel of retina specialists has recently established a grading system for MA based on optical coherence tomography (OCT) findings, named the Classification of Atrophy Meetings (CAM) criteria,[1] which was followed by a new classification system to describe atrophy in the context of neovascular AMD, by the CONAN group.[2] Furthermore, recent publications have focused on investigating the progression of macular atrophy, as well as the factors that might influence macular atrophy growth rates, particularly intravitreal anti-VEGF injections.[3–5]

The IVAN, HARBOR and CATT trials are large studies that have drawn attention to the comprehension of MA and its association with anti-VEGF agents, regimens, and doses. However, different imaging modalities and criteria were used to classify MA and neither one of the aforementioned reports considered MA as its primary study outcome. Other publications including post-hoc analyses of some of these participants in large trials, have reached other conclusions and raised new questions about anti-VEGF treatment, predictors of MA and clinical features of prognostic relevance.[4,6]

We aimed to describe and characterize the development of MA in a population of treatment-naïve neovascular AMD eyes submitted to anti-VEGF treatment throughout 5 years, according to the new standardized, reproducible CONAN classification.

METHODS

This was a retrospective cohort study including patients with neovascular AMD treated with anti-VEGF therapy (either ranibizumab or aflibercept) between 2016 and 2021 at the Coimbra University Hospital. The current research follows the tenets of the Declaration of Helsinki 2013 and all patients were provided written informed consent.

STUDY POPULATION

The inclusion criteria were as follows: patients diagnosed with nAMD using SD-OCT, fluorescein angiography (FA) and optical coherence tomography angiography (OCT-A) who were treatment-naïve and with a follow-up of 5 years after commencement of treatment with anti-VEGF, either ranibizumab (Lucentis, Genentech, San Francisco, CA) or aflibercept (Eylea, Regeneron, Tarrytown, NJ) in a *Pro re nata* or treat-and-extend regimen. Anti-VEGF choice and treatment regimen was at the discretion of the treating physician and a decision to switch to another anti-VEGF agent was made if visual acuity or subretinal fluid (SRF) failed to respond. Patients with concomitant retinal disorders such as diabetic retinopathy or myopic chorioretinal degeneration and patients submitted to laser photocoagulation or vitreoretinal surgery were excluded from the analysis. Clinical data were collected at baseline and after 1 and 5 years of treatment.

The detailed clinical protocol for MA assessment has been previously described.[2] All patients underwent clinical examination including best-corrected visual acuity (BCVA) using the Early Treatment Diabetic Retinopathy Study Scale (ETDRS) (letters), biomicroscopy and dilated fundus examination. Multimodal evaluation included spectral-domain OCT (SD-OCT) (Spectralis, Heidelberg Engineering Inc, Franklin, MA); color fundus photograph (CFP) using a Nikon D300 high resolution camera (Nikon Corporation, Tokyo, Japan) mounted on a TRC 50 DX fundus camera (TopCon Corporation, Tokyo, Japan), and at 5 years using Optos® ultra-widefield CFP; fundus autofluorescence (FAF) with an angiograph (Heidelberg Retina Angiograph 2, Heidelberg Engineering, Heidelberg, Germany) and at 5 years using Optos® ultra-widefield FAF; optical coherence tomography angiography (OCT-A, Carl Zeiss Meditec, Dublin, CA) and fluorescein angiography (FA) (Heidelberg Retina Angiograph 2, Heidelberg Engineering, Heidelberg, Germany). The total number of intravitreal injections of anti-VEGF was recorded.

