Prevalence and characteristics of macular atrophy in eyes with neovascular age-related macular degeneration. A study from a long-term observational dataset: the Fight Retinal Blindness! project

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ABSTRACT

Background To assess the prevalence and characteristics associated with macular atrophy (MA) in eyes with neovascular age-related macular degeneration (nAMD) treated with vascular endothelial growth factor (VEGF) inhibitors.

Methods This was a retrospective, cross-sectional study of nAMD eyes that commenced anti-VEGF between January 2006 and August 2016. MA (absent/extrafoveal/subfoveal) was graded by treating practitioners based on multimodal imaging from April 2016. The prevalence of MA over time and risk factors of MA were assessed.

Results The prevalence of MA in a cohort of 1689 eyes was 9.9% (22/222) in eyes within 1 year of starting treatment, 41.5% (71/171) after 5 years and 48.4% (30/62) after 9 years of treatment. Risk factors for subfoveal MA included the proportion of visits at which the lesion was graded as inactive ((adjusted OR (AOR) 3.72 for the highest vs lowest the quartile of frequency of inactive gradings (95% CI 2.33 to 6.07)), age (AOR 1.05 per year (95% CI 1.02 to 1.07)), baseline visual acuity (AOR 3.9 for ≤35 letters vs ≥70 letters (95% CI 2.4 to 6.4)) and the number of injections received (AOR 1.20 every 10 injections (95% CI 1.08 to 1.33)). Similar associations were observed with extrafoveal MA.

Conclusions The risk of MA appeared to drop in eyes that had not developed it within 5 years. Low choroidal neovascularisation activity was by far the strongest predictor. We could not determine whether the increased prevalence of MA with time was due to anti-VEGF treatment or the natural history of the condition.

INTRODUCTION

The estimated prevalence of late age-related macular degeneration (AMD), defined as either choroidal neovascularisation (CNV) or macular atrophy (MA),[1] is 1.4% at 70 years of age, rising to 5.6% by age 80% and 20.0% by 90 years.[2] MA and CNV are not necessarily mutually exclusive and can occur simultaneously or sequentially in the same eye. Patients with MA have developed CNV in various proportions ranging from 10%[3] to 45% over 5 years.[4 5]

Reports of MA co-existing with CNV at presentation have ranged widely from 7% to 47%.[6–9] This variation may be explained by differences in the populations studied, the lack of a standardised methodology for assessing MA or the use of different imaging techniques. The natural history of MA associated with CNV is to progress slowly over time independently of CNV development.[5] While randomised controlled trials of vascular endothelial growth factor (VEGF) inhibitors have reported significant improvements in vision in patients with CNV,[10–13] the development of atrophy of retinal pigment epithelium and choriocapillaries that resemble the appearance of de novo MA is a concern.[14] Later analyses suggested that VEGF inhibition might accelerate the development and progression of MA: 18%–33% of patients were reported to have developed MA 2 years after starting anti-VEGF therapy.[15–17] One study of long-term outcomes reported that MA that affected the fovea was present in over 90% of eyes treated for a mean of 7.3 years.[18] An analysis of long-term outcomes of eyes from the Fight Retinal Blindness! (FRB!) database reported that 39% of eyes that had lost 10 or more letters of vision after 6.5 or more years of treatment had MA that affected the centre of the fovea.[19]

Identifying characteristics associated with the development of MA in neovascular age-related macular degeneration (nAMD) is important to improve long-term outcomes of anti-VEGF therapy. The International Consortium for Health-care Outcome Measures (ICHOM) has subsequently included the presence of MA as part of the minimal standard set of outcomes to be measured for AMD.[20] Baseline predictors for the 5-year risk of MA in a recent report from the Comparison of Age-related Macular Degeneration Treatment Trials (CATT) study included older age, hypercholesterolaemia, worse visual acuity (VA) at start of anti-VEGF therapy, larger CNV area, retinal angiomatous proliferation lesion, MA in the fellow eye and the presence of intraretinal fluid.[21] Establishing the direct effect of anti-VEGF treatment on the development and growth of MA is more difficult and currently controversial. Whether the mechanisms of development of MA are similar with or without the presence of CNV remains to be determined. The overall rate of growth of MA in eyes with nAMD which were treated with anti-VEGF in CATT[21] was similar to that reported by studies of AMD without CNV.[22 23]

We assessed the prevalence of MA among a cohort of patients with nAMD treated with anti-VEGF for up to 9 years by treatment duration and number of injections received. The secondary objective was to assess the clinical characteristics associated with the presence of MA, including the frequency of visits where the CNV lesion was graded inactive.

