



REVIEW

A Review of Macular Atrophy of the Retinal Pigment Epithelium in Patients with Neovascular Age-Related Macular Degeneration: What is the Link? Part II

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ABSTRACT

Introduction: To explore the potential link between macular atrophy (MA) of the retinal pigment epithelium (RPE) in patients with neovascular age-related macular degeneration (nAMD) and anti-vascular endothelial growth factor (anti-VEGF) treatment.

Methods: Through a balanced overview of the field from a largely clinical perspective, we looked at available evidence on the topic of MA correlation with anti-VEGF therapy and examined possible risk factors for MA development in

the context of nAMD treatment with anti-VEGF.

Results: Links have been reported to connect both MA incidence and progression to treatment frequency and to the anti-VEGF drug type.

Conclusions: All reports agree on the fact that de novo development of MA in anti-VEGF-treated eyes is frequent and multifactorial. Research data shows an expansion of atrophy during anti-VEGF treatment. There are mixed conclusions about the correlation of MA incidence or progression with treatment-related risk factors. It mostly appears that there is no straightforward link. More clinical research is still needed to further understand this association.

Topical collection: Macular Atrophy of the Retinal Pigment Epithelium in Patients with Neovascular Age-Related Macular Degeneration: What is the link?.

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Keywords: Aflibercept; Anti-VEGF; Bevacizumab; Macular atrophy; Macular atrophy incidence; Macular atrophy progression; Neovascular age-related macular degeneration; Ranibizumab; Subfoveal choroidal thickness; Subretinal hyperreflective material

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Key Summary Points

De novo development of macular atrophy in anti-VEGF-treated eyes is frequent and multifactorial.

Research data shows an expansion of macular atrophy area during anti-VEGF treatment.

Links have been reported to connect both macular atrophy incidence and progression to treatment frequency and to the anti-VEGF drug type.

There are mixed conclusions about the correlation of macular atrophy incidence or progression with treatment-related risk factors. It mostly appears that there is no straightforward link.

INTRODUCTION

Anti-vascular endothelial growth factor (anti-VEGF) therapy has revolutionized the treatment of neovascular age-related macular degeneration (nAMD), proving both effective and safe in improving visual and anatomic outcomes in patients with nAMD [1–9]. In current practice, almost all patients diagnosed with nAMD are treated with anti-VEGF therapy.

VEGFA is a key factor in the pathogenesis of nAMD, yet plays an important role also in maintaining a healthy retina.

Several retinal cell types produce VEGF, with the retinal pigment epithelium (RPE) being one of the major sources. VEGFA is considered a survival factor for retinal neurons and a critical neuroprotectant during the adaptive response to ischaemic injury [10]. VEGF is released by the retina and RPE in response to tissue hypoxia, and this leads to choroidal neovascularization (CNV) in nAMD [11, 12].

Milestone clinical trials have demonstrated efficacy in terms of improving visual acuity (VA) with regular intravitreal injections of

bevacizumab, ranibizumab or aflibercept [1–9]. Aflibercept and ranibizumab were even found to protect the RPE against peroxidation through the modulation of NO release, apoptosis and autophagy [13].

The occurrence of macular atrophy (MA) in eyes treated for nAMD is a common cause of poor long-term visual function following initial short-term visual gains [14–16]. Although the actual cause of vision decline in eyes on long-term treatment with VEGF inhibitors is not known, data showed that atrophy in the macula was the most prominent chronic factor determining long-term vision [15, 17]. Both the presence of subfoveal atrophy and increased area of macular atrophy were associated with decreased best corrected visual acuity (BCVA), with the latter being the factor correlating most strongly with poor visual outcome [17].

There has been a growing concern that anti-VEGF therapy itself in eyes with nAMD may contribute to the development of new MA, and hence that excessive VEGF suppression could risk trading the consequences of neovascularization for the development of new MA. The hypothesized mechanisms are through counteracting physiological levels of VEGF which also has a neuroprotectant effect and/or excessive drying of the retina. Atrophic macular changes have been noted in the eyes of mice with genetically downregulated RPE-derived VEGF [18] and the deleterious effect of anti-VEGF drugs on VEGF production by RPE has been suspected in humans.

In this paper, we are offering a balanced overview of the field from a largely clinical perspective, aiming to provide an overview of available evidence on the topic of MA correlation with anti-VEGF therapy. The number of studies, clinical trials and papers exploring and investigating the potential correlation between anti-VEGF and MA is increasing. We have previously examined the possible risk factors reported for MA development in the context of nAMD treated with anti-VEGF, as well as possible potential protective factors [19]. In this paper, we examine again the data available about MA development in the context of nAMD treated with anti-VEGF, focusing, however, on

the particular potential relation between anti-VEGF agents and MA.

The pathogenesis of atrophic areas developing in the macula in treated nAMD is unclear and may or may not be clinically distinguishable from geographic atrophy (GA) that develops in the setting of purely non-neovascular AMD (non-nAMD). We have hence adopted the term ‘macular atrophy’ (MA) in this article to refer to areas of atrophy within the macula of eyes with nAMD, as it serves the intended purpose without claiming that these lesions are similar to or different from GA of non-nAMD.

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors.

SUMMARY OF CLINICAL STUDIES REPORTING ON MA

In a previous paper [19], we had reviewed the work of many clinical studies of significance that aimed to reach a better understanding of the possible aetiology and risk factors for developing de novo MA, and also for progression of MA. All reports agree on the fact that new MA development in anti-VEGF-treated eyes is frequent and multifactorial. We had previously described the methodology for the studies included in the review, and summarized their results. Table 1 similarly lists the main studies referred to in this paper.

MA DETECTION AND ASSESSMENT

The reviewed clinical studies have utilized quite varied imaging to detect and quantify MA. A recent proposition suggested Fourier-domain optic coherence tomography (OCT) as the reference standard imaging modality to diagnose and grade atrophy in the macula [53]. Other imaging modalities, including fundus autofluorescence (FAF), near-infrared reflectance (NIR), and colour fundus photography (CFP), amongst other modalities, were considered to provide complementary and confirmatory information,

especially in cases where OCT alone may not be sufficient for diagnostic purposes.

Indeed, the evaluation of atrophic changes in an eye with nAMD, particularly within the boundaries of the nAMD lesion, can be challenging especially on CFP, and to some extent also on fundus fluorescein angiography (FFA), where the intraretinal and subretinal fluid, CNV and fibrosis can potentially alter the retinal morphological features. In the same sense, fibrosis, pigment epithelial detachments (PED) and pigmentary changes could interfere with the visibility of choroidal vessels and the clear determination of the boundaries of atrophy both within and outside the lesion.

Grading and quantifying atrophy on OCT also can be especially difficult in the presence of concurrent exudative disease process because intraretinal and subretinal fluid renders the new macular atrophy borders quite challenging to identify.

Moreover, image quality can also be an issue in such a cohort of older patients with poor vision.

Table 2 lists the imaging modalities and diagnostic criteria used in assessing macular atrophy in relevant studies of MA in nAMD eyes treated with anti-VEGF. Figures 1 and 2 illustrate MA on multimodal imaging.

As displayed in Table 2, these studies have used various terms to label areas of atrophy within the macula of eyes with nAMD. The term ‘geographic atrophy’ (GA) has been applied inconsistently, especially in papers that are recording changes in atrophy related to nAMD and potentially its treatment as well. Other terminology included GA of the RPE, macular atrophy (MA), RPE atrophy and RPE loss.

Interestingly, the use of the new term ‘nascent macular atrophy’ (nMA) is arising. Nascent MA has been defined on the basis of the same OCT parameters for nascent GA (nGA) introduced previously [54, 55] as a series of structural changes in the outer retina on OCT B-scan in a patient with dry AMD that—in the presence of an apparently intact RPE—includes subsidence of both the outer plexiform layer (OPL) and inner nuclear layer (INL) and/or a hyporeflexive wedge-shaped band within the OPL limits [28]. Nascent MA can be thought of as the

Table 1 Relevant studies of macular atrophy in nAMD eyes treated with anti-VEGF

	Treated, followed up eyes assessed for MA	Mean follow-up duration (months)	Study eyes naively to treatment	Drug received in study during the study	Study design	Treatment protocol	Exclusions/limitations of relevance	Compared to control fellow eyes	All CNV types included?	Other considerations
Comparison of Age-related Macular Degeneration Treatments Trials	CATT (2 years) 2012 [20]	24	Tx naive	B, R	Px	Study eyes randomized to (a) monthly treatment always, (b) 3 monthly treatments followed by PRN always, (c) monthly treatments for a year followed by PRN for 1 year	-	No	Yes	-
	Grunwald et al. 2014 (for CATT 2 years) [14]	24	Tx naive				Eyes with baseline MA were excluded	No	Yes	-
	Grunwald et al. 2015 (for CATT 2 years) [21]	24	Tx naive				Eyes with baseline subfoveal GA were excluded	No	Yes	-
The SEVEN Year Observational Update of Macular Degeneration Patients Post-MARINA/ANCHOR and HORIZON Trials	CATT (5 years) 2016 [22]	66	Tx naive	B, R, A, any other		Same 2-year protocol, followed by any protocol at clinician's discretion for 3 years	-	No	Yes	-
	Grunwald et al. 2016 (for CATT 5 years) [23]	66	Tx naive	B, R, A, any other		Same 2-year protocol, followed by any protocol at clinician's discretion for 3 years	-	No	Yes	763 eyes analysed for GA incidence, 214 eyes analysed for GA growth
Alternative treatments to Inhibit VEGF in Age-related choroidal Neovascularisation (for IVAN)	SEVEN-UP [15–17]	88	Mixed (non-naive eyes included)	B, R, PDT, steroid, laser	Px	Variable (monthly R for 2 years followed by PRN R for 2 years, followed by any treatment type/regimen deemed appropriate by treating clinician)	-	No	No RAP	-
	IVAN [24, 25]	24	Tx naive	B, R	Px	Study eyes randomized to monthly treatments or PRN(3 monthly treatments followed by PRN)	-	No	Yes	-
	Bailey et al. 2019 [26]	24	Tx naive	B, R			-	Yes, fellow eyes with nAMD	Yes	Intralesional MA

Table 1 continued

	Treated, followed up eyes assessed for MA	Mean follow-up duration (months)	Study eyes naivety to treatment	Drug received in study during the study	Study design	Treatment protocol	Exclusions/limitations of relevance	Compared to control fellow eyes	All CNV types included?	Other considerations
p/Phase III, double-masked, multicentre, randomized, Active treatment-controlled study of the efficacy and safety of 0.5 mg and 2.0 mg Ranibizumab administered monthly or on an as-needed Basis (PRN) in patients with subfoveal neOvascular age-related macular degeneration	Sadda et al. 2018 (for HARBOR) [27]	24	Tx naive	R	Px	Study eyes randomized to 0.5 mg or 2 mg, monthly treatments or PRN (3 monthly treatments followed by PRN)	Excluded eyes with subfoveal atrophy	Yes, fellow eyes with nAMD/non-nAMD	No RAP	Atrophy within, adjacent and nonadjacent to CNV lesions (active or regressed) was included
	Rebhun et al. 2018 (for HARBOR) [28]	24	Tx naive	R	Rx	Monthly-treatments till VA stable, then PRN	–	Fellow eyes with nAMD/non-nAMD	No RAP	All eyes had PED at baseline
	Lois et al. 2013 [29]	16	§	R	Rx	Monthly-treatments till VA stable, then PRN	Eyes with RAP or PCV were excluded	No	No RAP	–
	Kumar et al. 2013 [30]	35	Non-naive	PDT, P, B, R, T, D	Rx	§	–	No	§	–
	Young et al. 2014 [31]	26	§	B, R	Rx	3 monthly treatments then T&E	–	Yes, fellow eyes with non-nAMD	§	–
	Gillies et al. 2015 [32]	78	Tx naive	B, R, A	Rx	Mostly T&E	–	No	Yes	Among 42 eyes that lost ≥ 10 letters: 13 eyes were found to show central GA
	Schürze et al. 2015 [33]	24	Tx naive	R	Px	Monthly treatments in first year, then PRN	–	Yes, fellow eyes with non-nAMD	§	–

