PROGRESSION OF MACULAR ATROPHY IN PATIENTS WITH NEOVASCULAR AGE-RELATED MACULAR DEGENERATION UNDERGOING ANTIVASCULAR ENDOTHELIAL GROWTH FACTOR THERAPY

NIZAR SALEH ABDELFATTAH, MD,*† HONGYANG ZHANG, MD,*†‡ DAVID S. BOYER, MD,§ SRINIVAS R. SADDA, MD*†

Purpose: To define the frequency and quantify the progression of macular atrophy (MA) in patients with neovascular age-related macular degeneration undergoing treatment with antivascular endothelial growth factor therapy for >2 years.

Methods: Fifty-four eyes of 46 patients (86.7 ± 6.8 years, 53.7% women) diagnosed with wet age-related macular degeneration were included in this retrospective study. Eyes that received photodynamic therapy or laser treatment were excluded. All eyes were imaged at baseline and after 2 years with the Cirrus spectral domain optical coherence tomography using a 512 × 128 macular cube scan protocol centered on the fovea. Optical coherence tomography en face fundus images were obtained for each 3-dimensional data set using the U.S. Food and Drug Administration–cleared Advanced RPE Analysis software, which automatically identifies atrophic areas by segmenting regions of increased reflectivity in en face choroidal slab images. Segmentation errors were manually corrected by trained Doheny Image Reading Center graders using a standardized grading protocol. The prevalence rates of atrophy at baseline and at 2-years follow-up and enlargement rates were computed. Baseline demographic factors and types and numbers of antivascular endothelial growth factor injections received over time were correlated with the development and enlargement of atrophy.

Results: Macular atrophy was noted at baseline in 32 (59.3%) eyes and progressed in all eyes over the next 2 years. Among the 28 eyes without atrophy at baseline, MA developed by 2 years in 6 eyes (21.4% of eyes without MA at baseline). Of note, 22 eyes (40.7% of overall cohort) never developed atrophy during the course of the study. Among eyes with atrophy at baseline, the annual growth rate of MA was found to be 0.89 ± 0.93 mm^2. A multiple regression analysis was performed to evaluate the influence of gender, age, smoking status, medication injected, and number of injections on MA. Except for the number of total injections (R^2 = 0.3, $P < 0.01$), the studied variables could not significantly predict development or progression of MA (F [0.73, 13] = 0.378, P = 0.86, R^2 = 0.05). However, the study was not powered to detect small effects.

Conclusion: Macular atrophy is a frequent finding in eyes with wet age-related macular degeneration both before and after antivascular endothelial growth factor therapy. The frequency of new optical coherence tomography–defined atrophy (21% at 2 years) after starting therapy was close to the rates reported in CATT, IVAN, and HARBOR. The rate of MA enlargement was positively correlated with the number of injections, but did not appear to be greater than that reported for atrophy in the absence of choroidal neovascularization.

RETINA 0:1–8, 2016

Age-related macular degeneration (AMD) has been the leading cause of blindness in the United States for many decades. Among individuals aged more than 75 years, geographic atrophy is present in 3.5%, with a prevalence of >22% in people aged >90.[1–3] Choroidal neovascularization (CNV) is the other manifestation of late AMD and, if left untreated, is frequently associated with rapid and severe vision loss because of progressive fibrosis and photoreceptor loss. The introduction of antiangiogenic therapies, in particular antivascular endothelial growth factor (anti-VEGF) drugs, to regress CNV has substantially reduced early vision loss from this mechanism, but long-term data from patients who were treated for ≥7 years suggests that atrophy and vision loss eventually ensue in most patients.[4] This has led to a revised disease concept that CNV may be an interval event in some patients, but that atrophy is the true end stage of the AMD disease process.[5] What has been less clear, however, is whether the mechanism and morphology of atrophy development with and without the presence of CNV are similar. For this reason, our group has preferred to use the more general term "macular atrophy," (MA) as opposed to geographic atrophy, to refer to atrophy in this setting. The role of anti-VEGF therapy in the development of this atrophy is also uncertain.

The CATT, IVAN, and HARBOR trials demonstrated that the development of new atrophy was a common occurrence (20–33%) even after only 2 years of starting therapy.[6–8] Consistent baseline risk factors for the development of atrophy across these trials included the presence of intraretinal cysts in the study eye and atrophy in the fellow eye, with the presence of subretinal fluid noted to be a protective factor.[6,9] These trials, however, were not specifically designed to assess the question of atrophy in the setting of CNV, and the methodology used for determining the presence of atrophy varied among the studies. As fundus autofluorescence (FAF) imaging was not collected, color photographs (CPs) and fluorescein angiograms were used to assess for atrophy.