METHODS

This paper followed the Strengthening the Reporting of Observational Studies in Epidemiology checklist items for reporting observational study data.[24]

Setting

Data were obtained from the FRB! database, which tracks real-world outcomes of nAMD during routine clinical practice, the details of which have been published previously.[25] This analysis included patients from Australia, New Zealand and Switzerland. Ethics committees in Australia and New Zealand approved the use of 'opt out' patient consent. The research described adhered to the tenets of the Declaration of Helsinki.

Data sources/measurements

The FRB! system collects data from each clinical visit including the number of letters read on a logarithm of the minimum angle of resolution (LogMAR) VA chart (best of uncorrected, corrected or pin hole) and lesion activity (lesions were graded at each visit as active 'if there was intraretinal or subretinal fluid attributable to leak from choroidal neovascularisation lesion or fresh haemorrhage' and this was definition displayed on the data collection form); lesion size and type were recorded from fluorescein angiography at baseline (defined as the visit at which anti-VEGF treatment was commenced). Lesion characteristics and treatment decisions, including choice of drug and treatment regimen, were entirely at the discretion of the practitioner in consultation with the patient, thereby reflecting real-world practice. Most eyes enrolled in FRB! likely received some variation of treat-and-extend, however, eyes from Switzerland were likely receiving pro re nata during their treatment journey.[26]

Grading of MA was implemented in April 2016 into FRB! to comply with the ICHOM macular degeneration standard set, and was recorded at each visit from then.[20] All eyes in the cohort were therefore assessed in a cross-sectional manner when this change was implemented. Documentation of MA based on clinical examination and spectral domain optical coherence tomography (SD-OCT) or fundus autofluorescence (FAF) imaging at the discretion of the investigator, thereby reflecting real-world practice, and recorded according to the ICHOM standard set as: absent/present, extrafoveal/subfoveal.[20] Images from a random sample of patients from five selected practices were assessed by an independent reading centre (Bern Photographic Reading Centre) to evaluate the accuracy of the gradings.

Study design

Retrospective cross-sectional study of a prospectively designed database.

Participants

Treatment-naïve eyes with nAMD tracked by the FRB! outcome registry that commenced anti-VEGF therapy between 1 January 2006 and 30 August 2016 were included in the analysis. Eyes that had a visit which included an MA grading in FRB! were included in the analysis. As documentation of MA was a recent addition to the FRB! system, it was unknown when atrophy developed during treatment or whether it was present at baseline for the majority of cases.

Variables

The primary outcome was the prevalence of MA versus number of injection received and duration of treatment. An adjusted prevalence for patient age was also calculated. A comparison of demographic and clinical characteristics including age, lesion size and type, VA at baseline and initial choice of treatment (aflibercept or ranibizumab) between nAMD with MA and without MA was performed. Eyes were grouped into equal quartiles by the proportion of visits where the CNV was graded as inactive (low=0%–20%; moderate=21%–43%; high=44%–73%; very high=74%–100%). These groupings only applied to eyes with a minimum of three visits.

Statistical analyses

Eyes were grouped by the number of years on active treatment or number of injection received. The prevalence of MA was measured for each year and per 10 injections as the proportion of eyes graded as having MA. Age-adjusted proportions were also calculated using logistic regression.

Comparison of baseline characteristics between patients with MA and no-MA groups was conducted using Student's t-test, Wilcoxon rank-sum test and χ^2 tests where appropriate. P values were adjusted using Bonferroni's correction for pairwise comparisons.

Multivariate adjusted ORs (AORs) for baseline characteristics and lesion activity comparing subfoveal and extrafoveal atrophy with the no-MA group were obtained by logistic regression. Multivariate models included baseline age, gender, baseline VA, lesion size, lesion type, initial injection type, CNV activity group and number of injections received.

