• Clinical Research •

OCT predictors of retinal atrophy in neovascular age-related macular degeneration treated with aflibercept

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Abstract

● **AIM:** To identify optical coherence tomography (OCT) features present at the diagnosis of neovascular age-related macular degeneration (nAMD) that could predict retinal atrophy (RA) and visual performance in patients treated with intravitreal aflibercept.

● **METHODS:** OCT data collected at the time of nAMD diagnosis (T0), after the first (T1) and third (T2) intravitreal aflibercept injection, and 5y post-diagnosis (T3) were analyzed. The study included 46 eyes from patients undergoing treatment. The association of OCT features with RA and visual acuity (VA) development over time were evaluated.

● **RESULTS:** Patients with RA at T3 exhibited worse VA (35.19±5.7 *vs* 8.90±2.3, *P*<0.001) and a lower rate of improvement or stability at T2 (90.48% *vs* 56.00%, *P*=0.019) and T3 (85.71% *vs* 8.00%, *P*<0.001). The development of RA at T3 was linked with type 2 macular neovascularization (MNV; 4.76% *vs* 36.00%, *P*=0.013), thinner outer nuclear layer (ONL, 88.89±7.82 μm *vs* 71.38±14.14 μm, *P*=0.033), presence of intraretinal fluid (IRF, 42.86% *vs* 80.00%, *P*=0.014), presence of IRF without subretinal fluid at T0 (SRF, 4.76% *vs* 32.00%, *P*=0.027), and reduced central foveal thickness at T3 (CFT, 190.14±22.79 μm *vs* 124.32±14.35 μm, *P*<0.001). The presence of SRF with or without IRF at the diagnosis was comparable between the two groups (90.48% *vs* 68.00%; *P*=0.084).

● **CONCLUSION:** Type 2 MNV, reduces ONL and CFT, and IRF presence at baseline may signal a higher risk of RA in treatment-naive nAMD patients, underscoring the importance of these OCT features in early risk assessment and management strategies.

● **KEYWORDS:** neovascular age-related macular degeneration; long-term prognosis; optical coherence tomography; OCT predictors; retinal atrophy
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INTRODUCTION

By 2040, due to the aging of the population, the number of people affected by age-related macular degeneration (AMD) is expected to increase by 50%[1-2]. In the European Region, the estimated prevalence rate is higher, reaching about 18.3% of individuals with a mean age range of 60-81y[3-7]. The occurrence of macular neovascularization (MNV) connotes the neovascular form of the disease known as neovascular AMD (nAMD), which is responsible for nearly 90% of the severe visual acuity (VA) loss (20/200 or worse)[8]. The pathophysiology of nAMD depends on immune and vascular factors, but causative mechanisms are still elusive. The retinal pigment epithelium (RPE) plays an undisputed role in the overexpression of the vascular endothelial growth factor (VEGF), one of the main molecular triggers of the MNV, promoting vascular leakage and endothelial cell proliferation[9]. Later stages of nAMD include sub-macular fibrosis, photoreceptor atrophy, and permanent loss of central vision[10]. Retinal atrophy (RA) is identifiable during the fundus oculi examination with the aspect of "geographic atrophy" defined as the presence of delimited atrophic lesions of the outer retina resulting from loss of photoreceptors, RPE, and choriocapillaris.

Swept-source optical coherence tomography (SS-OCT) is a noninvasive technique that provides high-resolution cross-sectional images of the retina and underlying structures. Nowadays, it is a leading diagnostic tool in nAMD, detecting new or recurrent neovascular disease activity and addressing

the best treatment[11-12]. The Consensus Definition for Atrophy Associated with Age-Related Macular Degeneration on OCT (CAM) designed OCT as the reference method to classify nAMD atrophy[13-14].

In 2004, the first anti-VEGF molecule was approved for the treatment of nAMD[15-16]. Intravitreal anti-VEGF agents can halt the progression of the disease, but nAMD fibrosis is irreversible. Different anti-VEGF regimens have been used, such as the *pro re nata* (as needed) or the treat and extend (fixed), both affected by pros and cons[17-20]. Main anti-VEGF agents are aflibercept, ranibizumab, brolocizumab, off-label bevacizumab and faricimab[21]. In 2011, the approval of aflibercept (marketed as EYLEA®) marked a significant step in the treatment of nAMD[22]. Aflibercept inhibits all forms of VEGF-A, VEGF-B, and the placental growth factor (PGF)[22-25]. VIEW trials showed that the clinical results of aflibercept were comparable to ranibizumab (0.5 mg) while necessitating five fewer injections in the first year[21]. Change in best corrected VA (BCVA) from the baseline showed an improvement of 7.6 Early Treatment Diabetic Retinopathy Study (ETDRS) letters among the groups initially assigned to receive intravitreal aflibercept either monthly or every two months (bimonthly) after 96wk of treatment. Nonetheless, anti-VEGF agents are burdened by a high frequency of intravitreal injections (IVT) and clinical examinations.

Moreover, the efficacy and safety comparison between anti-VEGF agents and the choice of treatment scheme remains controversial[26-27]. The administration of anti-VEGF agents does not prevent new recurrence[28], and in 66% of the treated patients, it is possible to detect persistent disease activity after the loading dose, defined as persistent intraretinal, subretinal or sub-RPE fluid, persistent or new hemorrhage and progressive lesion fibrosis[29-30].