MULTIMODAL EVALUATION

Lesions were graded by two experienced readers (R.P, C.F.) and unresolved discrepancies were reviewed by a third reader (M.L.C). All OCT scans were analyzed, and MA was classified into four categories according to the CONAN criteria: complete retinal pigment epithelium (RPE) and outer retinal atrophy (cRORA), incomplete RPE and outer retinal atrophy (iRORA), complete outer retinal atrophy (cORA) and incomplete outer retinal atrophy (iORA); if more than one type of atrophy was present, both were included in the data record. Ultra-widefield CFP and FAF were evaluated simultaneously for confirmatory classification of MA. Other OCT parameters were central macular thickness (CMT), intraretinal fluid (IRF), subretinal fluid (SRF) and pigment epithelium detachment (PED), whether fibrous or serous. Quantitative measurements on OCT (SRF height, PED height) were performed manually using the Spectralis software. At baseline, macular neovascularization (MNV) was classified into 3 types, according to the CONAN criteria, through SD-OCT, OCT-A and FA assessment, also, location (subfoveal, juxtafoveal or extrafoveal) and area of MNV were registered. The fellow eye was also evaluated in terms of MNV and MA type. Baseline and follow-up parameters and their definitions according to the CAM and CONAN reports are detailed in Supplemental Table 1.

STUDY OUTCOMES

The primary outcomes of this study were the prevalence and incidence of the different types of MA 5 years after beginning anti-VEGF treatment for neovascular AMD. Secondary outcomes were mean change in BCVA, and baseline factors associated with *de novo* cRORA and cORA at 5 years.

STATISTICAL ANALYSIS

SPSS software version 25.0 (SPSS Inc., Chicago, IL, USA) was used to perform all statistical analysis. Descriptive statistics were performed to report demographic and clinical data at the first visit. Poisson regression models were used to calculate cORA and cRORA incidence rates. Comparative statistical analysis was performed using Paired t-tests and Chi-square tests for continuous and categorical variables, respectively.

For prediction of de novo cORA and cRORA, logistic regression models were built. Eyes that presented with a given atrophy type at baseline were excluded from the models pertaining that atrophy type. Baseline characteristics and number of anti-VEGF injections were evaluated by univariate analysis (without adjustment for other covariants) as potential risk factors for cORA and cRORA development. The risk factors associated with $p<0.2$ were then included in a backward selection logistic regression with multivariate model. A 95% confidence interval with a 5% level of significance was adopted, and $p<0.05$ was considered statistically significant.

Furthermore, BCVA data were analyzed, including calculation of mean and standard-deviation (SD) according to clinical and imaging characteristics at each time-point as well as mean change between baseline and 5 years, using linear regression analysis.

RESULTS

A total of 45 eyes from 45 patients with treatment-naïve neovascular AMD were included. Patients' demographic and clinical characteristics at baseline, 1 and 5 years are summarized in Table 1. In brief, mean age at baseline was 77.5±6 years and 32/45 were women (71.1%). Study eyes received a total average of 14.18±9.02 anti-VEGF intravitreal injections.

Prevalence and incidence rates for each MA type are described in Table 1. All patients developed some type of MA at

Table 1. Descriptive statistics at baseline, and 1 and 5 years after anti-VEGF treatment.