Choice of treatment usage between aflibercept and ranibizumab was analysed using eyes beginning treatment from December 2012 to August 2016. Multivariate AORs comparing ranibizumab and aflibercept as first-choice therapy in patients with MA were obtained by logistic regression. Adjusted parameters included baseline age, gender, baseline VA, lesion size, lesion type, CNV activity group and number of injections received.

The Variance Inflation Factor was used to detect multicollinearity between variables in the multivariate model.[27] Cohen's kappa was used to measure the inter-rater agreement in MA grading between the FRB! database and the reading centre.[28] Analyses were conducted using R V.3.3.1.[29]

RESULTS

Study participants

We identified 1689 treatment-naïve eyes from 1392 patients who had MA grading entered in the FRB! database. From this sample, 1150 (68%) eyes were graded as having no macular atrophy, 235 (14%) eyes had subfoveal atrophy and 304 (18%) had extrafoveal atrophy. There were 297 (21%) patients who were receiving treatments in both eyes, of whom 45 (15%) had MA in one eye, 81 (27%) had MA in both eyes and the remaining 171 (58%) had no MA in either eye.

Prevalence of MA over time

The prevalence of MA was 9.9% (22/222) in eyes whose MA was graded within 1 year of treatment, 20.3% (69/339) at 2 years, 41.5% (71/171) at 5 years and 48.4% (30/62) in patients treated for 9 years (figure 1). This increase in prevalence persisted when

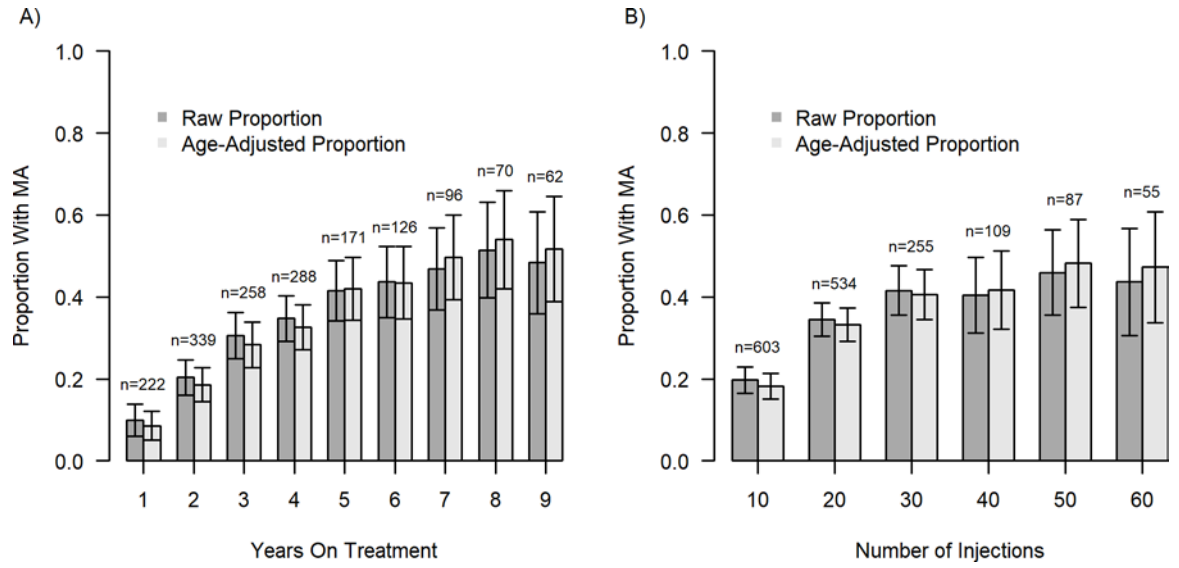

Figure 1 Raw and age-adjusted proportion of eyes graded as having macular atrophy (MA) (subfoveal or extrafoveal) with 95% CIs based on: (A) number of years on treatment from 2008 to 2016 and (B) number of injections received by increments of 10 up to 60 injections. Sample sizes are labelled above each pair of bars.

adjustment was made for patient age (8.6% at 1 year to 51.7% at 9 years; figure 1).