Table 1 continued

	Treated, followed up eyes assessed for MA	Mean follow-up duration (months)	Study eyes naively to treatment	Drug received in study eye during the study	Study design	Treatment protocol	Exclusions/limitations of relevance	Compared to control fellow eyes	All CNV types included?	Other considerations
Tanaka et al. 2015 [34]	81	59	Tx naive	B, R	Rx	Monthly treatments till stable followed by PRN	-	Yes, fellow eyes with non-nAMD	§	-
Cho et al. 2015 [35]	43	24	Tx naive	R	Rx	3 monthly treatments followed by PRN	Excluded: eyes with type 1 & 2 CNV, eyes with baseline GA	No	No, RAP only	-
Xu et al. 2015 [36]	94	29	Tx naive	B, R, A	Rx	T&E	Excluded central GA at baseline	No	Yes	PCV included
Kuroda et al. 2016 [37]	195	27	Tx naive	R	Rx	3 monthly treatments followed by PRN	RAP excluded	No	No RAP	PCV included
Kuroda et al. 2017 [38]	123	12	Tx naive	A	Rx	3 monthly treatments then bimonthly	RAP excluded	No	No RAP	PCV included
Arevalo et al. 2016 (for PACORES) [39]	292	60	Tx naive	B	Rx	Monthly treatment till stable followed by PRN	-	No	No RAP	-
Thavikulwat et al. 2016 [40]	63	40	Non-naive eyes included	R	Px	4 monthly treatments followed by PRN	Excluded eyes with subfoveal GA	Yes, fellow non-nAMD & nAMD eyes	Yes	-
Munk et al. 2016 [41]	49	74	§	R, A	Rx	R 3 monthly treatments then PRN with mandatory quarterly injections, followed by R T&E and/or A T&E	-	No	No	Sub- & juxtafoveal CNV, intra- & extraretinal MA

Table 1 continued

	Treated, followed up eyes assessed for MA	Mean follow-up duration (months)	Study eyes naivity to treatment	Drug received in study eye during the study	Study design	Treatment protocol	Exclusions/limitations of relevance	Compared to control fellow eyes	All CNV types included?	Other considerations
The phase IIIb, multicentre randomized controlled study of the safety, tolerability and efficacy of IVT 0.5 mg ranibizumab monthly compared to a <i>T</i> Reat & <i>E</i> Xtend Protocol in Patients with Wet Age-related Macular Degeneration	49	18	Tx naive	R	Px	Study eyes randomized to monthly or 3 monthly treatments followed by T&E	-	Yes, fellow non-nAMD eyes	Yes	-
Abdelfattah et al. 2017 (for TRES-AMD) [42]	55	18	Tx naive	R	Rx	3 monthly treatments then T&E; R or switched to A (from B/R)	-	Yes, non-nAMD fellow eyes	Yes	-
Fan et al. 2018 (for TRES-AMD) [43]	118	36	Non-naive eyes included	R, A	Rx	3 monthly treatments then T&E; R or switched to A (from B/R)	-	No	No RAP	CNV lesions were not included in the atrophy measurements with R. <i>all</i> had CNV-independent RPE loss at baseline
Wons et al. 2017 [44]	46	12	Tx naive	R, A	Rx	R 3 monthly treatments then PRN, or A 3 monthly treatments then bimonthly	-	No	No, type 1 & type 2 CNV not included	RAP only
Hata et al. 2017 [45]	74	56	Tx naive	B, R, A	Rx	T&E	Eyes with baseline MA/GA were excluded	No	Yes	
Zarubina et al. 2017 [46]	79	48	Tx naive	B, R, A	Rx	Inconsistent/variable	-	No	No RAP	No PCV
Li et al. 2017 [47]	52	64	Tx naive	B, R, A	Px	R 3 monthly treatments then PRN for 2 years, then R/A/B PRN	Eyes with baseline MA were excluded	§	§	
Sitnilska et al. 2018 [48]										

Table 1 continued

	Treated, followed up eyes assessed for MA	Mean follow-up duration (months)	Study eyes naivety to treatment	Drug received in study eye during the study	Study design	Treatment protocol	Exclusions/limitations of relevance	Compared to control fellow eyes	All CNV types included?	Other considerations
Age-Related Eye Disease Study 2 Report Number 15	334	48	Tx naive	§	Rx	§	-	No	§	-
Domalpally et al. 2018 (for the AREDS2) [49]										
Mantel et al. 2018 [50]	101	24	Tx naive	R, A	Px	2 identical separate studies for R & A: 3 monthly treatments followed by observe & plan (monthly observation, upon recurrence: treat and calculate the future treatment interval to be half a month shorter)	Eyes with no MA by end of study were excluded	Yes, fellow eyes with non-nAMD	Yes	No PCV
Mantel et al. 2019 [51]	149	24	Tx naive	R, A	Px	2 identical separate studies for R & A: 3 monthly treatments followed by observe & plan (monthly observation, upon recurrence: treat and calculate the future treatment interval to be half a month shorter)	Eyes with baseline MA were excluded	Yes, fellow eyes with non-nAMD	Yes	No PCV
Wada et al. 2019 [52]	150	60	Tx naive	R, A	Rx	R 3 monthly treatments then PRN, some switched to A 3 monthly treatments followed by PRN	-	No	Yes	PCV included

§ no data, *A* aflibercept, *B* bevacizumab, *CNV* choroidal neovascularization, *D* dexamethasone, *GA* geographic atrophy, *IIT* intravitreal, *MA* macular atrophy, *nAMD* neovascular age-related macular degeneration, *P* pegaptanib, *PCV* polypoidal choroidal vasculopathy, *PDT* photodynamic therapy, *PED* pigment epithelial detachment, *PRN* pro re nata (as needed), *Px* prospective, *R* ranibizumab, *RAP* retinal angiomatous proliferation, *Rx* retrospective, *I&E* treat and extend, *Tx* treatment

Table 2 Imaging modalities and criteria used in assessing macular atrophy in relevant studies of MA in nAMD eyes treated with anti-VEGF

Study	Term used for atrophy in the macula	Atrophy detection criteria	MA assessing imaging modality				
			CFP/FFA	FAF	OCT	NIR/NIA	
CATT [14, 20–23, 57, 58]	GA	Presence of ≥ 1 patches, within the macular vascular arcades, $\geq 250 \mu\text{m}$ in maximum linear dimension, of partial/complete depigmentation on CFP that had ≥ 1 of these additional characteristics: sharply demarcated borders on CFP and/or FFA, visibility of underlying choroidal vessels, excavated or punched out appearance on stereoscopic CFP or FFA, or uniform hyperfluorescence bounded by sharp borders on late-phase FFA	++	–	–	–	
			++	–	–	–	
SEVEN-UP [15–17]	MA	Areas meeting this definition surrounding a scar were not considered GA Definite decreased autofluorescence on FAF	–	++	–	–	
	GA		++	–	+	–	
IVAN [24, 25, 59]	MA	Area $\geq 175 \mu\text{m}$ in maximum linear dimension with ≥ 2 features on CFP (well-defined margins; visibility of underlying choroidal vessels; scalloped edges) <i>and</i> consistent finding on FFA (early hyperfluorescence persisting through the FFA sequence and fading in late images)	–	++	–	–	
	GA		++	–	+	–	
Bailey et al. 2019 (for IVAN) [26]	Intralesional MA, extralesional MA	(A) For intralesional MA, presence of <i>any</i> of the following features: (1) CFP: an area of pallor $\geq 175 \mu\text{m}$ in maximum linear dimension with ≥ 2 relevant features: well-defined margins; visibility of underlying choroidal vessels; scalloped edges (2) FFA: early hyperfluorescence persisting through the FFA sequence sometimes fading in the late phase, with identifiable large choroidal vessels (3) OCT: choroidal hypertransmission and thinning/absence of the outer retinal layers. On higher-quality or higher-resolution scans, the following additional features of MA could be used: dipping of the photoreceptor nuclear layer toward the RPE–Bruch’s membrane complex, absence of photoreceptor inner and outer segments, thinning of RPE–Bruch’s membrane complex, and absence of the choriocapillaris profile (B) For extralesional MA: An area of pallor on CFP $\geq 175 \mu\text{m}$ in maximum linear dimension with ≥ 2 relevant features: well-defined margins; visibility of underlying choroidal vessels; scalloped edges	++	–	++	–	
			++	–	++	–	

Table 2 continued

Study	Term used for atrophy in the macula	Atrophy detection criteria	MA assessing imaging modality				
			CFP/FFA	FAF	OCT	NIR/NIA	
HARBOR [1, 27, 60–62]	MA	Sharply demarcated areas of RPE depigmentation with visibility of underlying chorioidal vessels on CFP/FFA, $\geq 250 \mu\text{m}$ in diameter, corresponding to flat areas of well-demarcated staining on FFA	++	–	–	–	
Rebhun et al. 2018 (for HARBOR) [28]	MA and Nascent MA (nMA)	MA: An area $> 250 \mu\text{m}$ of loss of the outer nuclear layer, ellipsoid zone, and RPE, with chorioidal hypertransmission nMA: In the presence of an intact RPE, outer retinal changes of subsidence of both the outer plexiform layer and inner nuclear layer and/or a hyporeflective wedge-shaped band seen within the limits of the outer plexiform layer	–	–	++	–	
Lois et al. 2013 [29]	RPE atrophy	Reduced signal in both FAF and NIA of $\geq 0.05 \text{ mm}^2$ not related to haemorrhage, exudation or thought to be caused by blockage of the FAF/NIA signal related to the CNV itself	–	++	–	++	
Kumar et al. 2013 [30]	RPE loss	Areas of confluent absent autofluorescence $\geq 0.5 \text{ mm}$ in greatest linear diameter. Only areas of abnormal autofluorescence within a circle centred on the macula defined by the superior and inferior temporal arcades were analysed; areas of peripapillary atrophy were not included	–	++	–	–	
Young et al. 2014 [31]	RPE atrophy	RPE atrophy on OCT (without any minimum requirement) in areas within a 5-mm circle where RPE is absent or has lost integrity, along with chorioidal hypertransmission	–	–	++	–	
Gillies et al. 2015 [32]	GA	§	§	§	++	§	
Schütze et al. 2015 [33]	Focal RPE atrophy and GA	Using polarization-sensitive OCT-related algorithm, both GA and RPE atrophy other than GA (i.e. depigmented RPE without clearly defined boundaries) were defined Focal RPE atrophy: isolated atrophic regions in the RPE, not quantifiable as advanced GA by the segmentation algorithm GA: atrophic RPE lesions $\geq 0.1 \text{ mm}^2$	–	+	++	–	