Furthermore, despite a rapid initial response and visual recovery, several studies described a progressive decline in visual function in about 30% of affected eyes[31-32]. This phenomenon is attributable to the development of RA, which usually begins in the second year of treatment and manifests itself around the fifth year[31,33-36]. To date, the pathogenesis of RA is not known. Some authors suggest that it may constitute the natural progression of a concomitant dry variant of AMD[37], while others correlate its onset with anti-VEGF administration[31,33-36]. Chronic suppression of VEGF would eliminate its neuroprotective effect on the retina, and the involution of the MNV would interrupt the nutritional supply to the external retinal layers[38]. Morphological predictors of progression to RA have been investigated, although a conclusive response is lacking. Thus, their assessment and early recognition are crucial to obtaining the best use of available therapeutic resources and adequate preventive measures. Predictive models have been developed to assess the progression of AMD[39-41], but reproducible factors of progression to RA are not still well established. AMD is a common and increasing disease and it is crucial to identify reliable indexes of progression, facilitating adequate plans of treatment and prevention. In this study, we aimed to identify OCT features that may predict RA in patients with nAMD treated with aflibercept.

PARTICIPANTS AND METHODS

Ethical Approval The study was a retrospective, observational, cohort study, conducted at the Umberto I University Hospital and the Department of Sense Organs, Sapienza University of Rome. Data were collected from September 2014 to September 2021. All participants provided informed written research consent. The study was approved by the local ethics committee with protocol number 510/2014. This study follows the tenet of the Helsinki Declaration.

Participants To define possible candidates predictive of RA, a comparison was assessed between patients with and without RA at 5y from the nAMD OCT diagnosis. Participants were treated following a *pro re nata* scheme, with a loading phase consisting of an initial IVT at the OCT diagnosis of nAMD, followed by two injections at 1- and 2-month post-diagnosis, respectively. Subsequent IVTs were administered based on OCT-detected recurrences. Participants underwent monthly comprehensive ophthalmological exams, including OCT and fundus oculi, and were instructed to report any new visual symptoms.

Patients diagnosed with nAMD through OCT and indocyanine green angiography/fluorescein angiography, who required anti-VEGF treatment, were included in this study. Only eyes treated with aflibercept 4 mg/mL (Eylea®, Bayer, Leverkusen, Germany) and with a minimum 5-year follow-up were selected. In bilateral nAMD cases, only one randomly selected eye was included to prevent inter-eye correlation.

Exclusion criteria included the presence of RA detected on OCT and indocyanine green angiography/fluorescein angiography at baseline, other retinal diseases besides nAMD, prior retinal laser therapy, vitreoretinal surgery, or other anti-VEGF treatments, missing follow-up data at any time point, and unreliable OCT images.

Data were collected at baseline (T0), where a comprehensive ophthalmological examination was conducted, including BCVA assessment using the ETDRS scale, a dilated fundus examination, and SS-OCT. Additional data from SS-OCT and BCVA were gathered 1mo after the first and second loading injections (at T1 and T2, respectively), with a final evaluation taking place 5y post-initial injection (T3). The total number of IVTs, the number of recurrences, and the interval between the last IVT and the 5-year mark (T3) were recorded for each participant. BCVA stability was defined as a change of 4

ETDRS letters or fewer; improvement was marked by a gain of 5 or more ETDRS letters. RA was classified according to the OCT Classification of Atrophy Meeting Program[13].

SS-OCT scans, performed with the Triton DRI-OCT device (Topcon, Tokyo, Japan), featured a scanning rate of 100 000 A-scans per second and a 1050 nm wavelength for enhanced tissue penetration and clear visualization of deep ocular layers. Scans that were unreliable due to poor quality or the presence of artifacts were excluded. At baseline, SS-OCT assessed factors potentially indicative of RA development in nAMD patients treated with aflibercept including MNV type, intraretinal fluid (IRF), subretinal fluid (SRF), and outer nuclear layer (ONL) thickness. The largest MNV diameter and central foveal thickness (CFT) were measured, with ONL thickness assessed in the foveal region.

The presence and maximum height of pigment epithelium detachments (PEDs), quantification of hyperreflective foci (HRFs)[42], and outer retinal tubulations (ORTs)[43] were evaluated. Treatment response was determined *via* SS-OCT as the resolution of IRF or SRF and a decrease in retinal thickness.

Statistical Analysis Statistical analyses were carried out using IBM SPSS Statistics v.27.0.1. Continuous variables, reported as mean±standard deviation (SD), were tested for normal distribution by the Shapiro-Wilk test. To compare non-parametric values the Mann-Whitney test was employed, whereas the unpaired *t*-test was used to compare parametric values. To evaluate qualitative variables Fisher's exact test was used. When appropriate, we reported 95% confidence intervals (95%CI) and *P*-values.

RESULTS

During the clinical records review process, 1085 patient records were retrieved. Among these, 703 patients underwent treatment with aflibercept. Within this cohort, 653 patients did not meet the other inclusion criteria. A 5-year follow-up was available for 50 patients, but 4 were further excluded due to unreliable OCT images (Figure 1).