Demographic and clinical characteristics

Table 1 shows the demographic and clinical characteristics of patients with nAMD, grouped by the presence or absence of MA. Mean (SD) age at first presentation of nAMD of patients with MA was higher (subfoveal atrophy=81.7 (6.7) years; extrafoveal atrophy=81.1 (7.8) years) compared with patients without MA (78.5 (8.5) years; p<0.001 for both MA groups). Of note, the mean baseline VA in the extrafoveal MA group (63.6 (14.8) letters) was similar to that of eyes with no MA (p=0.468). Occult lesions were more prevalent in eyes with MA (subfoveal atrophy: 56.6%; p=0.023 and extrafoveal atrophy: 55.3%, p=0.031)

Table 1 Association of demographic and clinical characteristics between eyes graded with subfoveal, extrafoveal and no MA among 1689 treatment-naïve eyes from 1392 patients with an MA grading from the Fight Retinal Blindness project! database between 1 January 2006 and 30 August 2016

				P values pairwise comparisons*		
	No macular atrophy	Subfoveal atrophy	Extrafoveal atrophy	No MA vs subfoveal	No-MA vs extrafoveal	Subfoveal vs extrafoveal
Eyes	1150	235	304			
Patients	979	209	276			
Females, %	59.5%	64.7%	65.8%	0.500	0.170	1.000
Baseline age, (SD)	78.5 (8.5)	81.7 (6.7)	81.1 (7.8)	**<0.001**	**<0.001**	1.000
Baseline VA (SD)	62.1 (17.1)	52.9 (19.4)	63.6 (14.8)	**<0.001**	0.468	**<0.001**
≥70 letters, %	42.5%	24.3%	42.1%	**<0.001**	**1.000**	**<0.001**
36–69 letters, %	48.5%	56.6%	52.0%	0.077	0.866	0.981
≤35 letters, %	9.0%	19.1%	5.9%	**<0.001**	0.305	**<0.001**
Lesion size, median µm (Q1, Q3)	2348 (1400, 3000)	2400 (1448, 3000)	2230 (1221, 3438)	0.346	1.000	1.000
Lesion type, %				**0.030**	**0.017**	1.000
Predominantly classic (type II CNV)	27.2%	21.3%	18.8%	0.213	**0.010**	1.000
Minimally classic (type II CNV)	9.2%	11.5%	12.5%	1.000	0.331	1.000
Occult (type I CNV)	46.8%	56.6%	55.3%	**0.023**	**0.031**	1.000
Other	8.8%	4.7%	8.2%	0.146	1.000	0.433
Not recorded	8.0%	6.0%	5.3%	1.000	0.404	1.000
Proportion of visits with inactive lesion†						
Low (0%–20%)	31.5%	13.3%	10.7%	**<0.001**	**<0.001**	1.000
Moderate (21%–43%)	27.7%	21.9%	20.1%	0.252	**0.030**	1.000
High (44%–73%)	21.1%	30.0%	32.4%	**0.012**	**<0.001**	1.000
Very high (74%–100%)	19.7%	34.8%	36.8%	**<0.001**	**<0.001**	1.000

*P values adjusted using Bonferroni correction for pairwise comparisons.
†Minimum three visits.
CNV, choroidal neovascular; MA, macular atrophy; Q1, first quartile; Q3, third quartile;VA, visual acuity.

Table 2 Multivariate OR for subfoveal and extrafoveal atrophy

	Subfoveal vs no MA OR (95% CI)*	Extrafoveal vs no MA OR (95% CI)*
Baseline age per year	1.05 (1.02 to 1.07)	1.04 (1.02 to 1.06)
Gender		
Female	1	1
Male	0.91 (0.66 to 1.24)	0.92 (0.69 to 1.22)
Baseline VA		
≥70 letters	1	1
36–69 letters	1.98 (1.39 to 2.85)	1.10 (0.82 to 1.46)
≤35 letters	3.91 (2.38 to 6.41)	0.69 (0.38 to 1.20)
Lesion size (per 1000 µm)	1.03 (0.97 to 1.09)	1.05 (1.00 to 1.12)
Lesion type		
Predominantly classic (type II CNV)	1	1
Minimally classic (type II CNV)	1.47 (0.83 to 2.57)	1.55 (0.93 to 2.58)
Occult (type I CNV)	1.31 (0.89 to 1.93)	1.23 (0.86 to 1.77)
Other	0.79 (0.37 to 1.60)	1.46 (0.82 to 2.55)
Not recorded	1.41 (0.62 to 3.00)	1.75 (0.86 to 3.42)
Proportion of visits with inactive lesion†		
Low (0%–20%)	1	1
Moderate (21%–43%)	1.55 (0.94 to 2.59)	1.70 (1.06 to 2.75)
High (44%–73%)	3.07 (1.91 to 5.02)	3.78 (2.43 to 6.01)
Very high (74%–100%)	3.72 (2.33 to 6.07)	5.05 (3.25 to 8.02)
Injections (per 10 injections)	1.20 (1.08 to 1.33)	1.34 (1.22 to 1.47)