Table 2 continued

Study	Term used for atrophy in the macula	Atrophy detection criteria	MA assessing imaging modality				
			CFP/FFA	FAF	OCT	NIR/NIA	
Tanaka et al. 2015 [34]	GA of the RPE	An area of partial/complete RPE depigmentation, with thinning of the overlying neurosensory retina with the addition of ≥ 2 of the following (on CFP, and when available, red-free fundus photographs & FFA): roughly round/oval shape, sharp margins and visibility of underlying choroidal vessels	++	-	+	-	
Cho et al. 2015 [35]	GA	An area of hypopigmentation/hyperfluorescence of $\geq 250 \mu\text{m}$ at its minimum linear dimensions within the macular vascular arcades, which has ≥ 2 of the following: (1) circular shape, (2) sharply demarcated borders seen using CFP and/or FFA, and (3) visibility of underlying choroidal vessels with an “excavated or punched out” appearance on CFP stereoscopy and/or FFA Any GA lesions detected were confirmed by SD OCT findings of choroidal hypertransmission and RPE atrophic changes	++	-	++	-	
Xu et al. 2015 [36]	GA	A brighter area on NIR of $\geq 250 \mu\text{m}$ in its maximum linear dimension, of variable shapes but sharp borders, with choroidal hypertransmission on OCT. FAF was used as an adjunct when available	-	+	++	++	
Kuroda et al. 2016 & 2017 [37, 38]	RPE atrophy/MA	(1) Within the macular vascular arcade; (2) a roughly round/oval area of partial/complete RPE depigmentation, with thinning of the overlying neurosensory retina; (3) $\geq 250 \mu\text{m}$ in maximum linear dimension; (4) atrophic changes of RPE and photoreceptor layer with choroidal hypertransmission on OCT; and (5) ≥ 1 of the following additional characteristics: sharply demarcated borders, visibility of underlying choroidal vessels, or uniformly reduced autofluorescence with sharp borders on FAF	++	++	++	-	
Arevalo et al. 2016 (for PACORES) [39]	GA	An area of hypopigmentation/hyperfluorescence of $\geq 200 \mu\text{m}$ in its minimum linear dimension and has the following characteristics: circular shape, sharp borders and visibility of choroidal vessels	++	-	-	-	

Table 2 continued

Study	Term used for atrophy in the macula	Atrophy detection criteria	MA assessing imaging modality				
			CFP/FFA	FAF	OCT	NIR/NIA	
Thavikulwat et al. 2016 [40]	GA	On FAF: a region of hypoautofluorescence ≥ 0.05 mm ² in an area located within the vascular arcades that remained present across subsequent images and corresponded to ≥ 1 of the following criteria: (1) sharp margins and visible large choroidal vessels on CFP; (2) sharp margins and uniform hyperfluorescence on FFA; (3) RPE and outer retinal loss on OCT	+	++	+	–	
Munk et al. 2016 [41]	MA	Confluent hyperreflectivity with sharp margins on NIR together with corresponding choroidal hypertransmission, RPE absence, subsidence of the outer plexiform/Henle layer and loss of the ELM on SD-OCT	+	+	++	++	
Abdelatifrah et al. 2017 (for TRES-AMD) [42]	MA/RPE atrophy	FAF: graded using Region Finder software NIR: used to aid in the assessment of the foveal centre OCT: presence of ≥ 2 criteria in an area ≥ 125 μ m: choroidal hypertransmission, attenuation of the RPE band and collapse/loss of the outer retinal layers All imaging modalities were used to detect MA Quantification of atrophy was performed on the FAF image Three criteria to be met on OCT: (1) a contiguous region of ≥ 125 μ m of RPE attenuation (especially with an abrupt sharp step-down in thickness) (2) Loss of the overlying ellipsoid zone and external limiting membrane with thinning of the outer nuclear layer (3) Choroidal hypertransmission	+	++	+	+	
Fan et al. 2017 (for TRES-AMD) [43]	MA	Area of choroidal hypertransmission on OCT of > 300 μ m diameter in lesions without signs of suspected CNV on OCT, within the $20^\circ \times 15^\circ$ scan frame. CNV lesions were not included in the atrophy measurements	–	–	++	–	
Wons et al. 2017 [44]	CNV-independent RPE loss		–	–	++	–	

Table 2 continued

Study	Term used for atrophy in the macula	Atrophy detection criteria	MA assessing imaging modality				
			CFP/FFA	FAF	OCT	NIR/NIA	
Hata et al. 2017 [45]	RPE atrophy	(1) Within the macular vascular arcade; (2) a roughly round/oval area of partial/complete RPE depigmentation, with thinning of the overlying neurosensory retina; (3) > 250 μm in maximum linear dimension; (4) atrophic changes of RPE and photoreceptor layer with choroidal hypertransmission on OCT; and (5) ≥ 1 of the following additional characteristics: sharply demarcated borders, visibility of underlying choroidal vessels, or uniformly reduced autofluorescence with sharp borders on FAF	++	++	++	–	
Zarubina et al. 2017 [46]	MA	(1) NIR: A hyperreflective area with a sharp border $\geq 250 \mu\text{m}$ in maximum linear dimension, and (2) OCT: corresponding degeneration of RPE and outer retina with choroidal hypertransmission	–	–	++	++	
Li et al. 2017 [47]	MA	RPE subillumination analysis on OCT was used to automate identification of atrophy by segmenting regions of increased reflectivity in the choroidal layer on the B-scans and quantifying this area on the en face fundus images. Segmentation errors were manually corrected by trained graders. Three graders at first independently provided manual measurements of macular atrophy on OCT using stringent criteria that included disruption of the outer retina (RPE or ellipsoid zone loss) and choroidal hypertransmission	–	–	++	–	
Similka et al. 2018 [48]	MA/RPE atrophy	On CFP: a sharply demarcated area of RPE depigmentation $\geq 175 \mu\text{m}$ with increased visibility of choroidal vessels On OCT: an area $\geq 175 \mu\text{m}$ of thinning of the RPE band with abrupt/sharp thickness loss and/or loss of overlying ellipsoid zone and external limiting membrane, accompanied by thinning or atrophy of the outer nuclear layer	++	–	++	+	

Table 2 continued

Study	Term used for atrophy in the macula	Atrophy detection criteria	MA assessing imaging modality				
			CFP/FFA	FAF	OCT	NIR/NIA	
Domalpally et al. 2018 [49]	RPE atrophy/GA	On CFP: a minimum size of drusen 0.15 mm ² and ≥ 2 of the following criteria: roughly round or oval shape, sharp margins and visibility of underlying large choroidal vessels On FAF: a uniform region of well-defined homogeneous darkness with a minimum size of drusen 0.15 mm ² Hypoautofluorescence on FAF was designated as atrophy only if the CFP had atrophy in the corresponding area and there was an absence of pathologic changes that could cause blocked autofluorescence, such as blood, fibrosis, hard exudates and new CNV	++	++	–	–	
Mantel et al. 2018 & 2019 [50, 51]	MA	Dark zone $\geq 250 \mu\text{m}$ on FAF, with ≥ 1 of the following: increased visibility of the choroid on FFA/CFP, or sharply demarcated increased choroidal hypertransmission on OCT with absence of the RPE line	++	++	++	–	
Wada et al. 2019 [52]	MA/GA	Only FAF was use for area quantification §	+	–	++	–	

++ used as main imaging modality, + used as auxiliary imaging modality, – imaging modality not used, § no data, CFP colour fundus photograph, CNV choroidal neovascularization, ELM external limiting membrane, FAF fundus autofluorescence, FFA fundus fluorescein angiography, GA geographic atrophy, MA macular atrophy, NIA near-infrared autofluorescence, NIR near-infrared reflectance, NMA nascent MA, OCT optical coherence tomography, RPE retinal pigment epithelium

potential precursor of MA, hence the emergence of such studies expanding their focus to include nMA in addition to MA.

The use of OCT as a main diagnostic tool for MA assessment is becoming increasingly significant with time. OCT allows not only detection of subtle and subclinical signs of MA and its potential precursors but also a better understanding of its extent. A good example of that is the finding that RPE atrophy and photoreceptor layer thinning are common not only in areas of macular atrophy but also in areas of fibrotic scarring in the macula. Furthermore, photoreceptor loss appears to extend beyond the boundaries of clinically detectable atrophy and fibrotic scars [56].

MA INCIDENCE

A wide range of MA incidence rates have been reported (Table 3). Amongst a long list, discrepancies in protocols, inclusion/exclusion criteria, cohort sizes and diagnostic tools and criteria would render any direct comparison between these studies inadvisable. For some studies the expressed percentage was out of the group of study eyes that had no atrophy at the start of the study, whilst for others it was out of the whole cohort of study eyes. For some studies, eyes with baseline MA were excluded from either the analysis or from the whole study [14, 21, 27, 35, 36, 40, 46, 48, 51], others excluded eyes that did not develop MA by the end of the study [50], while the majority of the remaining reports included eyes with and without MA at baseline and also with and without MA at end of study.

CATT excluded eyes with baseline MA from the analysis [14], and so did others [35, 46, 48, 51], and in another report CATT excluded eyes with subfoveal GA at baseline [21], and others have followed as well [36, 40]. Again, Sadda et al. also excluded eyes with subfoveal atrophy at baseline, yet atrophy immediately within, adjacent and nonadjacent to CNV lesions (active or regressed) was included [27]. Some studies excluded eyes with RAP from analysis [17, 27–29, 37–39, 44, 47], whilst others only recruited eyes with RAP [35, 45].

