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Incidence and Growth of Geographic Atrophy during 5 Years of Comparison of Age-Related Macular Degeneration Treatments Trials

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Purpose: To estimate the incidence, size, and growth rate of geographic atrophy (GA) during 5 years of follow-up among participants in the Comparison of Age-Related Macular Degeneration Treatments Trials (CATT).

Design: Cohort within a clinical trial.

Participants: Participants included in CATT.

Methods: A total of 1185 CATT participants were randomly assigned to ranibizumab or bevacizumab treatment and to 3 treatment regimens. Participants were released from protocol treatment at 2 years and examined at approximately 5 years (N = 647). Two masked graders assessed the presence and size of GA in digital color photographs (CPs) and fluorescein angiograms (FAs) taken at baseline and years 1, 2, and 5. Cox proportional hazard models were used to identify risk factors for incidence of GA. Annual change in the square root of the total area of GA was the measure of growth. Multivariate linear mixed models including baseline demographic, treatment, and ocular characteristics on CP/FA and optical coherence tomography (OCT) as candidate risk factors were used to estimate adjusted growth rates, standard errors (SEs), and 95% confidence intervals (CIs).

Main Outcome Measures: Geographic atrophy incidence and growth rate.

Results: Among the 1011 participants who did not have GA at baseline and had follow-up images gradable for GA, the cumulative incidence was 12% at 1 year, 17% at 2 years, and 38% at 5 years. At baseline, older age, hypercholesterolemia, worse visual acuity, larger choroidal neovascularization (CNV) area, retinal angiomatous proliferation (RAP) lesion, GA in the fellow eye, and intraretinal fluid were associated with a higher risk of incident GA. Thicker subretinal tissue complex and presence of subretinal fluid were associated with less GA development. The overall GA growth rate was 0.33 mm/year (SE, 0.02 mm/year). Eyes treated with ranibizumab in the first 2 years of the clinical trial had a higher growth rate than eyes treated with bevacizumab (adjusted growth rate, 0.38 vs. 0.28 mm/year; $P = 0.009$). Geographic atrophy in the fellow eye, hemorrhage, and absence of sub–retinal pigment epithelium fluid at baseline were associated with a higher growth rate.

Conclusions: Development of GA is common 5 years after initiating therapy. Several risk factors identified at 2 years of follow-up persist at 5 years of follow-up. *Ophthalmology 2017;124:97-104 © 2016 by the American Academy of Ophthalmology*

*Supplemental material is available at www.aaojournal.org.

Age-related macular degeneration (AMD) is one of the most common causes of visual impairment in the United States.[1] In the later stages of AMD, visual acuity decreases because of the development of choroidal neovascularization (CNV) and geographic atrophy (GA).

We previously reported that during 2 years of follow-up in the Comparison of AMD Treatments Trials (CATT), a randomized clinical trial of ranibizumab and bevacizumab and of 3 different dosing regimens for the treatment of neovascular AMD, approximately 18% of eyes developed GA.[2] Eyes treated with ranibizumab had a higher risk of GA development than eyes treated with bevacizumab, and eyes treated monthly had a higher risk of GA development than eyes treated pro re nata (PRN).[2] At 2 years of follow-up, the growth rate of GA was higher for eyes treated with ranibizumab (0.49 mm/year) than eyes treated with bevacizumab (0.37 mm/year; $P = 0.03$).[3] Study eyes with CNV away from the fovea, predominantly classic lesions, or epiretinal membrane, and fellow eyes with GA also had higher GA growth rates.[3] In this article, we summarize the GA incidence, size, and growth rate during 5 years of follow-up participants of the CATT study. These additional 3 years of follow-up allow more time for assessment of pathology development and GA growth, and therefore can uncover additional information.

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Methods

The CATT participants and methods have been described in previous reports.[2–7] There were 1185 participants in the CATT who had AMD and untreated CNV or retinal neovascularization in the study eye. Participants were enrolled in 43 clinical centers in the United States between February 2008 and December 2009. Inclusion criteria have been described.[4,6] Participants at baseline had neovascularization or sequelae of neovascularization in the fovea and visual acuity between 20/25 and 20/320. In addition, they had evidence of leakage on fluorescein angiography (FA) and fluid on optical coherence tomography (OCT). Participants with GA in the foveal center of the study eye were excluded from the study. The study was approved by an institutional review board associated with each center and was compliant with the Health Insurance Portability and Accountability Act regulations. All participants provided written informed consent. The CATT was registered with ClinicalTrials.gov (NCT00593450).