Optical coherence tomography (OCT) has been suggested as a potentially useful method for the accurate and reproducible identification of atrophy in the setting of AMD, and U.S. Food and Drug Administration–cleared automated commercial software is available.[10] Although OCT data were available in CATT, IVAN, and HARBOR (only HARBOR had spectral domain OCT data in all subjects), analysis of atrophy by OCT has not yet been reported. Optical coherence tomography may be of particular benefit in the assessment of atrophy in the setting of CNV, as the features of exudation may obscure atrophy on color photograph and fluorescein angiogram, whereas the 3-dimensional visualization of the retinal layers on OCT may allow areas of suspected atrophy to be confirmed with greater specificity.

In this study, we use serial spectral domain OCT imaging to define the frequency and quantify the progression of MA in neovascular AMD patients undergoing treatment with anti-VEGF therapy over a 2-year period. We also evaluate potential risk factors for the development and progression of atrophy.

Methods

Description of Cohort

In this retrospective cohort study, subjects with neovascular AMD in one or both eyes were identified from the medical records of a private practice retina group (Retina-Vitreous Associates Medical Group) in Southern California. The study was approved by the Institutional Review Board of the David Geffen School of Medicine at the University of California in Los Angeles. The study adhered to the Health Insurance Portability and Accountability Act of 1996 and followed the tenets of the Declaration of Helsinki. An informed consent waiver was granted to allow retrospective analysis from the clinic. Inclusion criteria included a diagnosis of neovascular AMD in one or both eyes and a minimum of 3 annual sessions of OCT imaging using the Cirrus-HD OCT (Carl Zeiss Meditec Inc., Dublin, CA), obtained between January 2008 and January 2015. Eyes that received photodynamic therapy, laser treatment, intravitreal steroids, or pegaptanib at any point in their treatment course were excluded. A minimum of 3 annual OCT scans was required to ensure that all cases had at least a baseline OCT (designated as the visit just before the start of

From the *Doheny Image Reading Center, Doheny Eye Institute, Los Angeles, California; †Department of Ophthalmology, David Geffen School of Medicine at UCLA, Los Angeles, California; ‡Department of Ophthalmology, Guangdong General Hospital, Guangzhou, China; and §Retina Vitreous Associates Medical Group, Beverly Hills, California.

Presented in part as an oral presentation at the Annual Meeting of Association for Research in Vision and Ophthalmology, Denver, CO, May 3–7, 2015.

D. S. Boyer is a consultant for Aerpio, Alcon, Allergan, Bayer, Genentech, GS, KalVista, Neurotech, Nicox, Novartis, Ohr, Santaris, Santen, ThromboGenics, and Regeneron Pharmaceuticals. He receives honoraria from Alcon, Allergan, Genentech, Novartis, and Regeneron. S. R. Sadda is a consultant for Carl Zeiss Meditec, Optos, Allergan, Genentech, Alcon, Novartis, and Roche. He receives research funding from Carl Zeiss Meditec, Optos, Allergan, and Genentech. He also receives honoraria from Carl Zeiss Meditec, Optos, and Allergan. The remaining authors have no financial/conflicting interests to disclose.

Reprint requests: SriniVas R. Sadda, MD, 1355 San Pablo Street, Suite 100, Los Angeles, CA 90033; e-mail: ssadda@doheny.org

anti-VEGF therapy) and an OCT at 1 year and 2 years of follow-up (24 ± 2 months). Although 543 subjects met the initial criteria, OCT data were unfortunately archived in a nonretrievable format for 439 patients, and the required 3 annual visits were not available for another 58 patients, leaving only 46 subjects (54 eyes) for the final analysis.

Optical coherence tomography imaging was limited to the Cirrus OCT as this is the only device thus far for which U.S. Food and Drug Administration–cleared atrophy detection and measurement software are available (Advanced RPE Analysis, versions 6.0 and above). All patients underwent macular cube scans with 512 A-scans × 128 B-scans over a 6 × 6-mm square centered on the fovea. Raw OCT data (.dcm file format) for each subject were exported in a coded deidentified fashion for subsequent analysis at the Doheny Image Reading Center. Eyes with images of insufficient quality (signal strength <6) to permit reliable MA analysis (per the manufacturer's specification) were excluded. For eyes that did not have baseline atrophy, but developed atrophy by 24 months, OCTs at intervening visits were also assessed to determine the first visit at which atrophy appeared to allow progression rates to be defined.

All patients received treatment with intravitreal ranibizumab, aflibercept, and/or bevacizumab in the study eye, in accordance with the treating physician's preferred protocol (typically a treat-and-extend algorithm)—the agent received at each visit over the 24 months assessed in the study was recorded. Medical history, including hypertension, diabetes, coronary artery disease, and smoking status (current smoker, former smoker, or never smoked), were collected for each patient.