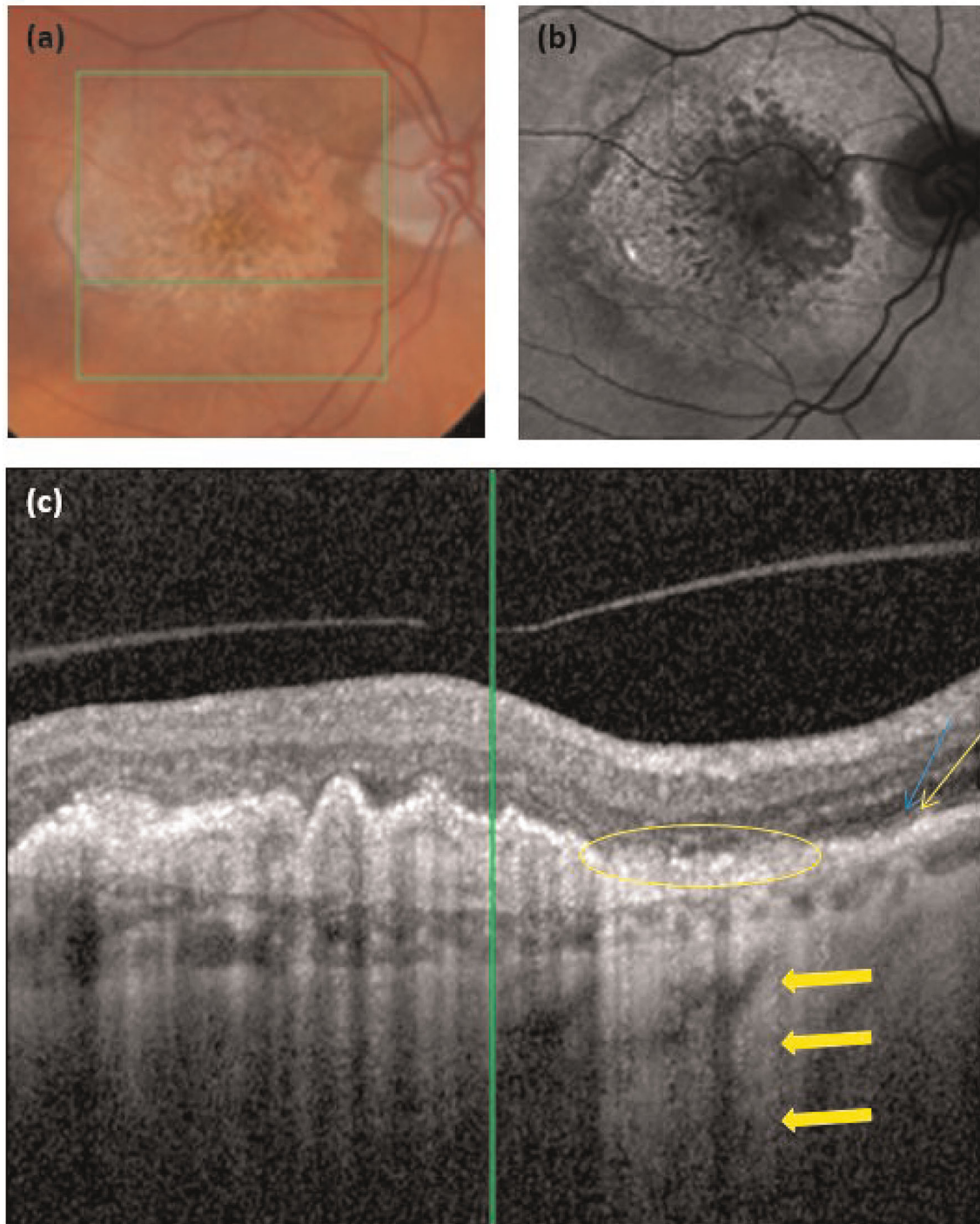
Few studies included eyes with PCV in their analysis [36–38, 52]. Rebhun et al. purely looked into nAMD eyes with PED at baseline [28]. When measuring the area of MA, Wons et al. excluded the CNV lesion area from the calculations [44]. Bailey et al. only included eyes with MA within the CNV lesion area [26].

Among the original cohort of 1212 eyes, a group of 131 eyes finished the study, as reported by Gillies et al. Out of those, 42 eyes lost at least 10 letters, 13 eyes of which were found to show central GA. This figure has been misquoted as being an MA incidence of 37% [32].

SEVEN-UP [15–17], Kumar et al. [30], Thavikulwat et al. [40] and Wons et al. [44] all included treatment non-naive eyes. Also, SEVEN-UP [15–17] and Kumar et al. [30] included eyes that received photodynamic therapy, laser photocoagulation or steroid intravitreal treatments during the follow-up period.

The highest incidence of MA was reported by many to be early in the course of the study follow-up. The reported figures show that the highest MA incidence was within the first year of the study. Thavikulwat et al. [40], Sadda et al. [27], Li et al. [47] and Sitnilska et al. [48] reported percentages of MA incidence within the first year of 85%, 75%, 65% and 50%, respectively. Over a follow-up period of 4 years, Domalpally also noted that most new occurrences of MA were within the initial 2 years [49]. Furthermore, Abdelfattah et al. reported that MA enlargement rate was higher in year 1 compared to year 2 [63]. Contrary to these observations, only Cho et al. reported a mere 25% of new MA to occur within the first year while the remaining majority of 75% occurred in the second year [35].

Amidst the plethora of figures and rates reported on MA, and given the above, the reports can appear contradictory or at least create confusion. To facilitate a better understanding of the reported figures, and by using the relevant information in each published report whenever specified in sufficient detail, we have determined the percentages out of the total number of study eyes that have been assessed up till the mean follow-up duration specified, displayed in Table 3 as follows: eyes with no baseline MA, eyes developing new MA



and the total number of eyes showing MA, both baseline and new.

Taking figures and results from all relevant studies into consideration, while expressing the

percentages out of the total number of study eyes that have been assessed up till the mean follow-up duration, the mean percentage of eyes with no baseline MA was 80%, with a

◀**Fig. 1** Macula of right eye with nAMD at 17 months after starting treatment with anti-VEGF, when a total of 14 injections were received. **a** CFP showing MA areas of depigmentation with sharply demarcated curved borders and visibility of underlying choroidal vessels. **b** FAF showing areas of confluent reduced/absent autofluorescence, with sharp borders, corresponding to areas of MA on CFP. **c** OCT scan at level of corresponding horizontal green line on CFP image, showing loss of RPE band, ellipsoid zone and external limiting membrane, accompanied by thinning of the outer nuclear layer (yellow oval), and choroidal hypertransmission (thick yellow arrows) caused by RPE band loss. External limiting membrane (thin blue arrow) and ellipsoid zone (thin yellow arrow) end abruptly at the border of the area of complete RPE loss and outer retinal thinning

median of 89%. The mean percentage of MA incidence is 29%, which was also the median. The mean prevalence of MA by the end of the study was 50%, the median was 46%. For the studies included, the number of studied eyes that were treated and continuously followed up till the end of the mean follow-up period ranged between 28 and 1024 eyes, with a median of 118 eyes, and a mean cohort size of 242 eyes.

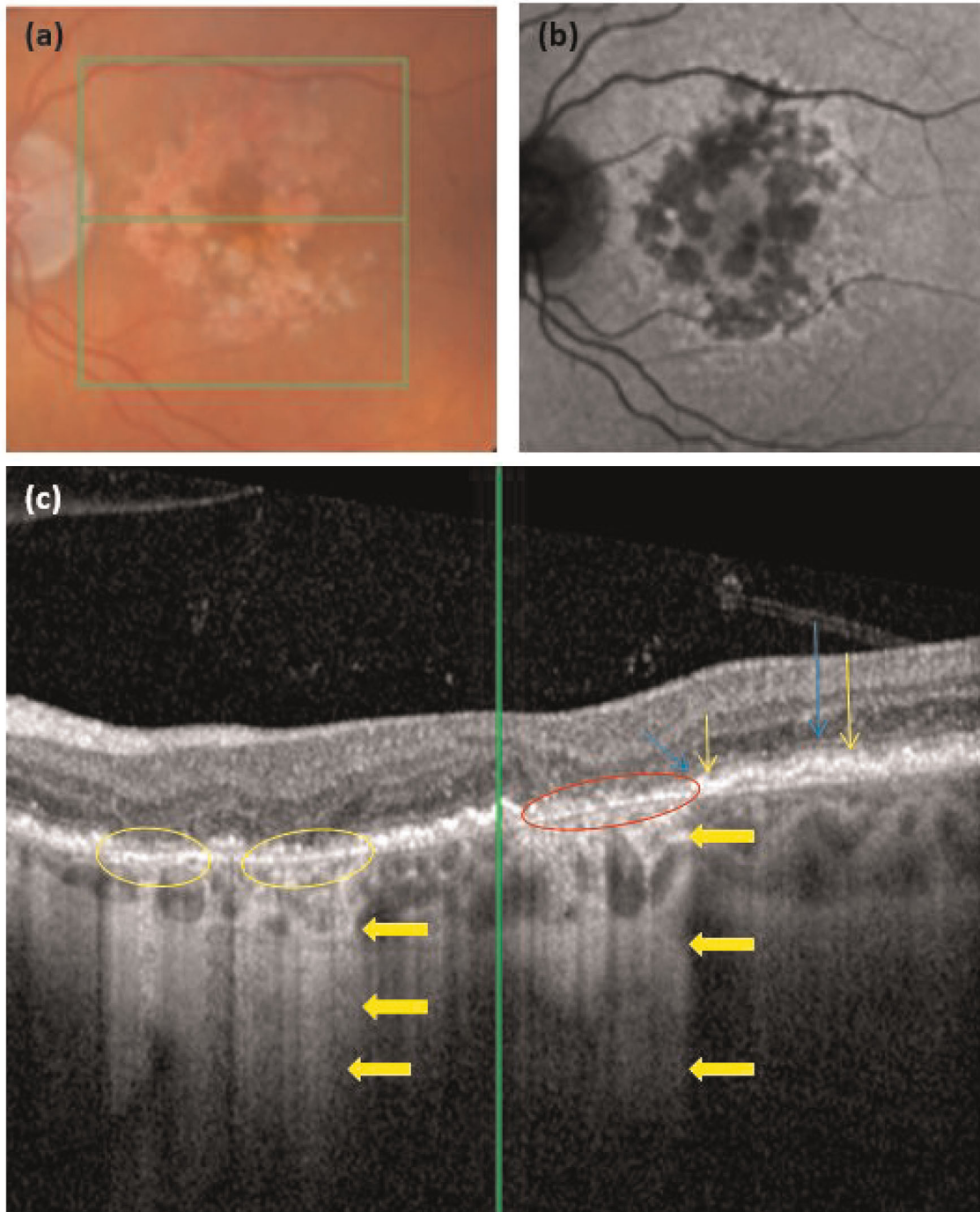
MA PROGRESSION

The change in total MA lesion area over time (mm^2/year) is the most frequently used and accepted endpoint for assessing MA progression, yet this figure is sometimes presented after square-root transformation (mm/year). Square-root transformation reduces the influence of baseline atrophy area size on calculated growth rates as it particularly adjusts for baseline area and allows for linearization of growth rate [64], because areas grow exponentially and are proportionally related to their lesion radius. An MA area analysis without square-root transformation would therefore implicate a greater enlargement rate. Table 4 displays reported rates of MA progression.

- CATT: At 2 years, MA growth rate was 0.43 mm/year. Despite the fact that most participants did not stay with their original treatment assignment during the 3 years

after the end of the clinical trial, ranibizumab was still associated with a significantly higher MA growth rate than bevacizumab at 5 years. Growth rate did not differ between eyes treated monthly and PRN. Poor baseline VA, epiretinal membrane (ERM) and an extrafoveal location of CNV were each associated with a higher MA growth rate, as was the presence of a classic CNV. Atrophy progression was also correlated with progression of GA in the fellow eye [21]. Most of the aforementioned appeared again as risk factors by 5 years, where the reported atrophy growth rate decreased slightly to become 0.33 mm/year [23]. Occult CNV appeared to significantly reduce the progression of atrophy at 2 years, yet this did not have a persistently strong independent effect at 5 years. GA that develops away from the CNV had approximately half of the growth rate, suggesting that there may be significant differences between these two types of GA [23].

- Young et al.: Progression of MA was higher in eyes with nAMD when compared to that of their fellow non-nAMD eyes. Older age, higher number of injections and treatment with bevacizumab were each correlated with a higher MA progression rate [31].
- Thavikulwat et al.: Similar growth rates were demonstrated between study nAMD eyes and fellow non-nAMD eyes. Progression rate in study eyes with baseline GA was 0.34 ± 0.26 mm/year, and in study eyes with incident new GA was 0.19 ± 0.12 mm/year [40].
- Schütze et al. reported that early RPE loss and GA progression was most significant during the initial intensive monthly treatment, and remained stable during PRN treatment that followed [33].
- Lois et al: The number of injections received was statistically significantly associated with the progression of atrophy at follow-up. In 84% of the eyes in which there was progression of atrophy, no atrophy was detected at baseline [29].
- Kuroda et al.: The mean overall progression rate of atrophy was 0.47 mm/year, ranging between 0.43 mm/year for pre-existing MA



and 0.50 mm/year for newly developed cases [37].