*The multivariate model included number of injections received, gender, baseline age, baseline VA, lesion size, lesion type, CNV activity group, proportion of visits with injection and initial treatment.
†Minimum three visits.
CNV, choroidal neovascularisation; MA, macular atrophy; VA, visual acuity.

versus no MA: 46.8%. Baseline lesion size was similar between MA and no-MA groups.

Risk factors of MA

The strongest risk factor for subfoveal MA was a higher frequency of visits at which the lesion was graded as inactive (AOR 3.72 for the highest vs lowest the quartile of inactive gradings (95% CI 2.33 to 6.07)) (table 2). Other independent characteristics associated with subfoveal MA included the number of injections received (AOR 1.20 every 10 injections (95% CI 1.08 to 1.33)), baseline age (AOR 1.05 per year (95% CI 1.02 to 1.07)), baseline VA (AOR 3.91 for ≤35 letters vs ≥70 letters (95% CI 2.38 to 6.41)) (table 2). The mean number of injections per year for the inactivity groups was 8.8, 7.6, 7.0, and 5.9 for the low, moderate, high and very high activity groups, respectively. Gender, lesion size and lesion type were not associated with the presence of subfoveal atrophy.

Ranibizumab versus aflibercept as an initial treatment

Physicians initiated treatment with ranibizumab in 56% eyes and with aflibercept in 44% of eyes that were subsequently graded as having subfoveal or extrafoveal MA (p=0.180) from December 2012 onwards when aflibercept was readily available in Australia and Switzerland, to August 2016. In patients without MA, the first injection was equally likely to be either drug (figure 2). The odds of initiating anti-VEGF therapy was similar with ranibizumab and aflibercept in patients with MA (AOR 1.16 for ranibizumab vs aflibercept (95% CI 0.81 to 1.65); online supplementary file table 1).

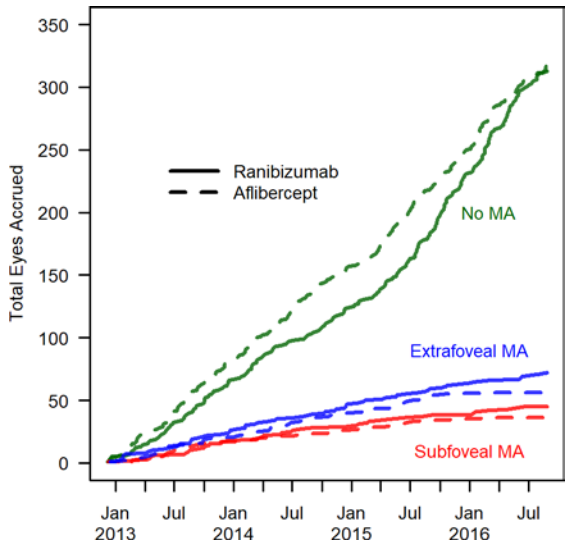

Figure 2 Uptake of ranibizumab vs aflibercept from December 2012 to August 2016 partitioned by macular atrophy (MA) grading. Physicians initiated treatment with ranibizumab in 56% eyes and with aflibercept in 44% of eyes that were subsequently graded as having subfoveal or extrafoveal MA (p=0.180) from December 2012 onwards when aflibercept was readily available in Australia and Switzerland. The odd of initiating anti-VEGF therapy was similar between ranibizumab and aflibercept in patients with MA (adjusted OR 1.16 for receiving initial injection of ranibizumab vs aflibercept (95% CI 0.81 to 1.65)).