Grading and Analysis Protocol

Optical coherence tomography B-scans and the en face OCT fundus image were evaluated for the presence of atrophy. The U.S. Food and Drug Administration–cleared Advanced RPE Analysis software (Cirrus Software Version 7.0; Carl Zeiss Meditec) was used to automatically identify and quantify areas of atrophy from the en face choroidal slab images (Figure 1). The graders, however, did not rely solely on the software for this determination. The software identifies atrophy based on increased transmission of signal into the choroid, which creates a well-demarcated region of hyperreflectivity in the en face OCT image obtained from a slab through the choroid. Areas of retinal pigment epithelium (RPE) depigmentation without RPE loss, however, can also potentially result in increased choroidal reflectivity. Thus, the graders used specific reading center OCT criteria for atrophy to make this determination. These criteria include 1) thinning of the RPE band, 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, and 3) increased signal transmission into the choroid (only the latter is used by the automated software). If all 3 criteria were present, the atrophy was deemed to be "definite," whereas if only 2 were present, it was deemed to be "questionable." Only one criterion was insufficient to make a diagnosis of atrophy. Both questionable and definite atrophic areas were included in the total atrophy quantification. The graders manually corrected the segmented borders on the choroidal slab en face image based on these criteria, and the area of atrophy was recomputed by the software.

All gradings were performed twice by two independent graders, who were also masked to the previous visits for these cases. In cases of disagreement, the graders met in open adjudication and discussed the case to achieve a consensus result. If consensus could not be achieved, per reading center protocol, the case was reviewed by the reading center medical director (S.R.S.) to make the final determination.

Statistical Analysis

Baseline demographic factors and types and numbers of anti-VEGF injections received over time were correlated with the development and enlargement of atrophy. A multiple regression analysis was performed to evaluate the influence of gender, age, smoking status, baseline MA area, presence of atrophy in the fellow eye, medication(s) injected, length of time (in months) each medication was administered, and number of injections (of each medication and in total) on the development of MA and presence of subretinal fluid or subretinal hyperreflective material or cysts, or pigment epithelial detachment at baseline on the development of MA. Chi-square analysis was used to identify the relationship between presence of MA before initiation of anti-VEGF therapy and presence and progression of atrophy at 2 years. Statistical analysis was performed with IBM SPSS Statistics for Windows (Version 22.0; IBM Corp., Armonk, NY).

Results

Demographic Information

Forty-six patients (54 eyes) met the eligibility criteria and were included in this analysis; 25 (54.3%) were women and 21 (45.7%) were men. The mean age of patients was 86.7 years (SD, 6.8),

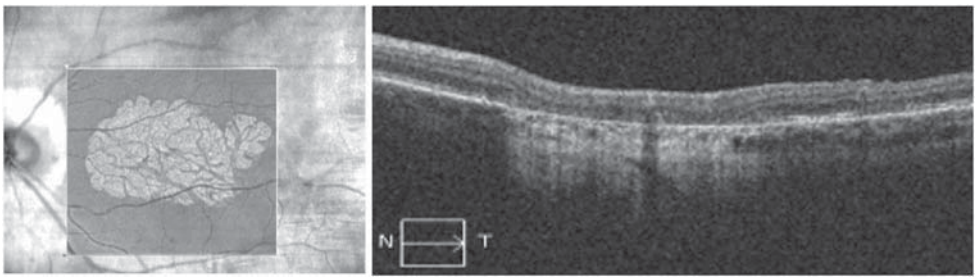

Fig. 1. En face OCT slab images generated through the choroid to facilitate identification of atrophy. Areas of atrophy seem as regions of hyperreflective transmission into the choroid.

and the median age was 88 years (range, 71–101 years). Patients were treated with various anti-VEGF agents: bevacizumab (1.25 mg/0.05 mL), ranibizumab (0.5 mg/0.05 mL), and/or aflibercept (2.0 mg/0.05 mL) per the treating physician's preference. Patients were primarily treated using a treat-and-extend protocol, and most patients were treated with only 1 agent during the course of the study (72%). Seventeen patients never smoked before (37%), whereas 22 patients were former smokers (47.8%), and none of the patients were current smokers. Six patients were noted to have diabetes (13%), 23 patients had hypertension (50%), and 21 had a history of coronary artery disease (45.7%). Table 1 summarizes patients' demographics and baseline ocular characteristics.