Totally 46 eyes were eligible for recruitment (mean age 78.37±1.90y; 32 women and 14 men) and started IVTs with aflibercept 4 mg/mL after an OCT diagnosis of nAMD (Figure 1). Twenty-one eyes did not show RA at 5y after the diagnosis (T3), while 25 eyes met the CAM criteria of RA. Non-atrophic eyes were categorized in group A, while atrophic ones in group B. The two groups did not differ by age (*P*=0.112; Table 1, Figures 2 and 3).

The BCVA showed no significant differences between the two groups at T0, T1, and T2. BCVA at T3 was significantly worse in patients with atrophy (35.19±5.7 *vs* 8.90±2.3; *P*<0.001). An improvement of BCVA was observed in group A at T2 (90.48% *vs* 56.00%; *P*=0.019) and T3 (85.71% *vs* 8.00%; *P*<0.001; Table 1).

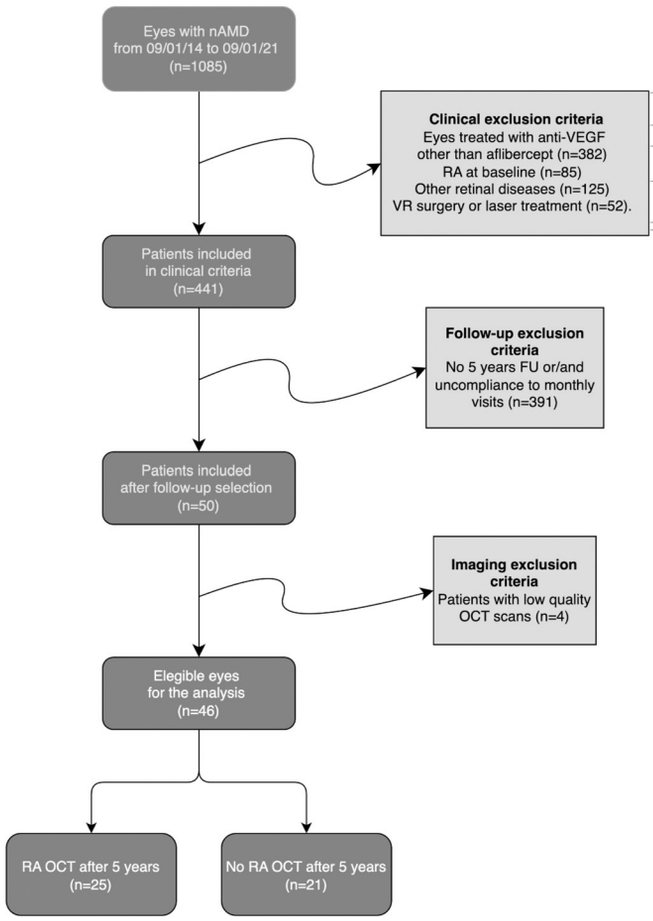

Figure 1 Flow diagram summarizing sample selection FU: Follow-up; nAMD: Neovascular age-related macular degeneration; OCT: Optical coherence tomography; RA: Retinal atrophy; VR: Vitreoretinal surgery; VEGF: Vascular endothelial growth factor.

The baseline prevalence rates of type 1, type 2, type 3, and mixed type MNV were 36.96%, 21.74%, 0, and 41.30%, respectively. Group B showed a higher frequency of type 2 MNV (4.76% *vs* 36.00%; *P*=0.013). No significant differences were found between the two groups for type 1 MNV (47.62% *vs* 28.00%; *P*=0.225), mixed type MNV (47.62% *vs* 36.00%; *P*=0.550), and MNV diameter (2724.24±432.32 µm *vs* 3134.16±514.89 µm; *P*=0.215; Table 1).

A thinner ONL at T0 (88.89±7.82 µm *vs* 71.38±14.14 µm; *P*=0.033) and a reduced CFT at T3 (190.14±22.79 µm *vs* 124.32±14.35 µm; *P*<0.001) were more frequent in group B.

The presence of SRF with or without IRF at the diagnosis was comparable between the two groups (90.48% *vs* 68.00%; *P*=0.084), whereas IRF was predominant in group B (42.86% *vs* 80.00%; *P*=0.014). Moreover, atrophic eyes showed more IRF without SRF at T0, compared with eyes without atrophy at 5y (4.76% *vs* 32.00%; *P*=0.027).

The number of IVTs (14.71±1.28 *vs* 16.68±1.61; *P*=0.427) and months between the last IVT and T3 (18.1±2.63 *vs* 17.6±2.83; *P*=0.931) showed no significant differences between the two groups.