Participants were randomly assigned to 1 of 4 treatment groups defined by drug (ranibizumab or bevacizumab) and by dosing regimen (monthly or PRN). At 1 year, participants initially assigned to monthly treatment retained their drug assignment but were reassigned randomly to monthly or PRN treatment. Participants were released from the study treatment protocol at the end of 2 years and were recalled for an eye examination at approximately 5 years (5.5±0.6 years).

At enrollment, participants provided a medical history and had bilateral color photography (CP) of the fundus, FA, and time-domain OCT. Follow-up examinations were scheduled every 28 days for 2 years. Color fundus photography and FA were performed again at 1, 2, and 5 years. Optical coherence tomography was performed monthly in PRN-treated eyes and at 1, 2, 3, 6, 12, 18, and 24 months and 5 years in eyes treated monthly. Morphologic features of study eyes on CP and GA at baseline and follow-up were evaluated at the CATT Fundus Photograph Reading Center. Two trained and certified readers graded images for signs of GA in the study eye and the fellow eye, in addition to features of neovascularization in the study eye.[4,6] Discrepancies between the 2 graders were adjudicated. Intergrader and grade/regrade reliability have been reported.[6]

The detailed protocol of GA assessment has been described.[2,3] Both CP and FA were used to evaluate GA. A diagnosis of GA required the presence within the macular vascular arcades of 1 or more areas, ≥250 μ in the longest linear dimension, of partial or complete depigmentation on the CP that had 1 or more of the following additional characteristics: sharply demarcated borders seen on CP or FA, visibility of underlying choroidal vessels, excavated or punched out appearance on stereoscopic viewing of CP or FA, or uniform hyperfluorescence bounded by sharp borders on late-phase angiography. The OCT scans were not used to identify GA. Non-GA was defined as an area of atrophy that did not meet the definition of GA.

ImageJ software[8] was used to measure the area of each individual GA lesion on a selected FA image. The boundaries were drawn manually on the same image by 2 independent graders. A scaling factor for this image was determined by measuring the distance between the center of the fovea and the center of the disc; this distance was considered to be 4.5 mm. When discrepancies in GA area between graders were beyond 50% or 2 mm^2, an open adjudication between the 2 graders was performed, and the area was redrawn or one of the previous drawings was accepted as the final measurement. Otherwise, the average of the areas determined by the 2 graders was used as the area measurement. The distance from the foveal center to the nearest GA border also was determined using ImageJ. Finally, for each individual GA lesion, an assessment was performed to determine whether the GA location was clearly outside the area of the total CNV lesion apparent at any previous visit or the current visit. The square root transformation of the area was used for all analyses of size and growth because this growth rate measurement assessment is less dependent on the GA lesion size.[3,9] Total CNV lesion included CNV, contiguous hemorrhage, serous pigment epithelium detachment, scar, blocked fluorescence, non-GA, and GA. For this project, we regraded photographs from CATT study eyes that had GA at 1 or more study visits. For each of these eyes, all study visit photographs were simultaneously examined for the presence of GA. Whenever GA was detected at the year 1, 2, or 5 visits, the previous visits were carefully analyzed for the presence of GA. The methodology of this study, which emphasized the quantitative and qualitative assessment of GA, in which all visits of a participant were assessed at the same time, yielded somewhat different results from those shown in our previous articles.[4,6] There were 19 eyes that had GA on the original grading but were reassessed as not having GA at baseline and year 1, 2, or 5 visits in the new grading performed for the current study.