Macular Atrophy Analysis

Macular atrophy was noted at baseline in 25 (46.3%) eyes and progressed in all eyes over the next 2 years (Figure 2). Among the 29 eyes without atrophy at baseline, MA developed within 2 years in 8 eyes (27.6% of eyes without MA at baseline). Of note, 21 eyes (38.9% of overall cohort) never developed atrophy during the course of the study. Among eyes with atrophy at baseline, the mean baseline size was 3.52 mm^2 and the annual growth rate of MA was found to be 0.89 ± 0.93 mm^2. Among eyes with no atrophy at baseline but which developed atrophy over the next 24 months (8 eyes), the mean size at the time of first detection (i.e., criteria for atrophy were met) was 0.93 mm^2 and the annualized growth rate of MA was 0.45 ± 1.29 mm^2. In these 8 eyes, analysis of the intervening OCTs between baseline and month 24 showed that 62.5% of them (5 eyes) developed MA before month 12, 25% (2 eyes) developed MA between month 12 and month 18 visits, and 12.5% (1 eye) developed MA between the month 18 and month 24 visits.

Risk Factors and Macular Atrophy Progression

The total number of injections administered (regardless of which medication) was found to be positively correlated with MA annual enlargement rate (ER) ($R = 0.54$, $R^2 = 0.3$, $P < 0.01$). Total number of injections administered, however, was

Table 1. Patient Demographics and Baseline Ocular Characteristics

	Study Participants
Age, years	
Mean (SD)	86.74 (6.79)
Range	71–101
Sex, n (%)	
Men	21 (45.7)
Women	25 (54.3)
Smoking, %	
Current smoker	0
Former smoker	56.4
Never smoked	43.6
Comorbid conditions, %	
Hypertension	48.9
Diabetes mellitus	12.8
Ischemic heart disease	44.7
Number of total injections	
Median	9
Range	2–28
Number of bevacizumab injections	
Median	0
Range	0–15
Number of ranibizumab injections	
Median	3.5
Range	0–26
Number of aflibercept injections	
Median	0
Range	0–18
Duration of total follow-up, months	
Mean (SD)	24 (3)
Range	21–27
Length of treatment time under bevacizumab, months	
Mean (SD)	4 (6.8)
Range	0–24
Length of treatment time under ranibizumab, months	
Mean (SD)	11.02 (10.52)
Range	0–24
Length of treatment time under aflibercept, months	
Mean (SD)	2.37 (5.97)
Range	0–24