Table 1 Comparison between the two groups of study mean±SD

Demographic, functional, and imaging variables	Group A (*n*=21)	Group B (*n*=25)	*P*
Demographic features			
Age, y, at T0	76.67±2.54	79.8±2.9	0.112
Female, *n* (%)	16 (76.19)	16 (64.00)	0.522
Pseudophakia, *n* (%)	10 (47.62)	14 (56.00)	0.767
Functional features			
VA at T0, letters	26.48±5.89	24.96±7.17	0.739
VA at T1, letters	31.34±6.12	27.52±7.47	0.420
VA at T2, letters	35±6.36	27.44±7.5	0.122
VA at T3, letters	35.19±5.7	8.9±2.3	<0.001
VA improvement or stability at T1, *n* (%)	18 (85.71)	17 (68.00)	0.188
VA improvement or stability at T2, *n* (%)	19 (90.48)	14 (56.00)	0.019
VA improvement or stability at T3, *n* (%)	18 (85.71)	2 (8.00)	<0.001
VA difference T1-T0 (mean)	4.86	2.56	0.326
VA difference T2-T0 (mean)	8.52	2.48	0.303
VA difference T3-T0 (mean)	8.71	-16.06	<0.001
Treatment-related features			
Total number of IVT	14.71±1.28	16.68±1.61	0.427
Time between the last IVT and T3, mo	18.1±2.63	17.6±2.83	0.931
OCT features at T0			
Type 1 MNV, *n* (%)	10 (47.62)	7 (28.00)	0.225
Type 2 MNV, *n* (%)	1 (4.76)	9 (36.00)	0.013
Type 3 MNV, *n* (%)	0	0	-
Mixed type MNV, *n* (%)	10 (47.62)	9 (36.00)	0.550
MNV diameter (μm)	2724.24±432.32	3134.16±514.89	0.215
CFT in patients without IRF (μm)	249±53.6	206.8±62.5	0.304
CFT in patients with IRF (μm)	287±75.8	345.85±61	0.292
ONL thickness (μm)	88.89±7.82	71.38±14.14	0.033
Presence of HRFs, (%)	20 (95.24)	25 (100)	0.456
PEDs maximum height (μm)	172.6±57.03	157.06±50	0.724
SRF with or without IRF, *n* (%)	19 (90.48)	17 (68.00)	0.084
SRF without IRF, *n* (%)	11 (52.38)	5 (20.00)	0.031
IRF, *n* (%)	9 (42.86)	20 (80.00)	0.014
IRF without SRF, *n* (%)	1 (4.76)	8 (32.00)	0.027
OCT features at T1 and T2			
Treatment response at T1, *n* (%)	12 (57.14)	12 (48.00)	0.568
Treatment response at T2, *n* (%)	19 (90.48)	18 (72.00)	0.151
HRFs reduction at T2, *n* (%)	15 (75.00)	15 (60.00)	0.538
OCT features at T3			
CFT at T3 (μm)	190.14±22.79	124.32±14.35	<0.001
ORT at T3, *n* (%)	1 (4.76)	4 (16.00)	0.357
Persistence of retinal cysts at T3, *n* (%)	2 (9.52)	6 (24.00)	0.260

Group A: Eyes without OCT retinal atrophy at 5y from nAMD diagnosis; Group B: Eyes developed OCT retinal atrophy at 5y from nAMD diagnosis. CFT: Central foveal thickness; HRFs: Hyperreflective foci; IRF: Intraretinal fluid; IVT: Intravitreal injection; MNV: Macular neovascularization; nAMD: Neovascular age-related macular degeneration; OCT: Optical coherence tomography; ONL: Outer nuclear layer; ORT: Outer retinal tubulation; PEDs: Retinal pigment epithelial detachments; SD: Standard deviation; SRF: Subretinal fluid; VA: Visual acuity.

Moreover, PEDs' maximum height (172.6±57.03 μm *vs* 157.06±50 μm; *P*=0.724), HRFs presence at T0 (95.24% *vs* 100%; *P*=0.456) and their reduction at T2 (75.00% *vs* 60.00%; *P*=0.538), the persistence of retinal cysts at T3 (9.52% *vs* 24.00%; *P*=0.260) and ORT at T3 (4.76% *vs* 16.00%; *P*=0.357) did not differ between atrophic and non-atrophic eyes (Table 1).

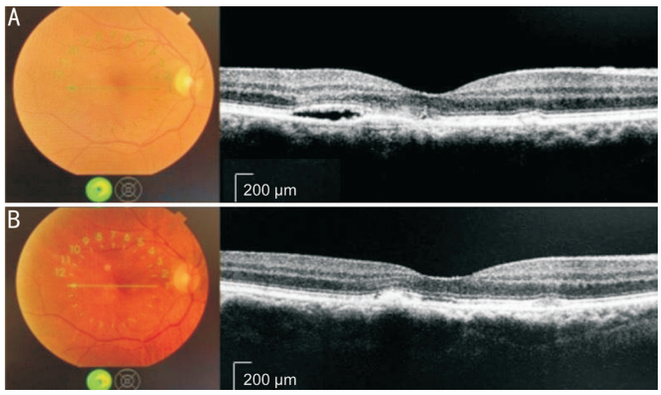

Figure 2 SS-OCT images of a participant belonging to group A A: OCT scan at T0; B: OCT scan at T3, showing no development of RA at 5y from nAMD diagnosis. nAMD: Neovascular age-related macular degeneration; SS-OCT: Swept source-optical coherence tomography; RA: Retinal atrophy.