- Munk et al.: Mean MA growth was 0.30–0.40 mm²/year, and after square-root transformation it was 0.10–0.12 mm/year. A

higher MA growth was observed in the presence of intraretinal cysts (IRCs), posterior vitreous detachment (PVD) and reticular pseudodrusen (RPD). The growth rate of the MA outside the CNV border was greater

◀**Fig. 2** Fellow non-nAMD eye (left eye) of same patient in figure [1]. **a** CFP shows MA areas of depigmentation with sharply demarcated curved borders and visibility of underlying choroidal vessels. **b** FAF shows areas of confluent reduced/absent autofluorescence, with sharp borders, corresponding to areas of MA on CFP. **c** OCT scan at the level of the corresponding horizontal green line on CFP image, showing loss of RPE band, ellipsoid zone and external limiting membrane, accompanied by thinning of the outer nuclear layer (yellow ovals). Loss of RPE band, ellipsoid zone, external limiting membrane and outer nuclear layer are shown as well (red oval), in addition to choroidal hypertransmission (thick yellow arrows) caused by RPE band loss. External limiting membrane (long thin blue arrow) and ellipsoid zone (long thin yellow arrow) end abruptly at the border of the area of complete RPE loss and complete outer retinal atrophy (short thin blue and yellow arrows)

when administering aflibercept than ranibizumab [41].

- Abdelfattah et al.: A higher growth rate of MA in the treat-and-extend (TRES) group was evident at all time points, compared to the monthly group [42]. The final analysis cohort included three groups: monthly, TRES and control fellow non-nAMD eyes. Mean progression rate of MA over 18 months was 0.39 mm² (monthly group), 1.1 mm² (TRES group) and 0.49 mm² (control group). Mean growth rate per group among the patients with baseline MA was 0.9 mm², 1.9 mm², and 1 mm², respectively [42].
- Wons et al: Mean progression rate before switch to aflibercept was 0.30 mm²/year and 0.39 mm²/year after switch [44], which is similar to the average rate of progression in the work by Bhisitkul et al. in SEVEN-UP [17].
- Hata et al.: Using square-root transformation, the RPE atrophy progression rate was 1.17 mm/year for eyes with newly developed RPE atrophy. The RPE atrophy growth rate was 1.11 mm/year for eyes treated with ranibizumab and 1.20 mm/year for eyes treated with aflibercept. Among baseline clinical factors, the progression rate of RPE atrophy was negatively correlated with

subfoveal choroidal thickness (SCT) at baseline [45].

- Mantel et al.: Mean atrophy surface area was 0.68 mm² at baseline and increased to 3.01 mm² by year 2. The mean square-root-transformed MA growth rate was 0.54 mm/year. This was 0.42 mm/year in eyes with baseline MA and 0.60 mm/year in eyes with incident MA. MA growth rate showed as significantly correlated with lower baseline visual acuities, PED (higher than 200 μm), MA growth rates in non-nAMD fellow eyes, and near-significantly with thicker subretinal tissue complexes (SHRM) and thinner subfoveal choroidal thickness. MA growth rate was not correlated with its location (intralesional/extralesional), the drug or the number of injections [50].

ANTI-VEGF TYPE AND TREATMENT FREQUENCY

Several studies have identified particular links between MA and certain risk factors, or alternatively noted particular factors that appeared as protective from MA. Tables 5 and 6 sum up the aforementioned assessed factors that have been previously covered [19]. However, of particular interest are papers assessing the potential links (both direct and indirect) with anti-VEGF drug type and total number of injections because of the growing concern that anti-VEGF therapy itself in eyes with nAMD may contribute to the development and/or the enlargement of MA.

The conclusions that have been reported should only be interpreted with caution though. Lois [29], Young [31] and Munk [41] did not state treatment naivety status of study eyes, while SEVEN-UP [15–17], Kumar [30], Thavikulwat [40] and Wons [44] had included non-naive eyes in their cohorts. More importantly, only the minority of the listed reports were based on prospective studies [1, 14, 20–25, 27, 33, 40, 42, 43, 48, 50, 51, 60, 61], and of those only CATT [14, 20–23], IVAN [24, 25], HARBOR [1, 27, 60, 61] and TRES-AMD [42, 43] had the study eyes randomized into groups

Table 3 MA incidence as reported by various clinical studies of macular atrophy in nAMD eyes treated with anti-VEGF

	Treated, followed up eyes assessed for MA	Percentage of total number of studied and followed up eyes			Notes
		Eyes with no baseline MA (%)	Eyes developing new MA (%)	Total eyes showing MA (baseline & new) (%)	
CATT (2 years) 2012 [20]	1012	93	15	22	
Grunwald et al. 2014 (for CATT 2 years) [14]	1024	100	18	18	
Grunwald et al. 2015 (for CATT 2 years) [21]	194	93	13	20	
CATT (5 years) 2016 [22]	515	§	§	41	
Grunwald et al. 2016 (for CATT 5 years) [23]	763	89	34	45	Study reported MA incidence rate of 39% out of analysed eyes with no baseline atrophy
SEVEN-UP [17]	58	§	§	98	
IVAN [24, 25]	596	~ 93	30	~ 37	
Bailey et al. 2019 (for IVAN) [26]	594	90.4	21	31.5	Percentages are of MA within the CNV lesion area (intralesional MA)
Sadda et al. 2018 (for HARBOR) [27]	893	88	29	41	Excluded eyes with subfoveal atrophy. Atrophy immediately within, adjacent and nonadjacent to CNV lesions was included
Rebhun et al. 2018 (for HARBOR) [28]	28	96	46	50	
Lois et al. 2013 [29]	72	53	29	76	

Table 3 continued

	Treated, followed up eyes assessed for MA	Percentage of total number of studied and followed up eyes	Eyes with no baseline MA (%)		Eyes developing new MA (%)	Total eyes showing MA (baseline & new) (%)		Notes
			with no baseline MA (%)	baseline MA (%)		baseline MA (%)	new MA (%)	
Kumar et al. 2013 [30]	124	41	20	20	79			
Young et al. 2014 [31]	258	33	18	18	85			
Gillies et al. 2015 [32]	131	§	§	§	10		Among 42 eyes that lost ≥ 10 letters: 13 eyes were found to show central GA	
Schürze et al. 2015 [33]	31	45	42	42	97		Only considering focal RPE atrophy	
Schürze et al. 2015 [33]	31	100	61	61	61		GA	
Tanaka et al. 2015 [34]	81	85	6	6	21			
Cho et al. 2015 [35]	43	100	37	37	37			
Xu et al. 2015 [36]	94	82	37	37	55			
Kuroda et al. 2016 [37]	195	95	5	5	10			
Kuroda et al. 2017 [38]	123	100	11	11	11			
Arevalo et al. 2016 (for PACORES) [39]	292	84	26.5	26.5	42.5			
Thavikulwat et al. 2016 [40]	63	65	11	11	46			

Table 3 continued

	Treated, followed up eyes assessed for MA	Percentage of total number of studied and followed up eyes			Notes
		Eyes with no baseline MA (%)	Eyes developing new MA (%)	Total eyes showing MA (baseline & new) (%)	
Munk et al. 2016 [41]	49	55	29	74	
Abdelfattah et al. 2017 (for TRES-AMD) [42]	49	57	12	55	
Fan et al. 2017 (for TRES-AMD) [43]	55	58	11	53	
Wons et al. 2017 [44]	118	§	§	68	CNV lesions were not included in the atrophy measurements. Eyes treated with R all had CNV-independent RPE loss at baseline
Hara et al. 2017 [45]	46	89	33	43	
Zarubina et al. 2017 [46]	74	100	51	51	
Li et al. 2017 [47]	79	87	47	60	
Sitnilska et al. 2018 [48]	52	100	58	58	
Domalpally et al. 2018 [49]	334	59	15	56	
Mantel et al. 2018 [50]	101	62	62	100	

Table 3 continued

	Treated, followed up eyes assessed for MA	Percentage of total number of studied and followed up eyes	Notes	
			Eyes with no baseline MA (%)	Eyes developing new MA (%)
Mantel et al. 2019 [51]	149	100	42	42
Wada et al. 2019 [52]	150	100	43	43

§ insufficient/missing data or not reported, ~ approximately, MA macular atrophy, CNV choroidal neovascularization, GA geographic atrophy, RPE retinal pigment epithelium

according to treatment type, dose or regimen. Tables 7, 8, 9 and 10 summarize the relevant conclusions to date.

- The 2-year report of CATT concluded that the development of geographic atrophy (GA) was higher in groups treated monthly than in the as-needed groups, with the monthly ranibizumab-treated group showing the highest proportion. Among studied eyes, 18% showed new GA by the end of 2 years, ranging among eyes with no baseline atrophy from 25.8% in the monthly ranibizumab group to 12.9% in the bevacizumab-PRN group [20]. At 2 years of follow-up, the growth rate of GA was higher for eyes treated with ranibizumab [14]. CATT results at 5 years reported the percentage of eyes with new incident GA rising further to 39%. Several risk factors identified at 2 years of follow-up appeared again to be significant at 5 years of follow-up. There was still a higher proportion of eyes originally assigned to ranibizumab with new GA than eyes assigned to bevacizumab, and also a higher proportion of eyes originally assigned to monthly treatment for 2 years with GA than eyes originally assigned to PRN treatment. However, these differences were less statistically significant [21, 22]. Despite the fact that most participants did not continue with the same original treatment assignment during the 3 years after the end of the clinical trial, ranibizumab was still associated with a significantly higher GA growth rate than bevacizumab at 5 years. Treatment frequency, on the other hand, did not impact the progression rate of atrophy [21].
- In IVAN, the percentage of new macular atrophy (MA) did not differ between drug groups, but was significantly lower in participants on discontinuous regimens than on continuous ones. At 2 years, GA incidence was similar in eyes treated with ranibizumab and those treated with bevacizumab, decreasing the possibility of a true effect of ranibizumab on MA occurrence. The association of monthly treatment with an increased rate of development of MA was more consistent [24].