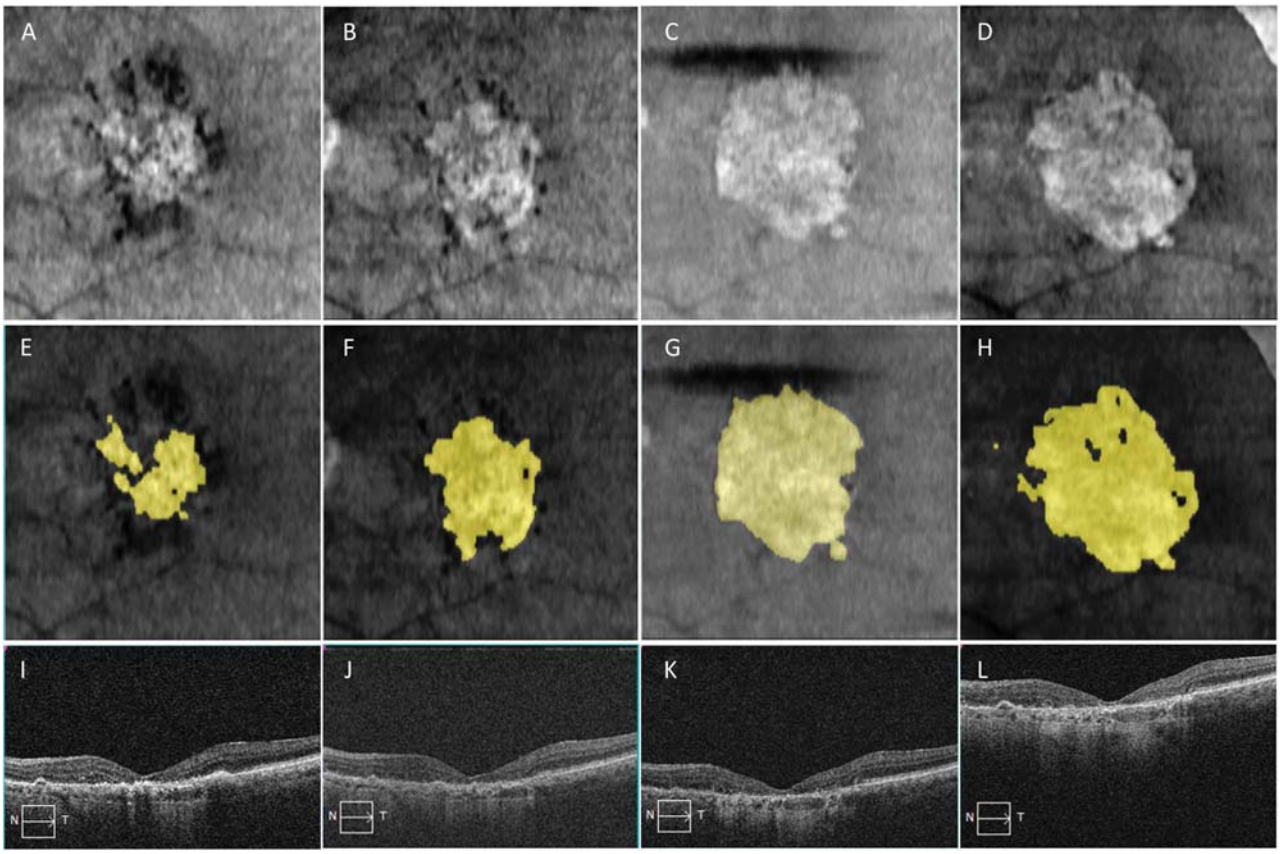

Fig. 2. Example of a patient with MA at baseline, which enlarged over a period of 3 years while receiving anti-VEGF therapy. Panels **A–D** show the progression of atrophy evident on the en face slab images, (**E–H**) show the segmentation of atrophy by the Advanced RPE Analysis software of Cirrus OCT, and (**I–L**) show the central B-scan through the atrophic lesion.

not significant for the development of new MA (R = 0.26, R^2 = 0.07, P = 0.17). Presence of coronary artery diseases, was found to be associated with development of MA after 2 years of anti-VEGF therapy (R = 0.48, R^2 = 0.23, $P < 0.05$). None of the other evaluated variables were found to predict development or progression of MA, F (0.73, 13) = 0.378, P = 0.86, R^2 = 0.05 (Tables 2 and 3).

Eyes with MA at baseline were found to have a more rapid enlargement of atrophy (by 2 years) than eyes without MA at baseline but which developed atrophy during the course of treatment, regardless of which anti-VEGF agent was used (ER, 0.89 ± 0.93 vs. 0.45 ± 1.29 mm^2, $P < 0.01$) (Φ = 0.90, P = 0.01).

As we had 3 data points (baseline, Year 1, and Year 2), we also looked to determine whether the ER was linear and similar between Year 1 and Year 2 in eyes that had MA at baseline. Among these eyes with baseline MA, the mean Year 1 ER (baseline to Year 1) was 1.21 ± 1.59 mm^2/year, which was higher than the mean Year 2 (Year 1 to Year 2) ER (0.6 ± 0.89 mm^2/year, r = 0.08, P = 0.1).

Discussion

In this study, we evaluated the presence and progression of atrophy in eyes undergoing treatment for neovascular AMD using serial spectral domain OCT. We observed that atrophy was frequently present (46.3%) at baseline in these individuals. This is a significantly higher rate than what was reported at baseline in CATT (7.3%).[6–8] However, it is important to note that atrophy determination in CATT was based on color photographs and fluorescein angiography. At baseline in the presence of active exudation, it may be very difficult to accurately identify the presence of atrophy in the absence of the 3-dimensional data and axial information provided by OCT—this may lead to a significant underestimation of the presence of baseline atrophy.

We also evaluated the progression or ER of atrophy, both in eyes that had atrophy at baseline and those that developed atrophy during the study period. The mean rate of atrophy enlargement was 0.89 mm^2/year (±SD, 0.93 mm^2) in eyes that had atrophy at baseline before

Table 2. Univariate Regression Analysis for Potential Risk Factors Affecting Annual MA ER

Dependent Variable: Annual ER	R	R^2	Significance
Age	0.02	0.000	0.93
Sex	0.13	0.02	0.52
Smoking	0.3	0.09	0.15
Diabetes mellitus	0.12	0.01	0.59
Hypertension	0.09	0.009	0.67
Coronary artery disease	0.12	0.02	0.56
Number of total injections	0.54	0.3	**0.01**
Number of bevacizumab injections	0.15	0.02	0.48
Number of ranibizumab injections	0.18	0.03	0.4
Number of aflibercept injections	0.2	0.04	0.32
Length of time under bevacizumab	0.09	0.01	0.64
Length of time under Ranibizumab	0.03	0.001	0.89
Length of time under aflibercept	0.19	0.04	0.36
Fellow eye atrophy	0.31	0.009	0.15
Baseline MA area	0.04	0.002	0.84

Bold values means Statistically significant, $P < 0.05$.