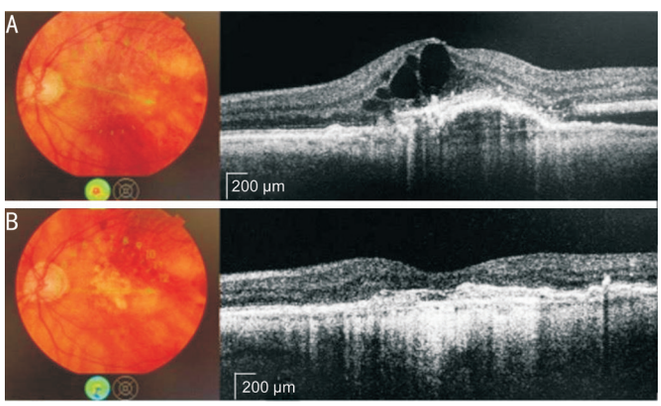

Figure 3 SS-OCT images of a participant belonging to group B A: OCT scan at T0; B: OCT scan at T3, showing retinal fluid regression, but the onset of RA. nAMD: Neovascular age-related macular degeneration; SS-OCT: Swept source-optical coherence tomography; RA: Retinal atrophy.

DISCUSSION

Our study showed that type 2 MNV, reduced ONL and CFT thickness, and the presence of IRF at baseline could be potential indicators of RA development in nAMD-naive patients treated with aflibercept. Over a follow-up period of 5y, 54.35% of the eyes progressed to new-onset RA, per CAM's criteria[13].

Demographic characteristics, including age, sex, and pseudophakia, had no impact on the development of RA at 5y. Instead, the presence of atrophy at T3 was influenced by morphological and functional factors (Table 1).

We found that the presence of IRF at diagnosis may suggest a negative prognosis in patients affected by nAMD, agreeing with the data available in the literature. The presence of IRF at baseline is related to a higher incidence of RA and poorer VA outcomes, as shown in both comparison of AMD treatments trials (CATT) and HARBOR studies[31,34,36,38,44-47]. Interestingly, we found that SRF at diagnosis was comparable between the two groups, suggesting no clear association with RA development after 5y of aflibercept treatment. In CATT and HARBOR studies SRF was found to be a protective factor against RA development after 2y of ranibizumab and bevacizumab administration. This discrepancy may be related to our sample size and the longer follow-up period. When SRF is present, the outer limiting membrane remains intact, acting as a barrier that prevents fluid from disrupting the outer retinal layers, unlike in the case of IRF[34,46]. Additionally, SRF typically occurs in locations distinct from IRF[48].

Thus, it has been theorized that subfoveal SRF might prevent the development of IRF in the same area, leading to foveal preservation with beneficial effects on macular health and VA[48-49]. According to this hypothesis, we found that IRF without SRF was significantly more frequent in eyes that developed RA, whereas SRF without IRF was more frequent in eyes without RA, suggesting a protective role of isolated SRF.

The MNV type appeared to affect RA development. The patients who developed RA had a higher percentage of type 2 MNV, rather than those who did not develop RA. This is consistent with a multicenter real-world study where type 1 MNV was less associated with RA and IRF, compared with type 2 MNV and mixed type MNV after 3y of anti-VEGF treatment in nAMD patients[50]. This result was confirmed also by the real-world Fight Retinal Blindness Registry data, where RA was more associated with type 2 MNV rather than type 1 MNV after a 5-year follow-up[51].

An explanation may be found considering the precise architecture of the internal retina, strictly regulated by the RPE-Bruch's membrane complex. Overcoming this barrier is crucial because intraretinal rather than subretinal collection of fluid spreads faster and is slower to re-adsorb, leading to a higher rate of RA[52].

Regarding treatment strategies, our data do not show significant results, but the number of IVTs does not appear to be related to the risk of de novo RA at 5y. The connection between the frequency and number of anti-VEGF injections and RA remains a topic of ongoing debate, with varying results across different studies. Some researchers report a higher rate of RA with fewer IVTs[53], while others find no link between the number of anti-VEGF injections and RA[38,54-55].

Conversely, some studies suggest that a higher number of injections is associated with an increased incidence of RA[56-57]. Although we cannot rule out a negative effect of antiangiogenic therapy, the adverse outcomes may also be attributed to the progression of the disease, which necessitates a higher number of IVTs.

Single retinal layers were analyzed to assess a potential link between their thickness and progression to RA. The appearance and integrity of the ONL on OCT are indicative

of photoreceptor function and health, with thinning reflecting photoreceptor degeneration. ONL thickness, as an OCT biomarker potentially indicative of RA development, has been reported in various chorioretinal disorders[58-60], including dry AMD[13]. However, its impact on nAMD is less understood, necessitating further research to determine its prognostic value. In our cohort, a thinner ONL at diagnosis appears to be a potential predictor of RA onset. Early thinning of the ONL may signal a more aggressive form of the disease, leading to a higher incidence of RA.

Furthermore, there was no significant difference in the presence of ORTs between the two study groups 5y post-diagnosis. The relationship between ORTs and RA has shown mixed results in various studies. While the CATT study found a correlation between the two, suggesting common risk factors for ORT and RA onset[61], the MAHALO cohort study found that the rate of atrophic area expansion was significantly lower in eyes with ORTs than those without[62]. In our cohort, the functional impact on eyes with RA at 5y was clear, with VA being 8.9±2.3 ETDRS chart letters, compared to 35.19±5.7 letters in non-atrophic eyes, as detailed in Table 1.