Table 4 Mean MA progression rate

Study	Eyes assessed	Mean MA progression rate	Mean MA progression rate after square-root transformation	Special notes
Grunwald et al. 2015 (for CATT, 2-year results) [21]	nAMD (study eyes)	§	0.43 mm/year	
Grunwald et al. 2016 (for CATT, 5-year results) [23]	nAMD (study eyes)	1.52 mm ² /year	0.33 mm/year	
Kumar et al. 2013 [30]	nAMD (study eyes)	0.94 mm ² /year	§	
Xu et al. 2015 [36]	nAMD (study eyes)	0.58 mm ² /year	0.54–1.43 mm/year	
Kuroda et al. 2016 [37]	nAMD (study eyes)	§	0.47 (0.43–0.50) mm/year	
Thavikulwat et al. 2016 [40]	nAMD (study eyes)	§	0.19–0.34 mm/year	
Munk et al. 2016 [41]	nAMD (study eyes)	0.3–0.4 mm ² /year	0.1–0.12 mm/year	
Abdelfattah et al. 2017 (for TRESX-AMD) [42]	nAMD (study eyes)	0.26–0.72 mm ² /year	§	
	Non-nAMD (control eyes)	0.33 mm ² /year	§	
Wons et al. 2017 [44]	nAMD (study eyes)	0.30–0.39 mm ² /year	0.12–0.14 mm/year	CNV lesions were not included in the atrophy measurements
	§	§	0.14–0.25 mm/year	Study eyes switched to aflibercept 'Ranibizumab-only' eyes and 'switched to aflibercept' eyes

Table 4 continued

Study	Eyes assessed	Mean MA progression rate	Mean MA after square-root transformation	Mean MA progression rate	Special notes
Hata et al. 2017 [45]	nAMD (study eyes)	§	1.11–1.20 mm ² /year	1.11–1.20 mm ² /year	Study eyes developing new MA
Li et al. 2017 [47]	nAMD (study eyes)	0.2–0.7 mm ² /year	§	0.2–0.7 mm ² /year	
Domalpally et al. 2018 [49]	nAMD (study eyes)	1.23–1.86 mm ² /year	0.35–0.39 mm ² /year	1.23–1.86 mm ² /year	
Mantel et al. 2018 [50]	nAMD (study eyes)	1.17 mm ² /year	0.54 (0.42–0.6) mm ² /year	1.17 mm ² /year	
Sunness et al. 2007 [65]	Non-nAMD (study eyes)	2.6 mm ² /year	§	2.6 mm ² /year	
Holz et al. 2007 [66]	Non-nAMD (study eyes)	0.38–1.81 mm ² /year	§	0.38–1.81 mm ² /year	
Ychoshua et al. 2015 [67]	Non-nAMD (study eyes)	1.2 mm ² /year	§	1.2 mm ² /year	
Beaver Dam Eye Study [68]	Non-nAMD (study eyes)	1.28 mm ² /year	§	1.28 mm ² /year	

§ insufficient/missing data, *CNV* choroidal neovascularization, *MA* macular atrophy, *nAMD* neovascular age-related macular degeneration, *Non-nAMD* non-neovascular age-related macular degeneration

Table 5 Risk factors for developing MA identified by relevant studies of macular atrophy in nAMD eyes treated with anti-VEGF

Risk factors for MA incidence/progression																					
CNV location	Duration of nAMD	CNV size	Central IRC	PED presence	PED height	SCT thinning	SHRM	Hb (RDP)	SDD (RDP)	RAP	Refractive drusen	Contralateral MA	Poor baseline VA	Depigmentation	PDT number of injections	Higher number of injections	Lower number of drug injections	Type of drug	Age of patient	Hypercholesterolemia	
Grunwald et al. 2014 (for CATT 2 years) [14]	++	\$	++	-	-	\$	-	\$	\$	++	\$	++	+	\$	\$	+	-	+	+	+	+
Grunwald et al. 2015 (for CATT 2 years) [21]	++	\$	-	\$	-	\$	-	\$	-	-	\$	++	+	\$	\$	-	-	+	-	-	\$
Grunwald et al. 2016 (for CATT 5 years) [23]	++	\$	++	-	-	\$	\$	++	\$	++	\$	++	++	\$	\$	+	-	++	++	++	++
IVAN [24, 25, 59]	++	\$	\$	++	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	++	-	-	-	\$	\$
Bailey et al. 2019 (for IVAN) [26]	+	\$	\$	-	\$	\$	\$	-	\$	\$	\$	++	\$	\$	\$	-	-	-	-	-	\$
HARBOR [1, 27, 60–62]	\$	\$	++	-	-	\$	\$	\$	\$	\$	\$	+	\$	\$	\$	+	-	\$	+	+	\$
Rebhun et al. 2018 (for HARBOR) [28]	\$	\$	++	--	-	\$	\$	\$	\$	\$	\$	++	-	\$	\$	\$	\$	\$	-	-	\$
Lois et al. 2013 [29]	\$	-	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	++	--	-	\$	\$	\$
Kumar et al. 2013 [30]	\$	++	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	++	\$	\$	\$	\$	\$	\$
Young et al. 2014 [31]	\$	\$	\$	\$	\$	++	\$	\$	\$	\$	\$	\$	\$	\$	\$	++	-	+	+	+	+
Schütze et al. 2015 [33]	\$	\$	+	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	+	-	\$	\$	\$	\$
Tanaka et al. 2015 [34]	++	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$
Cho et al. 2015 [35]	+	\$	\$	+	\$	++	\$	++	+	+	\$	++	-	\$	\$	-	-	\$	\$	\$	\$
Xu et al. 2015 [36]	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	+	-	\$	\$	\$	\$

Table 5 continued

Risk factors for MA incidence/progression																					
	CNV location of nAMD	Duration of nAMD	CNV size	Central IRC	PED presence	PED height	SCT thinning	SHRM	Hb	SDD (RPD)	RAP	Refractile drusen	Contralateral MA	Poor baseline VA	Depigmentation	PDT number of injections	Higher number of injections	Lower number of injections	Type of drug	Age of hyperlacia	
Kuroda et al. 2016 [37]	+	\$	\$	\$	\$	\$	-	\$	\$	\$	\$	\$	\$	+	\$	\$	-	+	\$	\$	\$
Kuroda et al. 2017 [38]	\$	\$	+	++	\$	\$	++	+	\$	\$	\$	\$	\$	+	\$	\$	-	-	\$	+	\$
Thavakulwat et al. 2016 [40]	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	+	+	\$	\$	-	++	\$	+	\$
Munk et al. 2016 [41]	+	-	\$	++	\$	\$	\$	\$	\$	++	\$	\$	\$	\$	\$	\$	-	-	+	\$	\$
Abdelfattah et al. 2017 (for TREX-AMD) [42]	\$	\$	\$	\$	-	++	++	++	++	\$	\$	\$	\$	\$	\$	\$	-	+	\$	\$	\$
Fan et al. 2017 (for TREX-AMD) [43]	\$	\$	\$	\$	\$	\$	++	\$	\$	-	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	-
Wons et al. 2017 [44]	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$
Hara et al. 2017 [45]	+	\$	\$	\$	\$	\$	++	\$	\$	\$	+	++	\$	\$	\$	\$	-	\$	+	-	\$
Zarubina et al. 2017 [46]	\$	\$	\$	\$	\$	\$	\$	\$	\$	++	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$
Li et al. 2017 [47]	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	-	\$	\$	-	-	-	++	\$
Stimlska et al. 2018 [48]	+	++	\$	+	\$	\$	\$	\$	-	\$	\$	\$	-	\$	\$	\$	-	-	-	-	\$
Mantel et al. 2018 [50]	-	\$	\$	-	+	++	+	++	\$	-	+	\$	+	++	-	\$	-	-	-	-	\$
Mantel et al. 2019 [51]	++	\$	-	++	-	++	-	+	++	++	++	\$	++	++	++	\$	-	+	-	-	\$
Wada et al. 2019 [52]	-	\$	-	\$	\$	\$	\$	\$	\$	\$	\$	\$	\$	++	\$	\$	-	+	-	-	\$

\$ insufficient/missing data, or not reported, + risk factor, ++ significant risk factor, --- not a risk factor, -- significantly not a risk factor, CNV choroidal neovascularization, Hb haemorrhage, IRC intraretinal cysts, IRF intraretinal fluid, MA macular atrophy, nAMD neovascular age-related macular degeneration, PCV polypoidal choroidal vasculopathy, PDT photodynamic therapy, PED pigment epithelial detachment, RAP retinal angiomatous proliferation, RPD reticular pseudodrusen, SCT subfoveal choroidal thickness, SDD subretinal drusenoid deposits, SHRM subretinal hyperreflective material, SRF subretinal fluid, VA visual acuity

Table 6 Protective factors against developing MA identified by relevant studies of macular atrophy in nAMD eyes treated with anti-VEGF

	Type I CNV	Blocked fluorescence	SRF	PCV	PED	Subretinal complex thickness	Vitromacular attachment
Grunwald et al. 2014 (for CATT 2 years) [14]	--	+	++	\$	+	++	++
Grunwald et al. 2015 (for CATT 2 years) [21]	++	\$	-	\$	-	-	\$
Grunwald et al. 2016 (for CATT 5 years) [23]	++	+/-	++	\$	+	++	+/-
Bailey et al. 2019 (for IVAN) [26]	--	\$	++	\$	++	\$	\$
HARBOR [1, 27, 60–62]	-	\$	++	\$	++	\$	\$
Rebhun et al. 2018 (for HARBOR) [28]	\$	\$	\$	\$	++	\$	\$
Xu et al. 2015 [36]	++	\$	\$	\$	\$	\$	\$
Kuroda et al. 2016 [37]	\$	\$	\$	++	\$	\$	\$
Kuroda et al. 2017 [38]	-	\$	\$	+	\$	\$	\$
Thavikulwat et al. 2016 [40]	+	\$	\$	\$	\$	\$	\$
Munk et al. 2016 [41]	-	\$	\$	\$	\$	\$	++
Abdelfattah et al. 2017 (for TRESX-AMD) [42]	-	\$	-	\$	--	--	\$
Li et al. 2017 [47]	-	\$	\$	\$	\$	\$	\$
Mantel et al. 2018 [50]	-	\$	-	\$	-	-	-
Mantel et al. 2019 [51]	\$	\$	++	\$	-	-	-
Wada et al. 2019 [52]	+	\$	\$	\$	\$	\$	\$

\$ no data/not assessed, - non-protective, -- significantly non-protective, + protective, ++ significantly protective, CNV choroidal neovascularization, MA macular atrophy, PCV polypoidal choroidal vasculopathy, PED pigment epithelial detachment, SRF SubRetinal fluid

Table 7 Studies concluding that the number of anti-VEGF injections correlated with MA incidence/progression

	Study design	Study eyes naivety to treatment	Treatment protocol
Grunwald et al. 2014 (for CATT 2 years) [14]	Px	Tx naive	Study eyes randomized to (a) monthly treatment always, (b) 3 monthly treatments followed by PRN always, (c) monthly treatments for a year followed by PRN for 1 year
Grunwald et al. 2016 (for CATT 5 years) [23]	Px	Tx naive	Same 2-year protocol, followed by any protocol at clinician's discretion for 3 years
IVAN [24, 25]	Px	Tx naive	Study eyes randomized to monthly treatments or PRN (3 monthly treatments followed by PRN)
HARBOR [1, 27, 60, 61]	Px	Tx naive	Study eyes randomized to 0.5 mg or 2 mg monthly treatments or PRN (3 monthly treatments followed by PRN)
Schütze et al. 2015 [33]	Px	Tx naive	Monthly treatments in first year, then PRN
Xu et al. 2015 [36]	Rx	Tx naive	T&E
Lois et al. 2013 [29]	Rx	§	Monthly treatments till VA stable, then PRN
Young et al. 2014 [31]	Rx	§	3 monthly treatments then T&E

§ no data, *MA* macular atrophy, *PRN* pro re nata (as needed), *Px* prospective, *Rx* retrospective, *T&E* treat and extend, *Tx* treatment