The following methods were described by DeCroos et al.[10] Two certified readers at the CATT OCT Reading Center independently analyzed all baseline scans for morphologic characteristics. Readers determined whether there was intraretinal fluid, subretinal fluid, or fluid external to the retinal pigment epithelium (RPE). When fluid was present, readers noted the location of fluid relative to the foveal center. They also identified the presence of subretinal hyper-reflective material, epiretinal membrane, and vitreomacular attachment. Readers quantified the thickness at the foveal center of the (1) retina, (2) subretinal fluid, and (3) subretinal tissue complex (defined as the distance from the outer retinal photoreceptor border to Bruch's membrane, excluding subretinal fluid). Disagreements between readers were arbitrated by an independent senior reader.

Three single nucleotide polymorphisms (SNPs) previously associated with the risk of developing AMD were evaluated for association with the incidence and growth of GA: (1) complement factor H Y402H (rs1061170), (2) age-related maculopathy susceptibility 2 (also called "*LOC387715*") A69S (rs10490924), and (3) complement component 3 R80G (rs2230199).[11,12] One SNP previously associated with protection against GA, Toll-like receptor 3 (rs3775291), also was evaluated.[13]

Statistical Methods

Geographic atrophy detected on CP or FA at baseline was considered to be prevalent GA. Geographic atrophy that was not detected at baseline but was present at 1, 2, or 5 years was considered as incident GA. The analysis included all participants except those with ungradable photographs at baseline or with all ungradable or missing follow-up photographs. Candidate risk factors for incident GA and GA growth included (1) patient factors: age, sex, smoking, hypertension, use of dietary supplements, visual acuity in the study eye; (2) GA characteristics: area, number and location of lesions, distance from the fovea, presence of GA in the fellow eye; (3) features on fundus photography: total CNV lesion size, CNV type and location, retinal angiomatous proliferation (RAP) lesion, hemorrhage; (4) features on OCT: intraretinal fluid, subretinal fluid, sub-RPE fluid, subretinal hyper-reflective material, epiretinal membrane; and (5) treatment characteristics in the first 2 years of the clinical trial: drug (ranibizumab or bevacizumab), regimen (monthly for 2 years, monthly in the first year, and PRN in the second year, or PRN for 2 years).

To account for deaths and losses to follow-up, we used the Kaplan–Meier method to estimate cumulative incidence and the Cox proportional hazard model to determine the risk factors for incident GA and to calculate the hazard ratios and their 95% confidence