The strengths of our study include strict inclusion criteria and the extended duration of the observation period. This study has limitations, including the sample size and the main reliance on OCT for defining RA. While OCT is the reference method for assessing RA, its limited scan field suggests that future studies might benefit from incorporating multiple imaging modalities. Exploring different treatment regimens and other available anti-VEGFs is warranted. Moreover, due to the retrospective nature of the study we were not able to describe the impact of other covariates such as lifestyle habits on the development of RA.

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REFERENCES

1 Keenan TDL, Cukras CA, Chew EY. Age-related macular degeneration: epidemiology and clinical aspects. *Adv Exp Med Biol* 2021;1256:1-31.

2 GBD 2019 Blindness and Vision Impairment Collaborators, Vision Loss Expert Group of the Global Burden of Disease Study. Causes of blindness and vision impairment in 2020 and trends over 30 years, and prevalence of avoidable blindness in relation to VISION 2020: the Right to Sight: an analysis for the Global Burden of Disease Study. *Lancet Glob Health* 2021;9(2):e144-e160.

3 Colijn JM, Buitendijk GHS, Prokofyeva E, *et al*. Prevalence of age-related macular degeneration in Europe: the past and the future. *Ophthalmology* 2017;124(12):1753-1763.

4 Augood CA, Vingerling JR, de Jong PT, *et al*. Prevalence of age-related maculopathy in older Europeans: the European eye study (EUREYE). *Arch Ophthalmol* 2006;124(4):529-535.

5 Querques G, Amblard JC, Andrao A, *et al*. Expert consensus on geographic atrophy in the EU: a call for urgent policy action. *Ophthalmol Ther* 2024;13(4):867-881.

6 Li JQ, Welchowski T, Schmid M, *et al*. Prevalence and incidence of age-related macular degeneration in Europe: a systematic review and meta-analysis. *Br J Ophthalmol* 2020;104(8):1077-1084.

7 Barbabella F, Cela E, Socci M, *et al*. Active ageing in Italy: a systematic review of national and regional policies. *Int J Environ Res Public Health* 2022;19(1):600.

8 Bourne RR, Stevens GA, White RA, *et al*. Causes of vision loss worldwide, 1990-2010: a systematic analysis. *Lancet Glob Health* 2013;1(6):e339-49.

9 Nebbioso M, Lambiase A, Armentano M, *et al*. The complex relationship between diabetic retinopathy and high-mobility group box: a review of molecular pathways and therapeutic strategies. *Antioxidants* (*Basel*) 2020;9(8):666.

10 Flores R, Carneiro Â, Vieira M, *et al*. Age-related macular degeneration: pathophysiology, management, and future perspectives. *Ophthalmologica* 2021;244(6):495-511.

11 Laíns I, Wang JC, Cui Y, *et al*. Retinal applications of swept source optical coherence tomography (OCT) and optical coherence tomography angiography (OCTA). *Prog Retin Eye Res* 2021;84:100951.

12 Zheng F, Deng XF, Zhang Q, *et al*. Advances in swept-source optical coherence tomography and optical coherence tomography angiography. *Adv Ophthalmol Pract Res* 2023;3(2):67-79.

13 Sadda SR, Guymer R, Holz FG, *et al*. Consensus definition for atrophy associated with age-related macular degeneration on OCT: classification of atrophy report 3. *Ophthalmology* 2018; 125(4):537-548.

14 Banister K, Cook JA, Scotland G, *et al*. Non-invasive testing for early detection of neovascular macular degeneration in unaffected second eyes of older adults: EDNA diagnostic accuracy study. *Health Technol Assess* 2022;26(8):1-142.

15 Formica ML, Awde Alfonso HG, Palma SD. Biological drug therapy for ocular angiogenesis: anti-VEGF agents and novel strategies based on nanotechnology. *Pharmacol Res Perspect* 2021;9(2):e00723.

16 Hussain RM, Shaukat BA, Ciulla LM, *et al*. Vascular endothelial growth factor antagonists: promising players in the treatment of neovascular age-related macular degeneration. *Drug Des Devel Ther* 2021;15:2653-2665.

17 Augsburger M, Sarra GM, Imesch P. Treat and extend versus pro re nata regimens of ranibizumab and aflibercept in neovascular age-related macular degeneration: a comparative study. *Graefes Arch Clin Exp Ophthalmol* 2019;257(9):1889-1895.

18 Faudi E, Gauthier AS, Delbosc B, *et al*. To investigate treat and extend versus pro re nata regimen in neovascular age-related macular degeneration: results from the IDEM study. *Graefes Arch Clin Exp Ophthalmol* 2022;260(7):2149-2156.

19 Kvannli L, Krohn J. Switching from pro re nata to treat-and-extend regimen improves visual acuity in patients with neovascular age-related macular degeneration. *Acta Ophthalmol* 2017;95(7):678-682.