Table 8 Studies concluding that the number of anti-VEGF injections correlated inversely with MA incidence/progression

	Study design	Study eyes naivety to treatment	Treatment protocol
Abdelfattah et al. 2017 (for TREX-AMD) [42]	Px	Tx naive	Study eyes randomized to monthly or 3 monthly treatments followed by T&E
Mantel et al. 2019 [51]	Px	Tx naive	2 identical separate studies for R & A: 3 monthly treatments followed by observe & plan
Thavikulwat et al. 2016 [40]	Px	Non-naive eyes included	4 monthly treatments followed by PRN
Wada et al. 2019 [52]	Rx	Tx naive	R 3 monthly treatments then PRN, some switched to A 3 monthly treatments followed by PRN
Kuroda et al. 2016 [37]	Rx	Tx naive	3 monthly treatments followed by PRN

A aflibercept, *MA* macular atrophy, *PRN* pro re nata (as needed), *Px* prospective, *R* ranibizumab, *Rx* retrospective, *T&E* treat and extend, *Tx* treatment

- Bailey et al. reanalysed the IVAN cohort, yet with a revised MA definition and with OCT contributing more significantly in atrophy assessment. Bailey found no significant correlation of the incidence nor progression of

the MA within the area of the CNV lesion (i.e. 'intralesional MA') with the drug used nor with the number of injections delivered over 2 years. The previous IVAN finding of

Table 9 Studies concluding that the number of anti-VEGF injections has no significant correlation with MA incidence/progression

	Study design	Study eyes naivety to treatment	Treatment protocol
Bailey et al. 2019 (for IVAN) [26]	Px	Tx naive	Monthly treatments or PRN (3 monthly treatments followed by PRN)
Sitnilska et al. 2018 [48]	Px	Tx naive	R 3 monthly treatments then PRN for 2 years, then R/A/B PRN
Mantel et al. 2018 [50]	Px	Tx naive	2 identical separate studies for R & A: 3 monthly treatments followed by observe & plan
Cho et al. 2015 [35]	Rx	Tx naive	3 monthly treatments followed by PRN
Kuroda et al. 2017 [38]	Rx	Tx naive	3 monthly treatments then bimonthly
Munk et al. 2016 [41]	Rx	§	R 3 monthly treatments then PRN, followed by R T&E and/or A T&E
Li et al. 2017 [47]	Rx	Tx naive	Inconsistent/variable

§ no data, *A* aflibercept, *B* bevacizumab, *MA* macular atrophy, *PRN* pro re nata (as needed), *Px* prospective, *R* ranibizumab, *Rx* retrospective, *T&E* treat and extend, *Tx* treatment

more frequent treatment causing more MA has thus not been replicated [26].

- At 2 years, HARBOR concluded that eyes receiving monthly ranibizumab had a higher incidence of GA when compared with PRN-treated ones [1, 60]. The dose of ranibizumab was not associated with MA. In the PRN arms, MA incidence did not appear to be associated with injection frequency [61].
- In SEVEN-UP, the progression of MA was observed even in the context of very low anti-VEGF injection frequency [15, 17].
- Lois et al. upon their retrospective review found that the number of injections received was statistically significantly associated with an increased incidence of new MA and with greater progression of atrophy at follow-up. In 84% of the eyes in which there was progression of atrophy, no atrophy was detected at baseline [29].
- Kumar et al. reported factors they found retrospectively to be correlated with RPE loss, and noted that no significant interaction with the type of drug used was found [30].
- Young et al. claimed that eyes with nAMD had greater progression of RPE atrophy and choroidal atrophy compared to those with non-nAMD. Progression of RPE atrophy and choroidal atrophy was independently associated with the total number of injections (of bevacizumab/ranibizumab). Choroidal atrophy was also independently associated with the number of anti-VEGF injections regardless of the drug used, and it was more pronounced in eyes treated with anti-VEGF therapy for nAMD than in controls. In the subgroup of 84 eyes with nAMD and without RPE atrophy at baseline, only bevacizumab was associated with the progression of RPE atrophy [31].
- Through their retrospective analysis, Gillies et al. reported that no correlation was found between GA and the frequency of injections [32].
- On analysing data from a prospective interventional case series of treatment-naive nAMD eyes, Schütze et al. [33] reported that early RPE loss and expansion of GA was most pronounced during initial intensive monthly treatment, consistent with findings

Table 10 Studies assessing the correlation of MA incidence/progression with the type of anti-VEGF drug injected

	Higher risk of MA incidence/progression according to type of drug	Drugs used to treat study eyes	Drug correlated with higher MA incidence/progression	Study design	Study eyes naivety to treatment	Treatment protocol
CATT (2 years) [14, 20, 21]	Yes	B, R	R	Px	Tx naive	Study eyes randomized to (a) monthly treatment always, (b) 3 monthly treatments followed by PRN always, (c) monthly treatments for a year followed by PRN for 1 year
CATT (5 years) [22, 23]	Yes	B, R, A, any other	R			Same 2-year protocol, followed by any protocol at clinician's discretion for 3 years
Hata et al. 2017 [45]	Yes	R, A	A	Rx	Tx naive	R 3 monthly treatments then PRN, or A 3 monthly treatments then bimonthly
Young et al. 2014 [31]	Yes	B, R	B	Rx	§	3 monthly treatments then T&E
Munk et al. 2016 [41]	Yes	R, A	A	Rx	§	R 3 monthly treatments then PRN, followed by R T&E and/or A T&E
IVAN [24, 25]	No	B, R	N/A	Px	Tx naive	Study eyes randomized to monthly treatments or PRN (3 monthly treatments followed by PRN)
Bailey et al. 2019 (for IVAN) [26]	No	B, R	N/A			
Sitnilska et al. 2018 [48]	No	B, R, A	N/A	Px	Tx naive	R 3 monthly treatments then PRN for 2 years, then R/A/B PRN
Mantel et al. 2018 [50]	No	R, A	N/A	Px	Tx naive	2 identical separate studies for R & A: 3 monthly treatments followed by observe & plan
Mantel et al. 2019 [51]	No	R, A	N/A	Px	Tx naive	2 identical separate studies for R & A: 3 monthly treatments followed by observe & plan

Table 10 continued

	Higher risk of MA incidence/ progression according to type of drug	Drugs used to treat study eyes	Drug correlated with higher MA incidence/ progression	Study design	Study eyes naivety to treatment	Treatment protocol
Wada et al. 2019 [52]	No	R, A	N/A	Rx	Tx naive	R 3 monthly treatments then PRN, some switched to A 3 monthly treatments followed by PRN
Wons et al. 2017 [44]	No	R, A	N/A	Rx	Non-naive eyes included	3 monthly treatments then T&E: R or switched to A (from B/R)
Li et al. 2017 [47]	No	B, R, A	N/A	Rx	Tx naive	Inconsistent/variable

§ no data, *A* aflibercept, *B* bevacizumab, *MA* macular atrophy, *PRN* pro re nata (as needed), *Px* prospective, *R* ranibizumab, *Rx* retrospective, *T&E* treat and extend, *Tx* treatment

from the CATT study [20], and remained stable during subsequent PRN-based therapy [33].

- Cho et al. looked at RAP cases treated with ranibizumab over 2 years: there was no significance found between injection number and GA development [35].
- Xu et al. stated that no other variables except for the number of anti-VEGF injections and the choroidal neovascularization type were related to GA development [36].
- Kuroda et al. reported in 2016 on MA in nAMD eyes treated with ranibizumab, where eyes receiving fewer injections appeared under a higher risk of developing new MA [37]. In their 2017 paper, where they used a fixed treatment regimen of aflibercept (per drug label), they could not find a difference in the number of injections between the newly developed macular atrophy eyes and the eyes with no new MA [38].
- In their post hoc analysis, Thavikulwat et al. reported that of the treatment-naive study eyes without GA at baseline, those who developed new GA had received fewer study injections on average compared with those who did not develop new GA [40].
- Over 6.2 years, Munk et al. assessed growth rate of MA both outside and within the CNV border. They found a higher growth rate for MA outside the CNV border with aflibercept, while growth rate was similar for aflibercept and ranibizumab for MA within the CNV. Notably, the number of administered injections did not seem to have an impact on the size of MA [41].
- TREX-AMD reported that ranibizumab did not statistically significantly influence new MA development in eyes with nAMD, whether dosed monthly or per a treat and extend regimen. However, a higher growth rate of MA in the TREX group was evident at all time points, compared to the monthly group [42, 43].
- As per Wons et al., a linear progression rate of RPE loss was found in patients treated with ranibizumab as well as in patients treated with aflibercept; however, no significant increase of progression rate was found after the switch from ranibizumab to aflibercept [44].
- Hata et al.'s results at 12 months showed that the percentage of eyes developing RPE atrophy among RAP eyes treated with aflibercept

without baseline RPE atrophy was twice that for eyes treated with ranibizumab [45].

- Li et al. found that the highest incidence of MA was within the first year of treatment. Age was the significant predictor of MA development and progression, whereas all the other factors, including drug type and number of injections, did not correlate with macular atrophy [47].
- Sitniska et al. correlated the onset of RPE atrophy mainly with the duration of the nAMD disease. No correlation was found with the total number of received anti-VEGF injections or the drug type. Through at least 3 years of follow-up for all studied eyes, 50% of new MA incidence occurred within the first year of treatment [48].
- Domalpally et al. demonstrated that most cases of new MA appeared within the initial 2 years of treatment. The drug type and treatment protocol were not stated in the report [49].
- Mantel et al. found that the number of injections was inversely correlated with the incidence of new MA, suggesting that a higher number of treatments is not a risk factor for MA development, and that MA may co-occur thus with low activity nAMD. No correlation was found between MA incidence and drug type. Furthermore, MA growth rate was not correlated with its location compared to the CNV lesion, the drug or the number of injections [51].
- The 5-year results from Wada et al. showed that undertreatment correlated with a higher MA incidence, and that a higher number of injections did not increase the risk for MA development. They reported also that treatment switching from ranibizumab to aflibercept was not associated with a higher MA occurrence [52].

ANTI-VEGF AND OTHER RELEVANT MA RISK FACTORS

Subfoveal Choroidal Thickness

A reduced subfoveal choroidal thickness (SCT) has been shown to increase not only the risk for

MA incidence [31, 35, 37, 38, 42, 43, 45, 51] but also for MA area growth rate [45, 50].

At 12 months, Hata et al. reported that the growth rate of RPE atrophy area was negatively correlated with baseline SCT [45]. In the reports on TREX-AMD, eyes with a thinner SCT at baseline also tended to have more MA at month 18 and vice versa [42, 43]. Kuroda et al. denied such a correlation in nAMD eyes treated with ranibizumab [37], yet 1 year later they reported results from a different group treated with aflibercept, and a thinner SCT at baseline was found to be associated with the development of MA [38]. Both Cho et al. and Mantel et al. also reported the same correlation between a reduced SCT and a higher incidence of MA [35, 51].