Table 3. Univariate Regression Analysis for Potential Risk Factors Affecting Development of MA by Month 24

Dependent Variable: MA Development by Month 24	R	R^2	Significance
Age	0.07	0.005	0.72
Sex	0.18	0.03	0.36
Smoking	0.39	0.15	0.06
Diabetes mellitus	0.36	0.13	0.09
Hypertension	0.13	0.02	0.55
Coronary artery disease	0.48	0.23	**0.02**
Number of total injections	0.26	0.07	0.17
Number of bevacizumab injections	0.04	0.001	0.85
Number of ranibizumab injections	0.16	0.03	0.41
Number of aflibercept injections	0.27	0.08	0.15
Length of time under bevacizumab	0.05	0.002	0.8
Length of time under ranibizumab	0.11	0.01	0.58
Length of time under aflibercept	0.18	0.03	0.36
Fellow eye atrophy	0.04	0.002	0.83
Presence of subretinal fluid at baseline	0.22	0.05	0.25
Presence of subretinal hyperreflective material at baseline	0.13	0.02	0.52
Presence of intraretinal cysts at baseline	0.02	0.001	0.91
Presence of pigment epithelial detachment at baseline	0.29	0.09	0.12

beginning therapy, and the annualized rate was 0.45 ± 1.29 mm^2/year in eyes that developed atrophy during the next 24 months after starting anti-VEGF therapy. The rates observed in our study appear comparable with those reported in previous nonneovascular AMD atrophy studies. For example, in the Beaver Dam Eye study,[11] a population-based study, the amount of atrophy enlargement over a period of 5 years was found to be 6.4 mm^2 or 1.28 mm^2/year. In a prospective natural history study, Sunness et al,[12] however, observed faster growth with a median ER of 2.1 mm^2/year. These studies, however, used color photographs for atrophy assessment. Atrophy studies based on FAF imaging have observed growth rates of 1.52 mm^2/year.[13] Using OCT, Yehoshua et al[14] observed a growth rate similar to our study, with a mean enlargement of 1.2 mm^2/year.

The considerable variance in growth rates of atrophy reported in the literature is consistent with the large SD in growth rate observed in our study and reflects the variability in the disease process. One factor that has been shown to be an important confounder in the rate of growth is the baseline size of the lesion, with faster growth seen in larger lesions.[14] This is not surprising because atrophic lesions expand at their border and larger lesions will have larger circumferences. To account for this confounder related to baseline lesion size, researchers have proposed adjustments such as the use of a square root transformation or the circularity index.[15,16] Unfortunately, most of the previous studies providing information on progression rates did not include baseline lesion sizes for the individual cases, thus making it difficult to apply corrections to allow comparisons between studies. Because most commonly used spectral domain OCT scanning protocols (including the Cirrus protocols used in our study) generally only cover a 20° field of view, they will be biased to feature smaller lesions than studies using color photos or FAF, which typically use at least a 30° field of view. Indeed, the mean baseline size of the atrophic lesion in our study was 3.52 mm^2, compared with a mean baseline lesion size of 10.4 mm^2 in the study by Sunness et al, though ours is in the setting of neovascular disease. The atrophic lesion was seen to extend to the border of the scan area in 32.3% of cases. In addition, it is possible that some cases had atrophy only in areas outside the central 6 mm. Failure to include all atrophy within the scanning window would presumably lead to an underestimate of the MA area. However, the ER for atrophic lesions seemed to be similar irrespective of whether these cases with atrophy extending to the scan

border were included (ER with cases included = 0.89 mm^2/year vs. 0.79 mm^2/year with cases excluded). Of note, the rate of atrophy enlargement observed in our study was greater than that reported in CATT (0.43 mm^2/year), though this is probably attributable to the use of different imaging methods for atrophy assessment.[17]