	Baseline	1 year	5 years	*p*-value (baseline and 5 years)
Age		77.5±6		
Gender (female)		32 (71.1%)		
BCVA, mean±SD	56.9±15.1	61.9±18.3	35.1±26.3	**<0.001**
Injections, cumulative mean±SD		7.95±2.18	14.18±9.02	
SD-OCT				
MA (prevalence) , n (%)				
iORA	18 (40.9%)	27 (62.8%)	36 (80%)	0.809
cORA	11 (25%)	25 (58.1%)	33 (73.3%)	0.434
iRORA	8 (18.2%)	34 (79.1%)	36 (80%)	0.537
cRORA	3 (6.8%)	15 (34.9%)	17 (38.6%)	0.274
MA cumulative incidence, % (n)				
iORA		50% (13/26)	80.8% (21/26)	
cORA		45.5% (15/33)	69.7% (23/33)	
iRORA		75% (27/36)	77.8% (28/36)	
cRORA		34.9% (15/43)	39.6% (17/43)	
MA at the foveal center, n (%)				
iORA	5 (11.4%)	5 (11.6%)	8 (17.8%)	0.302
cORA	2 (4.5%)	5 (11.6%)	11 (24.4%)	
iRORA	4 (9.1%)	14 (32.6%)	14 (31.1%)	0.413
cRORA	0	6 (14%)	9 (20%)	
MA type associated with primary MNV lesion, n (%)				0.784
None	22 (50%)			
iORA	13 (29.5%)	11 (25.6%)	8 (18.2%)	
cORA	6 (13.6%)	7 (16.3%)	8 (18.2%)	
iRORA	1 (2.3%)	14 (32.6%)	18 (40.9%)	
cRORA	2 (4.5%)	11 (25.6%)	10 (22.7%)	
Colocalization of MA with MNV, n (%)				
Within MNV area		20 (47.6%)	21 (47.7%)	
Outside MNV area		1 (2.4%)	2 (4.5%)	
Mixed		21 (50%)	21 (47.7%)	
Central subfoveal thickness, µm	246.2±123.3	192.7±96.9	299.4±206.4	0.445
IRF, n (%)	31 (70.5%)	19 (44.2%)	15 (33.3%)	0.692
SRF, n (%)	35 (79.5%)	15 (34.9%)	9 (20.5%)	0.083
SRF height, µm	138.2±77.108	34.24±64.3	165.55±86.915	0.688
PED, n (%)	37 (82.2%)	37 (86%)	26 (57.8%)	0.341
PED height, µm	242.1±169.6	182.9±157.4	205.56±146.795	0.069
OCT-A and FA				
MNV type, n (%)				
Type 1	19 (48.7%)	20 (74.1%)		
Type 2	8 (20.5%)	1 (3.7%)		
Mixed type 1 and type 2	5 (12.8%)	4 (14.8%)		
Type 3	7 (17.9%)	2 (7.4%)		
MNV location, n (%)				
Subfoveal	31 (77.5%)	20 (74.1%)		
Juxtafoveal	6 (15%)	5 (18.5%)		
Extrafoveal	3 (7.5%)	2 7.4%)		
MNV area (mm^2)	8.3±6.6	6.8±5.2		

Table 1. Descriptive statistics at baseline, and 1 and 5 years after anti-VEGF treatment (continued).

	Baseline	1 year	5 years	*p*-value (baseline and 5 years)
Widefield CFP				
Soft drusen, n (%)	31 (81.6%)	22 (73.3%)	11 (25%)	0.08
Hyperpigmentation, n (%)	13 (36.1%)	16 (59.3%)	16 (36.4%)	
Depigmentation, n (%)	12 (33.3%)	18 (66.7%)	29 (65.9%)	
Fellow eye				
MNV, n (%)	18 (40.9%)		15 (34.1%)	
MA, n (%)				
Absent	27 (61.4%)	16 (37.2%)	17 (38.6%)	
iORA	3 (6.8%)	10 (23.3%)	4 (9.1%)	
cORA	1 (2.3%)	1 (2.3%)	2 (4.5%)	
iRORA	7 (15.9%)	7 (16.3%)	10 (22.7%)	
cRORA	6 (13.6%)	9 (20.9%)	11 (25%)	

BCVA: best-corrected visual acuity; CFP: color fundus photography; cORA: complete outer retinal atrophy; cRORA: complete RPE and outer retinal atrophy; ETDRS: early treatment diabetic retinopathy study; FA: fluorescein angiography; FAF: fundus autofluorescence; IRF: intraretinal fluid; iORA: incomplete outer retinal atrophy; iRORA: incomplete RPE and outer retinal atrophy; MA: macular atrophy; MNV: macular neovascularization; PED: pigmented epithelium detachment; SD: standard deviation; SD-OCT: spectral domain optical coherence tomography; SRF: subretinal fluid; Paired t-tests for continuous and χ2-tests for dichotomous and categorical variables. $p<0.05$ were considered statistically significant (bolded).

Table 2. Association between baseline parameters and the development of cRORA at 5 years on univariate analysis.