20 Victor AA, Putri YM. Pro re nata versus fixed aflibercept regimen for neovascular age-related macular degeneration: a systematic review and meta-analysis. *Int J Retina Vitreous* 2022;8(1):67.

21 Heier JS, Khanani AM, Quezada Ruiz C, *et al*. Efficacy, durability, and safety of intravitreal faricimab up to every 16 weeks for neovascular age-related macular degeneration (TENAYA and LUCERNE): two randomised, double-masked, phase 3, non-inferiority trials. *Lancet* 2022;399(10326):729-740.

22 Holash J, Davis S, Papadopoulos N, *et al*. VEGF-Trap: a VEGF blocker with potent antitumor effects. *Proc Natl Acad Sci U S A* 2002;99(17):11393-11398.

23 Rudge JS, Holash J, Hylton D, *et al*. VEGF Trap complex formation measures production rates of VEGF, providing a biomarker for predicting efficacious angiogenic blockade. *Proc Natl Acad Sci U S A* 2007;104(47):18363-18370.

24 Anguita R, Tasiopoulou A, Shahid S, *et al*. Correction to: a review of aflibercept treatment for macular disease. *Ophthalmol Ther* 2021;10(3):429.

25 Kanda A, Noda K, Saito W, *et al*. Aflibercept traps galectin-1, an angiogenic factor associated with diabetic retinopathy. *Sci Rep* 2015;5:17946.

26 Clearkin L, Ramasamy B, Wason J, *et al*. Anti-VEGF intervention in neovascular AMD: benefits and risks restated as natural frequencies. *BMJ Open Ophthalmol* 2019;4(1):e000257.

27 Volkmann I, Knoll K, Wiezorrek M, *et al*. Individualized treat-and-extend regime for optimization of real-world vision outcome and improved patients' persistence. *BMC Ophthalmol* 2020;20(1):122.

28 Garweg JG, Traine PG, Garweg RA, *et al*. Continued anti-VEGF treatment does not prevent recurrences in eyes with stable neovascular age-related macular degeneration using a treat-and-extend regimen: a retrospective case series. *Eye* (*Lond*) 2022;36(4):862-868.

29 Tan CS, Lim LW, Ngo WK, *et al*. Predictors of persistent disease activity following anti-VEGF loading dose for nAMD patients in Singapore: the DIALS study. *BMC Ophthalmol* 2020;20(1):324.

30 Chong Teo KY, Nguyen V, Gemmy Cheung CM, *et al*. The impact of disease activity on 5-year outcomes in patients undergoing treatment for neovascular age-related macular degeneration. *Retina* 2022;42(1):95-106.

31 Gillies MC, Daien V, Nguyen V, *et al*. Re: comparison of age-related macular degeneration treatments trials (CATT) research group, et al. five-year outcomes with anti-vascular endothelial growth factor treatment of neovascular age-related macular degeneration: the comparison of age-related macular degeneration treatments trials (*ophthalmology* 2016;123:1751-1761). *Ophthalmology* 2017;124(3):e31-e32.

32 Rofagha S, Bhisitkul RB, Boyer DS, *et al*. Seven-year outcomes in ranibizumab-treated patients in ANCHOR, MARINA, and HORIZON: a multicenter cohort study (SEVEN-UP). *Ophthalmology* 2013;120(11):2292-2299.

33 Hirabayashi K, Yu HJ, Wakatsuki Y, *et al*. OCT risk factors for development of atrophy in eyes with intermediate age-related macular degeneration. *Ophthalmol Retina* 2023;7(3):253-260.

34 Jaffe GJ, Ying GS, Toth CA, *et al*. Macular morphology and visual acuity in year five of the comparison of age-related macular degeneration treatments trials. *Ophthalmology* 2019;126(2):252-260.

35 Domalpally A, Danis RP, Trane R, *et al*. Atrophy in neovascular age-related macular degeneration: age-related eye disease study 2 report number 15. *Ophthalmol Retina* 2018;2(10):1021-1027.

36 Heesterbeek TJ, Lorés-Motta L, Hoyng CB, *et al*. Risk factors for progression of age-related macular degeneration. *Ophthalmic Physiol Opt* 2020;40(2):140-170.

37 Gupta OP. Ten-year follow-up of age-related macular degeneration in the age-related eye disease study: AREDS report No. 36. *Yearb Ophthalmol*. 2023

38 Sadda SR, Tuomi LL, Ding BY, *et al*. Macular atrophy in the HARBOR study for neovascular age-related macular degeneration. *Ophthalmology* 2018;125(6):878-886.

39 Banerjee I, de Sisternes L, Hallak JA, *et al*. Prediction of age-related macular degeneration disease using a sequential deep learning approach on longitudinal SD-OCT imaging biomarkers. *Sci Rep* 2020;10:15434.

40 Seddon JM, Rosner B. Validated prediction models for macular degeneration progression and predictors of visual acuity loss identify high-risk individuals. *Am J Ophthalmol* 2019;198:223-261.

41 Hanson RLW, Airody A, Sivaprasad S, *et al*. Optical coherence tomography imaging biomarkers associated with neovascular age-related macular degeneration: a systematic review. *Eye* (*Lond*) 2023;37(12):2438-2453.