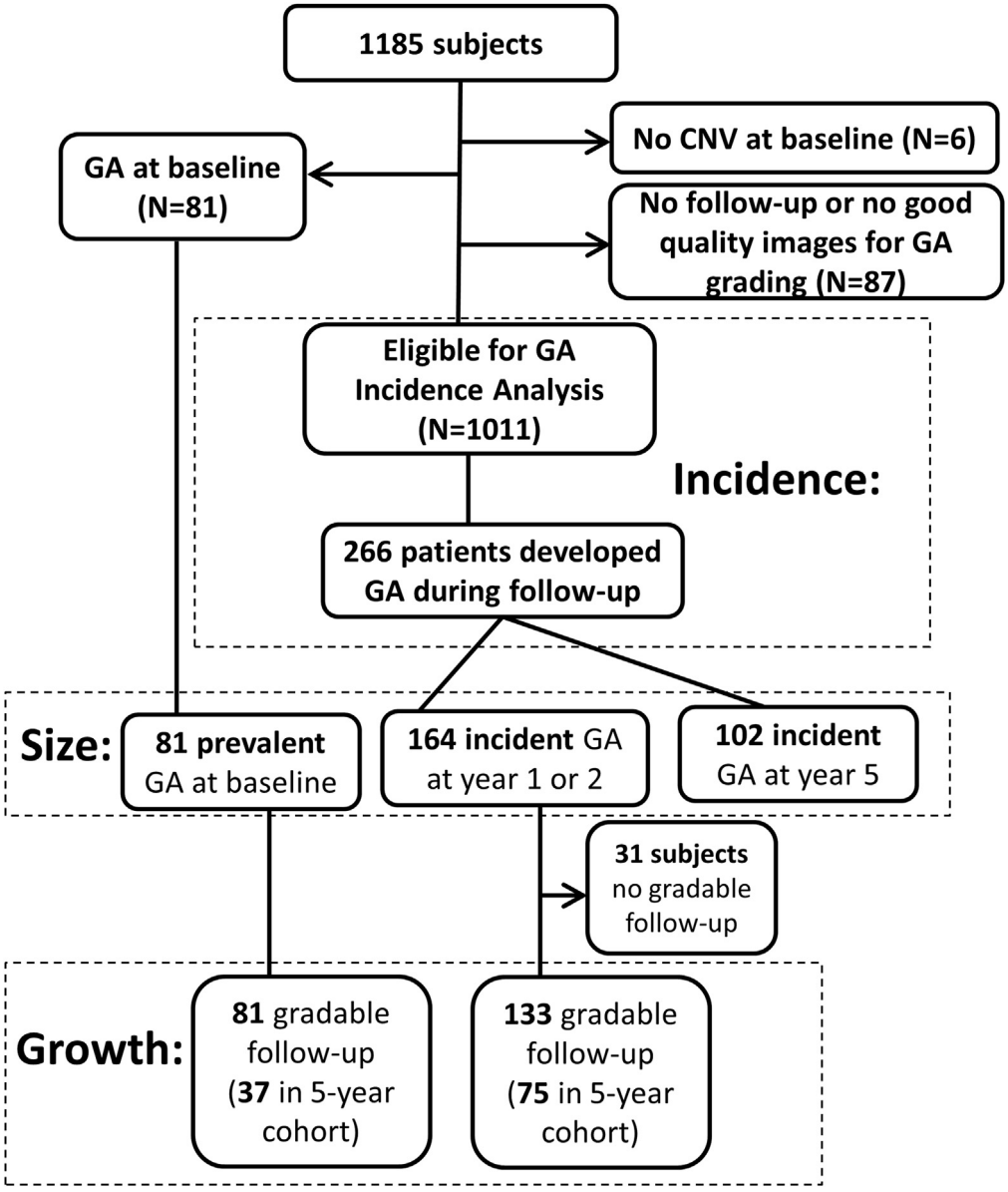

Figure 1. Flowchart describing the study participants. CNV = choroidal neovascularization; GA = geographic atrophy.

intervals (CIs). We used linear mixed-effects models to estimate the GA growth rate. In these mixed-effects models, the GA area was modeled as a function of time (relative to the first observation of GA), candidate risk factor(s), and interaction term(s) of risk factor(s) with time. By modeling slopes and intercepts as random effects within subjects, we calculated the mean growth rate and 95% CIs for the difference in mean growth rate between groups. Each risk factor was first evaluated by univariate analysis (without adjustment for other covariates). The risk factors with a *P* value less than 0.20 in the univariate analysis were included in the multivariate analysis. The final multivariate model was created by applying a backward selection procedure that retained only those risk factors with a *P* value less than 0.05, with the exception that drug and dosing regimen were included in all multivariate models.

To determine whether 4 SNPs were associated with incident GA, both univariate analysis and multivariate analyses (with adjustment by age, sex, and smoking status) were performed for each SNP. The linear trend *P* value was calculated from logistic regression by counting the number of risk alleles of the genotype (0, 1, or 2). The approach of controlling the false discovery rate was used to correct *P* values for testing of multiple SNPs.[14] All statistical analyses were performed with SAS software version 9.4 (SAS Institute Inc., Cary, NC).

Results

Among 1185 participants, 1183 had evaluable photographs at baseline, 1061 at year 1, 1012 at year 2, and 517 at year 5. Of these, 81 had GA at baseline, 122 developed GA during year 1, 42 developed GA during year 2, and 102 developed GA between the year 2 and the year 5 visit (Fig 1). Among the participants with GA, growth of GA could be determined from 2 or more visits in 81 prevalent cases and in 114 cases in which GA was detected at year 1 and 19 at year 2.