Although we evaluated a number of potential factors, we were only able to identify number of injections and coronary artery disease as relevant to the development or progression of atrophy. Our findings would appear to be consistent with the study by Lois et al,[18] which observed a statistically significant association between number of anti-VEGF injections received and progression of atrophy at follow-up (odds ratio = 1.35, 95% confidence interval = 1.05–1.73, $P = 0.02$). However, that study featured variable follow-up with intervals as short as 3 months. In addition, the study by Lois et al[18] excluded eyes with RAP lesions, which may be more prone to develop RPE atrophy.[19] In our study, we found that follow-up of $\leq$1 year could have missed the development of new atrophy in 37.5% of cases. However, among those cases that had MA by month 24, 87.5% did develop MA by 18 months. The ER, however, did not seem to be linear through the 2-year period, with a faster rate in Year 1 compared with Year 2. We also attempted to evaluate the relationship between the specific anti-VEGF agent and the development of atrophy. In the reanalysis of the CATT study data, the CATT investigators observed a higher risk of atrophy in ranibizumab-treated patients compared with bevacizumab-treated patients – this was not observed in IVAN. This was difficult to analyze in our study as many patients were switched between agents during the course of their therapy. We did, however, attempt to correlate the number of injections of each agent received with the development and progression of atrophy but did not find any significant association. Duration of time receiving each type of injection, baseline atrophy area, and presence of fellow eye atrophy were also not associated with the development or progression of atrophy. Presence of subretinal fluid, subretinal hyperreflective material, or pigment epithelial detachment at baseline visits was not associated with the development of atrophy in this cohort. We did not, however, study whether choroidal thickness or retinal angiomatous proliferation were associated with atrophy. In addition, given our sample size, our study was not powered to detect risk factors with small effects. Nonetheless, the fact that atrophy ERs are not higher than GA studies in nonneovascular AMD would seem to argue against the concern that anti-VEGF agents are directly promoting atrophy.

Our study is not without limitations, in addition to the sample size. First, this is a retrospective study and prone to ascertainment bias. Ascertainment bias is a particular concern in our cohort because only a small proportion of cases had retrievable OCT data because of problems with the archival format. We would not expect, however, that a technical problem with OCT retrieval should yield a systematic bias in a particular direction. Second, we relied exclusively on OCT for our determinations. Although OCT may be less confounded by obscuring effects from exudative features (compared with color and fluorescein angiogram), a multimodal approach integrating all modalities (including FAF) may have been more sensitive and specific. Unfortunately, as this analysis was retrospective, such a data set was not available. However, use of other modalities may have introduced an unwanted bias into our analysis. We know that identifying and segmenting atrophy from color photographs may be challenging and only moderately reproducible.[20–24] Fundus autofluorescence assessment of atrophy is also not without concerns, as some have questioned whether the absence of autofluorescence always translates into corresponding loss of retinal pigment epithelium or photoreceptors.[25] The blocking effect of macular pigment also makes foveal involvement by atrophy difficult to assess on FAF imaging.[14] In addition, the presence of fibrosis may further confound assessment of atrophy by FAF, as these areas may also appear hypoautofluorescent because of blockage. Optical coherence tomography, however, is not immune to confounders for detecting atrophy. Despite the cross-sectional/3-dimensional information, exudation and loss of signal may make it difficult to assess the status of the photoreceptor and RPE bands in some cases. Finally, another limitation of our study is the lack of preexisting consensus OCT criteria for atrophy despite the availability of U.S. Food and Drug Administration–cleared algorithms for measuring atrophy in OCT. Correlative studies have shown good agreement between OCT and FAF assessments of atrophy[26]; however, it is not clear that this is an adequate validation as the gold standard for atrophy assessment is uncertain.

Our study also has several strengths, which should also be considered including the use of masked, independent, certified, experienced reading center OCT graders; a standardized grading protocol and definition for atrophy; and demonstration of high levels of grading reproducibility.

In summary, MA is a frequent finding in eyes with neovascular AMD both before and after anti-VEGF therapy. The frequency of new atrophy (27.6% at 2 years) after starting therapy was somewhat higher, but

not dissimilar to the values reported in CATT, IVAN, and HARBOR. In addition, the rate of atrophy progression in our study (0.89 ± 0.93 mm^2) was higher than that reported by CATT and not higher than the ER of atrophy observed in nonneovascular AMD GA natural history studies. Eyes that had atrophy at baseline, however, did seem to show faster progression of atrophy, especially in the first year of treatment. Although larger prospective studies will be necessary to confirm our findings, our results do highlight the potential utility of OCT for assessing atrophy in this setting.

Key words: aflibercept, bevacizumab, choroidal neovascularization, geographic atrophy, macular degeneration, neovascular AMD, optical coherence tomography, ranibizumab, treat-and-extend protocol, wet macular degeneration.