Reading centre evaluation

A total of 78 patients were randomly sampled from five contributing practices and assessed by an independent reading centre. The random sample contained 39 patients graded as not having any MA, 19 patients with extrafoveal MA and 20 patients with subfoveal MA according to the gradings in the FRB! database. Of this sample, 51 (65%) patients matched the grading provided by the reading centre and 12 (15%) recorded the MA in the wrong location (ie, subfoveal was recorded instead of extrafoveal). Of the remainder, eight (10%) recorded false negatives (no MA recorded when MA was present) and seven (9%) were false positives (MA recorded when no MA was present). Cohen's kappa (95% CI) for the inter-rater agreement was estimated to be 0.45 (0.29 to 0.61) suggesting weak agreement. If we only consider whether MA was absent versus present regardless of location, practitioner grading was accurate in 80% of cases and Cohen's kappa (95% CI) was 0.62 (0.44 to 0.79) suggesting moderate agreement.

DISCUSSION

The prospectively designed observational registry of the FRB! project allowed us to assess the prevalence of MA in nAMD eyes treated for up to 9 years. The rate of development of MA appeared to drop in eyes that had not developed it after their first 5 years of treatment. We found a higher age-adjusted prevalence of atrophy with both increasing duration of disease and increasing number of anti-VEGF injections received. The quartile of eyes whose lesion was graded as active least often were 3.7 times more likely to develop MA than the quartile that was graded as active most often. Other characteristics associated with the presence of subfoveal MA were worse VA at first presentation of nAMD, increasing treatment (disease) duration and patient age at baseline.

Our 5-year prevalence of MA was very similar to those of the CATT study but our 9-year estimate (48.4%) was lower than the Seven-Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials (SEVEN-UP) study. The prevalence of MA in the CATT study was 7% at baseline, 24.6% after 2 years of treatment[17] and 49.7% after 5 years,[21] compared with 10.0% at 1 year, 20.3% at 2 years and 41.5% at 5 years in the present study. The SEVEN-UP study reported that 98.0% of participants had MA with a mean follow-up of 7.3 years.[18]

Estimates of prevalence may vary between studies due to differences in the definition and assessment of MA. In SEVEN-UP, the MA grading was based on the presence of a decreased signal on FAF imaging[18] while in CATT it was based on colour photographs and fluorescein angiograms.[21] MA was graded in the present study from clinical examination and SD-OCT or FAF imaging at the discretion of the investigator. Previous studies could show that there may be a discrepancy for MA presence between colour fundus imaging and FAF imaging of up to 43%.[30]

An important practical question is whether the risk of MA is directly related to the number of anti-VEGF injections received. Lois *et al* and Abdelfattah *et al* reported such an association of injection number with the risk of progression of MA.[7 8] A monthly anti-VEGF regimen was associated with a higher incidence of MA than pro re nata treatment after 2 years in the Inhibit VEGF in Age-related choroidal Neovascularisation (IVAN) and CATT trials.[15 17] This difference was not statistically significant after 5 years in the CATT study, possibly because none of the participants continued on a monthly regimen for the ensuing 3 years after the first 2 years of CATT study.[21] Another recent study found that the treatment duration and the number of administered drugs did not affect the size of MA in patients receiving a mean of eight intravitreal injections per year over a mean period of 6.2 years.[9] In the present study, we also found a significant association between the number of anti-VEGF injections received and the presence of MA. However, given that the prevalence of MA increases with time, it is difficult to determine whether anti-VEGF treatment is directly involved in the development of MA or whether it is simply the natural history of the condition.

Another important consideration is whether the risk of MA development or progression differs between VEGF inhibitors. The CATT investigators observed a higher risk of MA in ranibizumab-treated patients compared with bevacizumab-treated patients after 2 years of therapy.[17] There was a borderline increased risk of MA in eyes initially randomised to receive ranibizumab through 5 years of follow-up (p=0.06), although 80% of the eyes originally assigned to ranibizumab treatment and 70% of the eyes originally assigned to bevacizumab received other anti-VEGF treatment or no treatment in the ensuing 3 years.[21] In contrast, the IVAN 2-year trial did not find a significant difference in the risk of development of MA between ranibizumab and bevacizumab.[15] We did not find a significant difference between prevalence of MA and initial use of ranibizumab or aflibercept. Long-term data on the effect of aflibercept on MA development are currently lacking.