A potential causative connection between choroidal thickness and anti-VEGF treatments was also reported in several studies. Subfoveal choroidal thinning is thought to potentially be caused or aggravated by anti-VEGF treatment, and could therefore serve as a factor that increases the risk for MA. Progression of choroidal atrophy was found by Young et al. to be independently associated with the total number of injections of bevacizumab and ranibizumab, similar to their findings that a higher injection number increases the risk of MA incidence and progression [31]. Choroidal atrophy was also independently associated with the number of anti-VEGF injections regardless of the drug used, and it was more pronounced in eyes treated with anti-VEGF therapy for nAMD than in the non-nAMD control eyes [31]. Similarly, Kaya found that SCT decreased significantly in eyes treated with ranibizumab or aflibercept at 1, 3 and 6 months, yet aflibercept-treated eyes showed a significant further reduction in SCT when compared to ranibizumab [69]. Kim et al. noted a greater decrease in SCT in eyes treated with aflibercept than in eyes treated with ranibizumab. This difference was more marked in PCV than in other subtypes of nAMD [70]. Mazaraki et al. noted that aflibercept induced a reduction in SCT in both treatment-naive and pretreated eyes with nAMD [71].

Choroidal perfusion and vasculature affects the choroidal thickness. Takasago et al. found that the choriocapillaris (CC) nonperfusion area and MA area were significantly correlated as these

areas markedly overlapped. They concluded that choroidal ischaemia might be thus involved in the pathogenesis of MA in treated nAMD, and that CC nonperfusion after anti-VEGF might be associated with the development of MA [72]. Mastropasqua et al. reported intravitreal administration of aflibercept to be associated with a significant reduction of flow in both native retinal and choroidal vasculature in patients' treated eyes [73]. An *in vivo* study in primates by Julien et al., reported that the area of the choriocapillaris was significantly reduced after both ranibizumab and aflibercept compared to controls, but the relevant vascular and intravascular changes were more pronounced and more frequent after aflibercept, which caused hypertrophy and death of individual RPE cells [74].

Subretinal Hyperreflective Material

Subretinal hyperreflective material (SHRM) is a morphological feature seen on OCT as hyperreflective material located external to the retina, and internal to the RPE in nAMD. At baseline, SHRM was present in 76.3% of CATT study eyes, decreasing to 54% at 104 weeks. With time, anti-VEGF treatments appear to reduce the presence of SHRM. A strong connection was found between presence of SHRM and scar formation [57]. Unlike scar formation, GA developed more in eyes with resolved SHRM compared to eyes with persistent SHRM at week 52. CATT found the difference to become non-significant at week 104 though [57].

Kuroda et al. reported SHRM as a risk factor for MA development [38]. Abdelfattah et al. correlated the presence of SHRM at baseline in addition to the SHRM thickness at baseline with a higher incidence of MA [42]. Mantel et al. correlated a thicker SHRM at baseline to higher MA growth rate [50], yet not to an increased MA incidence [51].

COMPARISON OF NAMD-RELATED AND NON-NAMD-RELATED MA

Like typical GA occurring in advanced non-nAMD, MA associated with anti-VEGF therapy

for nAMD is characterized by the irreversible loss of the outer retina, RPE and choriocapillaris [21, 33, 75–77]. However, some authors have noted that, compared with typical GA, MA occurring in the setting of anti-VEGF therapy is often smaller in size and of a more diffuse distribution [33]. Zanzottera et al. showed histologic differences in RPE morphology, basal laminar deposit and the descent of the external limiting membrane toward Bruch's membrane at the atrophy border in eyes with non-nAMD versus those with nAMD [78, 79].

Compared to GA in non-nAMD, presenting with larger RPE atrophy lesion [80–83], RPE atrophy in nAMD shows multiple smaller and more diffusely distributed focal atrophic RPE lesions. The multilobular MA structure frequently observed in eyes with CNV in the study by Schütze et al. [33] may represent an underlying disease substrate, for example, of the choroidal vasculature, recently reported by Xu et al. [83]. Patients with CNV undergoing therapy frequently developed these discrete RPE discontinuities increasing in size and distribution during follow-up. Kumar et al. demonstrated that the RPE loss in nAMD was different from that typically seen with GA in that it involved the centre of the macula from the start, in distinction from GA, which usually develops in a perifoveal location. Also, RPE loss expanded outward from the centre [30].

In non-nAMD, although atrophic lesions typically appear first in the perifoveal macula, sparing the foveal centre, over time these lesions often expand and coalesce to include the fovea [84]. In non-nAMD, progression from non-central to central GA occurs in 45% of eyes over 5 years [85]. Of those without central involvement at first detection, the median time to foveal atrophy is approximately 2 years [86].

The primary insult in GA in non-nAMD appears to be at the level of the RPE and there is an intimate relationship between RPE atrophy and secondary choriocapillaris degeneration. In nAMD, choriocapillaris degeneration can occur in the presence of viable RPE. The RPE in regions of vascular dropout are presumably hypoxic, which may result in an increase in VEGF production by the RPE and stimulation of CNV [87]. Nonetheless, the photoreceptors,

RPE, Bruch's membrane and choriocapillaris have together been described as a functionally integrated complex with a "mutualistic symbiotic relationship" [88]. These layers are so interdependent anatomically and functionally that there can be no damage to one layer without corresponding dysfunction and disruption of the other layers. Consequently, there may be no primary insult leading to atrophy but rather a concerted deterioration affecting the entire complex [89].

Baseline SCT in eyes with MA is statistically significantly less than in those without MA in both the non-nAMD and nAMD. Eyes with AMD and MA had less baseline SCT than those without MA. Eyes with less baseline SCT also appeared to be at higher risk to develop MA within 18 months [43].

In non-nAMD, lesion characteristics that were prognostic for either a higher MA progression rate or future MA development included a larger baseline lesion size, non-foveal location/progression toward periphery, vitreoretinal traction, GA in the fellow eye, outer retinal tubulations (ORT) and reticular pseudodrusen [84]. All these characteristics have also been reported to be of a similar prognosis in nAMD studies [14, 19–21, 30, 46, 58].

Recently, it has been shown that MA progression rates in non-nAMD—after square-root transformation—have a linear progression using different imaging modalities [14]. Overall, GA progression rates reported in the literature for total study populations in non-nAMD GA natural history studies range from 0.53 to 2.6 mm²/year. Holz et al. reported a median growth rate of 1.52 mm²/year using FAF imaging [66]. Sunness et al. reported a median growth rate of 2.6 mm²/year using CFP imaging [65]. By using the en face OCT projection image, estimated GA growth rate was 1.2 mm²/year in a relatively small cohort [67]. In the Beaver Dam Eye Study, the mean enlargement of area of GA was 6.4 mm² over 5 years, equivalent to 1.28 mm²/year [68]. Of note, it has been reported that eyes with nAMD had greater progression of RPE atrophy and choroidal atrophy compared with those with non-nAMD, upon comparing eyes with nAMD with their fellow

eyes with non-nAMD [31]. Table 4 lists the reported MA progression rates.

Several variations in FAF pattern in the junctional zone of GA of eyes with non-nAMD have been reported: none, focal, banded, patchy and diffuse (reticular, branching and fine granular) [90]. Atrophy in each of these categories shows a different growth rate, ranging between a minimum of 0.38 mm²/year in the 'none' type and a maximum of 1.81 mm²/year in the 'banded' type, as reported by Holz et al. [66]. Wons et al. have additionally described the RPE loss in nAMD eyes to show patterns comparable to the aforementioned patterns known in GA [44].

FELLOW NON-NAMD EYES

In nAMD eyes, Young et al. noted a macular atrophy progression rate and choroidal atrophy, both of which were significantly higher, in comparison to their non-nAMD fellow eyes [31].

In non-nAMD fellow control eyes analysed by Thavikulwat et al., none of the eyes that had no baseline GA developed any new GA by the end of the study [40].

Highly significant inter-eye concordance regarding MA prevalence by the final visit was reported by Mantel et al. In 92% of the fellow eyes analysed, there was no baseline MA in either the fellow non-nAMD eyes or their study nAMD eyes. Moreover, Mantel et al. pointed out additionally the high inter-eye symmetry in MA distributions and high inter-eye correlation in the MA area growth rates [50, 51].

In addition to reporting on their study of 81 nAMD eyes, Tanaka et al. analysed data from their 35 non-nAMD fellow control eyes. Compared to the study eyes, the fellow non-nAMD eyes showed a close figure for the percentage of eyes with baseline GA [34].

DISCUSSION

Neovascular AMD (nAMD) and associated oedema can be controlled today with regular anti-VEGF treatments; however, macular atrophy (MA)—once it occurs—appears irreversible.

MA is associated with photoreceptor loss; therefore, a central location of MA would lead to central vision impairment.

All reports agree on the fact that de novo development of MA in anti-VEGF-treated eyes is frequent and multifactorial. To date, most of the identified risk factors are ocular, with little evidence for influence of the treatment type and no evidence for systemic risk factors.

Research data shows an expansion of atrophy during anti-VEGF treatment. This could be consistent with the natural evolution of AMD or possibly as collateral damage related to the CNV lesion. Alternatively, this can potentially be related to a direct toxicity of the anti-VEGF or to an anti-VEGF blocking the neurotrophic effect of VEGF [91]. Another explanation could be that the progression of atrophic changes may be furthered by decreased perfusion and resulting ischaemia, as the regression of CNV with anti-VEGF may eliminate the only remaining blood supply for the outer retina [92]. Published reports demonstrate a potential protective effect of sub-RPE choroidal neovascularization (type 1 CNV) in slowing macular atrophy in eyes with nAMD [21, 23, 36, 40, 52, 93–95].

A direct comparison between untreated and treated eyes with nAMD would provide significant clues towards the cause of MA; however, such a comparison is impossible for ethical reasons.

Comparisons have been made between the nAMD eyes and their fellow non-nAMD ones.

On comparing the reports of research studies, mixed and rather contradictory conclusions are reached regarding correlation of MA development or progression with drug type, treatment frequency and other factors, as detailed above and also summarized in Tables 5 and 6. It mostly appears that there is no straightforward link.

Despite their significant weight, the studies of CATT, IVAN and HARBOR do have a limitation in common: they all lacked FAF which represents a gold standard for evaluation of MA [96, 97]. Also, even in the studies that have relied on FAF, to our knowledge, a classification of the junctional zone FAF pattern in the nAMD-related MA has not been reported. This is an important MA potential characteristic that

might affect its growth rate. Had such information been available, it would have helped define the meaningfulness of the results reported by the nAMD studies above. OCT, which now represents the reference standard imaging modality to diagnose and grade MA, was not utilized in either CATT or HARBOR to assess MA.

As summarized in Tables 1 and 2, not all the studies were of the same size or design, and hence they were not of the same strength. The studies had relatively different inclusion criteria, and for MA detection and follow-up they relied on different imaging modalities. The criteria used to define MA also varied throughout the studies.

In patients with diabetic macular oedema or retinal vein occlusion on anti-VEGF treatment, frequent injections of anti-VEGF agents have not—to date—been reported to cause MA in such patients in whom MA is not part of the natural history of their disease. The question as to whether anti-VEGF accelerates nAMD-related MA development therefore requires additional clarification. It would be premature to conclude that anti-VEGF agents cause MA and that clinicians and patients should feel that it is critical to minimize use of anti-VEGF agents to avoid MA. On the basis of the currently available data, undertreatment rather than overtreatment probably would be a greater risk for visual loss in patients with CNV. However, data highlights the need for agents that can prevent or minimize MA. There are currently more clinical studies looking at the association of MA and anti-VEGF therapy, but more clinical research is still needed to further understand this association.

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