References

1. Klein R, Klein BE, Franke T. The relationship of cardiovascular disease and its risk factors to age-related maculopathy. The Beaver Dam Eye Study. Ophthalmology 1993;100:406–414.
2. Vingerling JR, Dielemans I, Hofman A, et al. The prevalence of age-related maculopathy in the Rotterdam Study. Ophthalmology 1995;102:205–210.
3. Hirvelä H, Luukinen H, Läärä E, et al. Risk factors of age-related maculopathy in a population 70 years of age or older. Ophthalmology 1996;103:871–877.
4. Bhisitkul RB, Mendes TS, Rofagha S, et al. Macular atrophy progression and 7-year vision outcomes in subjects from the ANCHOR, MARINA, and HORIZON studies: the SEVEN-UP study. Am J Ophthalmol 2015;159:915–924.e2.
5. Sarks JP, Sarks SH, Killingsworth MC. Evolution of geographic atrophy of the retinal pigment epithelium. Eye (Lond) 1988;2:552–577.
6. Martin DF, Maguire MG, Fine SL, et al. Ranibizumab and bevacizumab for treatment of neovascular age-related macular degeneration: two-year results. Ophthalmology 2012;119:1388–1398.
7. Chakravarthy U, Harding SP, Rogers CA, et al. Ranibizumab versus bevacizumab to treat neovascular age-related macular degeneration: one-year findings from the IVAN randomized trial. Ophthalmology 2012;119:1399–1411.
8. Busbee BG, Ho AC, Brown DM, et al. Twelve-month efficacy and safety of 0.5 mg or 2.0 mg ranibizumab in patients with subfoveal neovascular age-related macular degeneration. Ophthalmology 2013;120:1046–1056.
9. Fleckenstein M, Schmitz-Valckenberg S, Adrion C, et al. Progression of age-related geographic atrophy: role of the fellow eye. Investig Ophthalmol Vis Sci 2011;52:6552–6557.
10. Chen Q, de Sisternes L, Leng T, et al. Semi-automatic geographic atrophy segmentation for SD-OCT images. Biomed Opt Express 2013;4:2729–2750.
11. Klein R, Meuer SM, Knudtson MD, Klein BEK. The epidemiology of progression of pure geographic atrophy: the Beaver Dam Eye Study. Am J Ophthalmol 2008;146:692–699.
12. Sunness JS, Margalit E, Srikumaran D, et al. The long-term natural history of geographic atrophy from age-related macular degeneration: enlargement of atrophy and implications for interventional clinical trials. Ophthalmology 2007;114:271–277.
13. Holz FG, Bindewald-Wittich A, Fleckenstein M, et al. Progression of geographic atrophy and impact of fundus autofluorescence patterns in age-related macular degeneration. Am J Ophthalmol 2007;143:463–472.
14. Yehoshua Z, Rosenfeld PJ, Gregori G, et al. Progression of geographic atrophy in age-related macular degeneration imaged with spectral domain optical coherence tomography. Ophthalmology 2011;118:679–686.
15. Feuer WJ, Yehoshua Z, Gregori G, et al. Square root transformation of geographic atrophy area measurements to eliminate dependence of growth rates on baseline lesion measurements: a reanalysis of age-related eye disease study report no. 26. JAMA Ophthalmol 2013;131:110–111.
16. Domalpally A, Danis RP, White J, et al. Circularity index as a risk factor for progression of geographic atrophy. Ophthalmology 2013;120:2666–2671.
17. Grunwald JE, Pistilli M, Ying GS, et al. Growth of geographic atrophy in the comparison of age-related macular degeneration treatments trials. Ophthalmology 2015;122:809–816.
18. Lois N, McBain V, Abdelkader E, et al. Retinal pigment epithelial atrophy in patients with exudative age-related macular degeneration undergoing anti-vascular endothelial growth factor therapy. Retina 2013;33:13–22.
19. McBain VA, Kumari R, Townend J, Lois N. Geographic atrophy in retinal angiomatous proliferation. Retina 2011;31:1043–1052.
20. Sunness JS, Ziegler MD, Applegate CA. Issues in quantifying atrophic macular disease using retinal autofluorescence. Retina 2006;26:666–672.
21. Scholl HPN, Peto T, Dandekar S, et al. Inter- and intra-observer variability in grading lesions of age-related maculopathy and macular degeneration. Graefes Arch Clin Exp Ophthalmol 2003;241:39–47.
22. Pirbhai A, Sheidow T, Hooper P. Prospective evaluation of digital non-stereo color fundus photography as a screening tool in age-related macular degeneration. Am J Ophthalmol 2005; 139:455–461.
23. Davis MD, Gangnon RE, Lee LY, et al. The Age-Related Eye Disease Study severity scale for age-related macular degeneration: AREDS Report No. 17. Arch Ophthalmol 2005;123: 1484–1498.
24. Sunness JS, Bressler NM, Tian Y, et al. Measuring geographic atrophy in advanced age-related macular degeneration. Invest Ophthalmol Vis Sci 1999;40:1761–1769.
25. Hwang JC, Chan JWK, Chang S, Smith RT. Predictive value of fundus autofluorescence for development of geographic atrophy in age-related macular degeneration. Investig Ophthalmol Vis Sci 2006;47:2655–2661.
26. Lujan BJ, Rosenfeld PJ, Gregori G, et al. Spectral domain optical coherence tomographic imaging of geographic atrophy. Ophthalmic Surg Lasers Imaging 2009;40:96–101.