Intraretinal fluid was associated with a higher risk of MA in the CATT study, while the presence of subretinal fluid was associated with a lower risk.[21] The strongest risk factor for MA in the present analysis was a higher proportion of visits at which the lesion was graded as inactive. The grading of disease activity in the present study included both subretinal and intraretinal fluid, so we were unable to differentiate the effect on the development of MA between the two fluid types. The large effect between the lowest and highest quartiles of disease activity (AOR 3.72 (95% CI 2.33 to 6.07) for subfoveal MA and AOR 5.05 (95% CI 3.25 to 8.02) for extrafoveal MA) is interesting and suggests that disease activity, that is, fluid seen on the OCT, appears to be protective for the development of MA. Looked at another way, the most inactive group in the present analysis received the highest mean number of injections per year. This is at least consistent with the finding that subretinal fluid was protective in the CATT study. Understanding why some fluid might be protective is of great interest and will likely affect our treatment protocols which currently all aim to totally dry the retina.[31] We note that this apparent association would also be consistent with the hypothesis that MA directly reduces lesion activity. Another consideration is that disease activity is likely to reduce with more frequent or prolonged anti-VEGF treatment. However, if inactive CNV is the primary driver behind the development of MA, then prolonged anti-VEGF usage may be safe provided that some fluid is allowed during treatment.

The strengths of this study include the availability of an observational cohort of 1689 treatment-naïve eyes. This analysis included the location of MA, either subfoveal or extrafoveal, which is of particular importance because VA and associated characteristics were not similar for both locations. However, we were unable to determine whether MA was within or outside the CNV lesion as well as the growth of MA over time as this information is not recorded in the FRB! registry. The prevalence of MA in patients treated for a long time may have been underestimated because those who developed MA may have dropped out from the study more frequently than those without MA. The recent introduction of MA grading to the FRB! database limited the present analysis to being cross-sectional rather than longitudinal as data on atrophy grading were not available for visits entered prior to April 2016 and we could not identify when MA developed. Moreover, we were unable to determine whether MA was related to anti-VEGF treatment or if it simply reflected the natural history of the condition.

The lack of a reading centre to grade MA may be seen as a limitation of this study, however reading centres are not available to guide clinicians in real-world practice. There may be disagreements among experts over whether MA is present or absent in its early stages, but this decreases significantly over time as atrophy enlarges, progresses and becomes more obvious.[30 32] We can be confident that the agreement between retinal specialists of whether MA is present will be high after 9 years of progression in the present study. A reading centre evaluation of practitioner grading found the presence or absence of any MA, the main outcome, was accurate in 80% of cases (moderate agreement). The agreement was 'weak' when location was taken into account. This may be because of variable interpretation by some practitioners by how far atrophy extended into the fovea to be graded as subfoveal. While the best way to identify and measure MA is still controversial, grading of MA will inevitably have to be left to practitioners in routine clinical practice if a treatment becomes available.

Increased risk of MA was observed in eyes that received more injections, had low starting VA and had a higher proportion of visits at which the lesion was graded as inactive. The prevalence of MA increased with treatment duration and the number of anti-VEGF injections, but we cannot rule out the possibility that this simply reflects the natural history of nAMD progression. The inverse association of disease activity with risk of MA is intriguing and suggests a complex interplay exists between the need for VEGF for cell survival and the need to reduce exudation from neovascular tissue to avoid fibrosis and cell death. Learning more about this balance will lead to better long-term result with anti-VEGF treatments.

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Contributors VD, VN, MCG and DB were involved in the conception and design of the study. RWE, RG, JJA, MCG and DB were involved in the data collection. VD, VN, RWE, RG, JJA, MM, LC, MCG and DB were involved in the analysis and interpretation of the data. VD wrote the first draft of the manuscript. All authors were involved in the critical revision and final approval of the article. VD, VN, MCG and DB were involved in the conception and design of the study. RWE, RG, JJA, MCG and DB were involved in the data collection. VD, VN, RWE, RG, JJA, MM, LC, MCG and DB were involved in the analysis and Interpretation of the data. VD wrote the first draft of the manuscript. All authors were involved in the critical revision and final approval of the article.

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Competing interests MCG and DB are inventors of the software used to collect the data for this analysis. MCG and JJA are members of advisory boards for Novartis, Bayer and Allergan. JJA reports personal fees and other from Novartis, other from Bayer, outside the submitted work.

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