42 Fragiotta S, Abdolrahimzadeh S, Dolz-Marco R, *et al*. Significance of hyperreflective foci as an optical coherence tomography biomarker in retinal diseases: characterization and clinical implications. *J Ophthalmol* 2021;2021:6096017.

43 Arrigo A, Aragona E, Battaglia O, *et al*. Outer retinal tubulation formation and clinical course of advanced age-related macular degeneration. *Sci Rep* 2021;11(1):14735.

44 Core JQ, Pistilli M, Hua PY, *et al*. Predominantly persistent intraretinal fluid in the comparison of age-related macular degeneration treatments trials. *Ophthalmol Retina* 2022;6(9):771-785.

45 Sadda SR, Abdelfattah NS, Lei JQ, *et al*. Spectral-domain OCT analysis of risk factors for macular atrophy development in the HARBOR study for neovascular age-related macular degeneration. *Ophthalmology* 2020;127(10):1360-1370.

46 Metrangolo C, Donati S, Mazzola M, *et al*. OCT biomarkers in neovascular age-related macular degeneration: a narrative review. *J Ophthalmol* 2021;2021:9994098.

47 Heier JS, Pieramici D, Chakravarthy U, *et al*. Visual function decline resulting from geographic atrophy: results from the chroma and spectri phase 3 trials. *Ophthalmol Retina* 2020;4(7):673-688.

48 Siedlecki J, Fischer C, Schworm B, *et al*. Impact of sub-retinal fluid on the long-term incidence of macular atrophy in neovascular age-related macular degeneration under treat & extend anti-vascular endothelial growth factor inhibitors. *Sci Rep* 2020;10(1):8036.

49 Albanese GM, Visioli G, Iannetti L, *et al*. Does choroidal thickness predict persistent subretinal fluid after rhegmatogenous retinal detachment repair? A retrospective study with fellow eye comparison. *Acta Ophthalmol* 2023;101(4):413-421.

50 Llorente-González S, Hernandez M, González-Zamora J, *et al*. The role of retinal fluid location in atrophy and fibrosis evolution of patients with neovascular age-related macular degeneration long-term treated in real world. *Acta Ophthalmol* 2022;100(2):e521-e531.

51 Sánchez-Monroy J, Nguyen V, Puzo M, *et al*. Subretinal fluid may protect against macular atrophy in neovascular age-related macular degeneration: 5 years of follow-up from Fight Retinal Blindness registry. *Acta Ophthalmol* 2023;101(4):457-464.

52 Gemenetzi M, Lotery AJ, Patel PJ. Risk of geographic atrophy in age-related macular degeneration patients treated with intravitreal anti-VEGF agents. *Eye* (*Lond*) 2017;31(1):1-9.

53 Mantel I, Dirani A, Zola M, *et al*. Macular atrophy incidence in anti-vascular endothelial growth factor-treated neovascular age-related macular degeneration: risk factor evaluation for individualized treatment need of ranibizumab or aflibercept according to an observe-and-plan regimen. *Retina* 2019;39(5):906-917.

54 Abdelfattah NS, Al-Sheikh M, Pitetta S, *et al*. Macular atrophy in neovascular age-related macular degeneration with monthly versus treat-and-extend ranibizumab: findings from the TREX-AMD trial. *Ophthalmology* 2017;124(2):215-223.

55 Guymer RH, Markey CM, McAllister IL, *et al*. Tolerating subretinal fluid in neovascular age-related macular degeneration treated with ranibizumab using a treat-and-extend regimen: fluid study 24-month results. *Ophthalmology* 2019;126(5):723-734.

56 Eshtiaghi A, Issa M, Popovic MM, *et al*. Geographic atrophy incidence and progression after intravitreal injections of anti-vascular endothelial growth factor agents for age-related macular degeneration: a Meta-Analysis. *Retina* 2021;41(12):2424-2435.

57 de Carlo Forest TE, Gill Z, Lisker-Cervantes A, *et al*. Association between quantitative and qualitative imaging biomarkers and geographic atrophy growth rate. *Am J Ophthalmol* 2024;264:168-177.

58 Ozdemir I, Eren A, Ersöz G. Outer nuclear layer thickness at the central fovea relation with symptom duration in central serous chorioretinopathy. *Int Ophthalmol* 2019;39(6):1323-1328.

59 Wang DL, Agee J, Mazzola M, *et al*. Outer retinal thickness and fundus autofluorescence in geographic atrophy. *Ophthalmol Retina* 2019;3(12):1035-1044.

60 Visioli G, Alisi L, Mastrogiuseppe E, *et al*. OCT biomarkers as predictors of visual improvement in diabetic macular edema eyes receiving dexamethasone implants. *Int J Retina Vitreous* 2023;9(1):35.

61 Lee JY, Folgar FA, Maguire MG, *et al*. Outer retinal tubulation in the comparison of age-related macular degeneration treatments trials (CATT). *Ophthalmology* 2014;121(12):2423-2431.

62 Hariri A, Nittala MG, Sadda SR. Outer retinal tubulation as a predictor of the enlargement amount of geographic atrophy in age-related macular degeneration. *Ophthalmology* 2015;122(2):407-413.