P	Univariate analysis OR (95% CI)	*p*-value	Multivariate analysis B coefficient	*p*-value
Total number of anti-VEGF injections	0.54 (0.29-1.02)	**0.05**	-0.133	0.088
cORA	4.12 (0.91-18.52)	**0.064**	3.08	**0.024**
iRORA	4.8 (0.75- 30.55)	**0.097**		0.912
MNV type (in relation to type 1)		**0.098**		0.169
Type 1	1			
Type 2	4.33 (0.66-28.11)	**0.124**		0.132
Mixed type 1 and type 2	6.5 (0.73-57.82)	0.93		0.238
Type 3	5.77 (3.81-18.76)	**0.078**		0.029
PED	0.045 (0.003-0.75)	**0.031**		0.150
IRF	3.75 (0.69-20.37)	**0.124**		0.283

cORA: complete outer retinal atrophy; cRORA: complete RPE and outer retinal atrophy; IRF: intraretinal fluid; iRORA: incomplete RPE and outer retinal atrophy; MA: macular atrophy; MNV: macular neovascularization; PED: pigmented epithelium detachment; Univariate and multivariate logistic regression models were built. $p<0.2$ and $p<0.05$ were considered statistically significant in univariate analysis and multivariate analysis, respectively (bolded).

1 year and more than one type of MA was frequently detected during follow-up evaluations. The MA type with the highest incidence was iRORA (75%) and iORA (80.8%) at 1 and 5 years of follow-up, respectively. The most prevalent MA type related to the MNV lesion was iORA at baseline (29.5%) and iRORA at 5 years (40.9%).

There was a significant decrease of central subfoveal thickness at 1 year from 246.2±123.3 µm to 192.7±96.9 µm (p=0.003), after which it increased again to 299.4±206.4 µm (p=0.081) at 5 years. The proportion of eyes with SRF or IRF decreased from baseline (79.5% and 70.5%, respectively) to 5 years (20.5% and 33.3%, respectively) although these differences were not statistically significant.

The most frequent MNV type at baseline was type 1 (48.7%), followed by type 2 (20.5%) and the location of MNV was predominantly subfoveal (77.5%).

On univariate analysis, the baseline risk factors associated with de novo cRORA at 5 years were the presence of cORA (odds ratio (OR) (95% confidence-interval (CI)): 4.12 (0.91-18.52), p=0.064), iRORA (OR (95% CI): 4.8 (0.75-30.55), p=0.097), MNV type (p=0.098), with type 3 having the highest OR (95% CI): 5.77 (3.81-18.76), p=0.078, and IRF (OR (95% CI): 3.75 (0.69-20.37), p=0.124). Baseline parameters with a significant inverse association with cRORA development were PED (OR (95% CI): 0.045 (0.003-0.75), p=0.031), irrespective of PED height (p=0.952), and total number of anti-VEGF injec-

tions (OR (95% CI): 0.90 (0.80-1.02), *p*=0.01). After 1 year of treatment, the number anti-VEGF injections also showed an inverse association with cRORA development at 5 years (OR (95% CI): 0.54 (0.29-1.02), *p*=0.05), as well as the presence of a PED (OR (95% CI): 0.32 (0.06-1.73), *p*=0.189).

In multivariate analysis, the only baseline predictor associated with the development of cRORA was cORA (OR (95% CI): 21.83 (1.5-315), *p*=0.024) (Table 2). The Hosmer-Lemeshow test supports that the proportional odds assumption was not violated (χ^2=9.24, *p*=0.322).

The only risk factor associated with de novo cORA was baseline PED height (OR (95% CI): 0.99 (0.99-1), p=0.179); when we excluded the eyes that had cORA at baseline, 93.9% of the remaining eyes in the analysis had PED.

Considering fellow eye status in terms of MA type or MNV presence, incidence of cORA and cRORA at 5 years was similar irrespective of irrespective of MA or MNV in the fellow eye at baseline (*p*=0.928 and *p*=0.656, respectively).

VISUAL ACUITY DATA

Average pretreatment BCVA was 56.9±15.1 letters in ETDRS scale, and there was significant improvement after the first year of treatment (mean BCVA 61.9±18.3, *p*=0.006). At 5 years, BCVA worsened significantly to 35.1±26.3 letters (*p*<0.001).