Table 1. Characteristics at First Observation of Prevalent and Incident Geographic Atrophy among All Trial Participants by Drug Assigned in the Clinical Trial

					Incident GA					
		Prevalent GA (Baseline)			Year 1 or 2			Year 5		
Characteristics	Drug Assigned	N	Mean (SD)	P Value	N	Mean (SD)	P Value	N	Mean (SD)	P Value
No. of atrophic lesions per eye	All	81	2.06 (1.64)	0.30	164	1.53 (1.04)	0.03	102	1.56 (1.28)	0.33
	Ranibizumab	46	1.87 (1.34)		88	1.70 (1.24)		57	1.46 (1.09)	
	Bevacizumab	35	2.31 (1.95)		76	1.33 (0.70)		45	1.69 (1.49)	
Subfoveal, n (%)	All	81	5 (6)*	0.04	164	26 (16)	0.65	102	40 (39)	0.50
	Ranibizumab	46	5 (11)*		88	15 (17)		57	24 (42)	
	Bevacizumab	35	0 (0)		76	11 (14)		45	16 (36)	
Distance of closest border to foveal center (mm)	All	81	0.68 (0.41)	0.62	164	0.49 (0.41)	0.70	102	0.37 (0.46)	0.31
	Ranibizumab	46	0.68 (0.41)		88	0.48 (0.39)		57	0.31 (0.38)	
	Bevacizumab	35	0.68 (0.43)		76	0.51 (0.44)		45	0.46 (0.55)	
Total area (mm^2)	All	81	2.69 (6.12)	0.07	164	2.39 (3.25)	0.07	102	7.09 (8.63)	0.99
	Ranibizumab	46	3.47 (7.86)		88	2.67 (3.46)		57	6.83 (8.46)	
	Bevacizumab	35	1.68 (2.11)		76	2.05 (2.97)		45	7.42 (8.92)	

GA = geographic atrophy; N = number of eyes; SD = standard deviation.
*Eligibility criteria specified no subfoveal GA. However, these 5 cases were entered into the clinical trial.

Characteristics of Geographic Atrophy Lesions

Characteristics of prevalent and incident GA lesions at year 1, 2, or 5 are shown in Table 1. Mean number of GA lesions per study eye was 2.06 (SD, 1.64) for prevalent cases and 1.53 (1.04) for incident cases at years 1 or 2, and 1.56 (1.28) for incident cases at year 5. Distance to the fovea was 0.68 mm (0.41 mm) for prevalent cases and 0.49 mm (0.41 mm) for incident cases at years 1 or 2, and 0.37 mm (0.46 mm) for incident cases at year 5. When GA was detected, it involved the foveal center in 26 incident cases (16% of eyes with GA at that time point) at years 1 or 2, and 40 incident cases (39%) at year 5. Mean total GA area of was 2.69 mm^2 (6.12 mm^2) at baseline for prevalent cases and 2.39 mm^2 (3.25 mm^2) for incident cases at the time of first GA detection at years 1 or 2, and 7.09 mm^2 (8.63 mm^2) for GA incident cases first detected at year 5 (Table 1).

Geographic Atrophy Incidence

Among the 1011 study eyes included in the CATT study that did not have GA at baseline and had gradable follow-up images for determining incident GA, the estimated cumulative incidence was 12% (95% CI, 10−14) at 1 year, 17% (95% CI, 0.14−19) at 2 years, and 38% (95% CI, 34−42) at 5 years. When only the participants who completed the 5-year follow-up were analyzed, the GA cumulative incidence rates were similar (13%, 18%, and 39%, respectively).

Tables S2, S3, and S4 (available at www.aaojournal.org) show baseline characteristics and associated hazard ratios by univariate analysis for incident GA throughout 5 years of follow-up for all participants enrolled in the trial. Upon univariate analysis, increasing age ($P < 0.001$), hypercholesterolemia ($P = 0.04$), monthly dosing regimen during the first 2 years ($P = 0.06$) (Table S2, available at www.aaojournal.org), worse vision at baseline in the study eye ($P < 0.001$) and the fellow eye ($P = 0.002$), subfoveal location of the total CNV lesion ($P = 0.002$), presence of RAP ($P < 0.001$), presence of hemorrhage less than 1 disc area (DA) in size that is associated with the CNV lesion ($P < 0.001$), presence of CNV/scar in the fellow eye ($P = 0.055$), presence of GA in the fellow eye ($P < 0.001$) (Table S3, available at www.aaojournal.org), greater retinal thickness in the foveal center ($P < 0.001$), and presence of intraretinal fluid ($P < 0.001$) (Table S4, available at www.aaojournal.org) were all associated with increased risk of GA development.