We investigated the relationships between OCT parameters and BCVA at each time-point by univariate analysis. Eyes with SRF were associated with better BCVA at baseline (59.87±13.62, *versus* 41.83±14.27, *p*=0.006) but not at 5 years (*p*=0.931). No association was found between BCVA and IRF at neither follow-up time. As might be expected, central 1-mm iRORA and cRORA were associated with worse BCVA at baseline (40.25±8.53 *versus* 58.97±14.53, *p*=0.017) and at 5 years (38.79±26.73 *versus* 20±19.15, *p*=0.007). Analyzing BCVA change between baseline and 5 years, eyes with IRF at baseline had a more significant decrease in BCVA (-22.3±25.18 *versus* -9.3±22.59, *p*=0.170) and eyes that received more anti-VEGF injections lost fewer letters at 5 years (*p*=0.018) as depicted in Fig. 1.

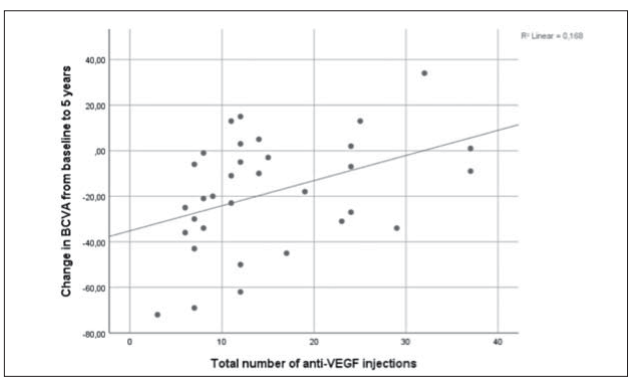

Figure 1. Dispersion graph and linear adjustment of BCVA (ETDRS letters) change from baseline to 5 years and total number of anti-VEGF injections.

DISCUSSION

In this study, we analyzed 45 eyes with treatment-naïve neovascular AMD submitted to anti-VEGF injections and evaluated the incidence of the four different types of MA according to the CONAN classification over a five-year period. At 5 years, all patients had developed some type of MA; iORA had the highest incidence rate (80.8%), followed by cORA (69.7%) and iRORA (77.8%). More than one type of MA was frequently present. Previous studies with a 5-year follow-up have found significantly lower incidence rates of MA (38% in the CATT trial using CFP and FA and 22.4% in a study adhering to the CONAN classification but excluding eyes with IRF – a risk factor for the development of cRORA, according to our analysis).[7,8] Using FA and CFP, Berg *et al* also described the development of some type of atrophy in all study-eyes at 5 years.[9]

We also aimed to identify baseline predictors of *de novo* cORA and cRORA at 5 years of follow-up using univariate and multivariate regression analyses. The PED height was the only baseline risk factor for *de novo* cORA and this association was weak. We interpret lack of significant association of other baseline factors with cORA development to be a consequence of smaller participant enrollment in this analysis (n=33), due to exclusion of eyes with cORA at baseline. Presence of cORA and iRORA at baseline and IRF were associated with *de novo* cRORA at 5 years. The MNV type at baseline was also significantly associated with cRORA and type 3 MNV showed the highest odds ratio of progression to cRORA. The total number of anti-VEGF injections and the presence of a PED at baseline were inversely associated with *de novo* cRORA at 5 years. In multivariate analysis, the only significant baseline predictor of the development of cRORA was cORA; this makes sense, as loss of outer retinal layers has been previously described as risk factor for atrophy development.[10] Parameters associated with cRORA development at 5 years with statistical significance on univariate analysis are further detailed below.

Eyes with a PED at baseline were less likely to develop cRORA at 5 years and patients with MNV type 1 at baseline developed less cRORA at 5 years in comparison to other MNV types. These findings are complementary as a PED is commonly a biomarker of type 1 MNV. In a small case series, results showed that RPE atrophy rarely developed directly over the PED in MNV type 1.[11] In type 1 MNV the neovascular membrane that grows under the RPE recapitulates the choriocapillaris and nutritionally supports the ischemic complex RPE/outer retina, thus preventing its atrophy.[12,13] Eyes with MNV types 2 and 3 were 4.3 and 5.7 times more likely to develop cRORA at 5 years, respectively, compared to MNV type 1, in line with previous studies.[10,11] Type 3 lesions are usually preceded by migration of RPE cells into the neurosensory retina, which may result in RPE monolayer atrophy.[10]

Regarding fluid analysis, BCVA was significantly better in eyes with SRF, both at baseline and after 1 year of treatment (treatment-resistant fluid), consistent with previous findings.[7,8,11,14,15] It has been proposed that SRF might be a sign of MNV perfusion and a protective mechanism against hypoxia and macular degeneration and a buffer against toxic effects of MNV,[7,8,14,15] and one study found SRF to be associated with less MA development, though this was not confirmed in our analysis.[10] The presence of IRF at baseline (70.5%) was associated with

an increased risk of developing cRORA at 5 years on univariate analysis, and IRF has been previously associated with the development of MA.[7,8,16,17] Also, eyes with IRF at baseline lost twice as much letters as eyes with IRF, after 5 years (-22.3±25.18 *versus* -9.3±22.59) and a similar pattern of results was described in one other 5-year analysis.[18] These findings might influence MNV management in a clinical context, as treatment targeting IRF and tolerance of stable SRF can lead to preservation of visual function on the long term and alleviate treatment burden.

Univariate analysis showed fewer injections of anti-VEGF to be associated with an increased risk of cRORA development at 5 years. Two recent studies with a similar methodology to ours – treatment-*naïve* neovascular AMD eyes treated with more than one anti-VEGF agent – also found an inverse relationship between total number of anti-VEGF injections and the development and growth rate of cRORA at 2 years.[19,20] Other reports found no association between total number of anti-VEGF injections and foveal involvement of MA or MA development.[13,16,21] Three large studies support the theory that neovascular AMD could evolve to MA regardless of type and frequency of anti-VEGF injections. The first one reports an incidence of MA of approximately one third in five years in eyes with untreated MNV, based on macular depigmentation area on CFP analysis; 22 however, an area of RPE atrophy adjacent to a subretinal fibrous scar was not considered to be MA, so the true incidence could be underestimated. The second and third ones, post-hoc analyses of the HARBOR trial using the CAM criteria for the diagnosis of cRORA, found no differences in the incidence or progression rates of new MA between anti-VEGF treatment regimens or doses.[10,23] Moreover, our study demonstrated that eyes receiving a higher number of anti-VEGF injections showed fewer ETDRS letters lost from baseline.

We found great variability of results among studies on MA development, and we believe this could be due to the ambiguous definitions of the terms "geographic atrophy", "dry AMD" and "macular atrophy". Besides, previous studies evaluating incidence, progression or growth rates of MA should be carefully interpreted regarding the imaging methods used to report MA. For instance, in the IVAN 6 and CATT 8 trials, atrophy was defined mainly through CFP and FA analysis, where areas of fibrosis could mimic atrophy, leading to incorrect classification.[24] Also, the SEVEN-UP study[25] reported a 98% incidence of geographic atrophy based on FAF, and with this imaging modality fibrosis or bleeding can also produce a decreased signal that could be incorrectly classified as atrophy. In this study we used multimodal imaging to characterize MA, using criteria defined by the CONAN group, to accurately report and characterize MA in neovascular AMD. When using an internationally recognized classification of several lesions, results between various studies can be readily compared and a consensus will be within reach.

Limitations of this study include the following. The anti-VEGF agent in each patient was either ranibizumab or aflibercept and some were switched from one agent to the other. Also, our study sample was small and there were not enough eyes to power some statistical findings.

In summary, after 5 years of treatment, all neovascular AMD eyes progressed to some type of MA and more than one type was frequently present in the same eye. Patients who received more anti-VEGF injections developed less cRORA at 5 years, which reinforces our confidence in the safety of anti-VEGF injections for AMD treatment in the long term. The only significant predictor of cRORA at 5 years was cORA, also no modifiable baseline feature significantly associated with de novo cORA was found. Intraretinal fluid at baseline was associated with higher odds of cRORA development and with greater BCVA loss at 5 years. On the other hand, SRF was associated with better visual outcomes at each time point analysis, and both these findings could make clinicians rethink their approach towards fluid management in MNV. Larger studies using a similar methodology for MA characterization including assessment of modifiable clinical predictors are warranted.

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RP: Conceptualization, Writing Original Draft.
RP, MS, PM, CF, MdLC: Methodology, Investigation.
CF, RS, JM: Conceptualization, Supervision, Project Administration.

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