However, more subretinal fluid thickness in the foveal center ($P = 0.01$), more subretinal tissue complex thickness in the foveal center ($P < 0.001$), more subretinal fluid ($P < 0.001$), and vitreomacular attachment ($P = 0.03$) were associated with decreased risk of GA development (Table S4, available at www.aaojournal.org) throughout 5 years of follow-up.

The results of the final multivariate analysis for baseline predictors of GA are shown in Table 5. Relative to participants aged 50 to 69 years, older participants had an increasingly higher risk of developing GA; participants older than 80 years of age had an adjusted hazard ratio (aHR) of 1.58 (95% CI, 0.96−2.58). Hypercholesterolemia was associated with an aHR of 1.47 (95% CI, 1.09−1.97) compared with participants with normal cholesterol. Relative to eyes with a baseline visual acuity of 20/25 to 20/40, eyes with worse visual acuity had an increasingly higher risk of developing GA; visual acuities of 20/50 to 20/80 and 20/100 to 20/160 was associated with aHRs of 1.65 (95% CI, 1.15−2.36) and 1.76 (95% CI, 1.15−2.68), respectively. Relative to eyes with smaller baseline CNV lesions, larger lesions (>4 DAs) had an increasingly higher risk of GA development. Lesions larger than 4 DAs were associated with an aHR of 1.99 (95% CI, 1.21−3.28) in comparison with lesions equal to or smaller than 1 DA. Eyes with RAP lesions had an increased risk of developing GA (aHR, 2.02; 95% CI, 1.36−3.00).

When GA was present in the fellow eye, the study eye was more likely to develop GA (aHR, 2.31; 95% CI, 1.51−3.54). Eyes with intraretinal fluid in the foveal center (aHR, 2.27; 95% CI, 1.49−3.44) or away from it (aHR, 1.83; 95% CI, 1.17−2.87) had a higher risk of developing GA when compared with eyes with no intraretinal fluid.

However, the risk of GA decreased with increasing subretinal tissue complex thickness in the foveal center; relative to eyes with subretinal tissue complex thickness ≤75 μ, eyes with thickness >275 μ were associated with an aHR of 0.29 (95% CI, 0.18−0.47). Compared with eyes without subretinal fluid, a lower risk of developing GA was seen in eyes with subretinal fluid in the foveal center (aHR, 0.37; 95% CI, 0.24−0.56) or subretinal fluid not in the foveal center (aHR, 0.61; 95% CI, 0.42−0.89).

When compared with eyes treated with bevacizumab during the first 2 years of CATT, the aHR for ranibizumab was 1.32 (95% CI, 0.98−1.76) (Table 5). The aHR for eyes treated monthly for the first 2 years of CATT, relative to eyes treated PRN for the first

Table 5. Multivariate Analysis for Association between Baseline Factors and Development of Geographic Atrophy by 5 Years among All Trial Participants

Baseline Patient Characteristics	Patients at Risk, N	Hazard Ratio (95% CI)	P Value*
Age, yrs			0.04
50–69	124	1.00	
70–79	334	1.09 (0.65–1.83)	
≥80	508	1.58 (0.96–2.58)	
Hypercholesterolemia			0.01
No	409	1.00	
Yes	557	1.47 (1.09–1.97)	
Drug group in first 2 yrs			0.06
Bevacizumab	470	1.00	
Ranibizumab	496	1.32 (0.98–1.76)	
Regimen group in first 2 yrs			0.17
PRN	486	1.00	
Switched	240	1.06 (0.75–1.52)	
Monthly	240	1.38 (0.98–1.93)	
Baseline visual acuity in study eye			0.02
20/25–40	348	1.00	
20/50–80	357	1.65 (1.15–2.36)	
20/100–160	202	1.76 (1.15–2.68)	
20/200–320	59	1.78 (0.95–3.35)	
Baseline CNV area (DA)			0.01
≤1	392	1.00	
>1–≤2	201	0.79 (0.52–1.21)	
>2–≤4	183	1.40 (0.94–2.08)	
>4	91	1.99 (1.21–3.28)	
Unknown	99	1.08 (0.64–1.80)	
RAP lesion			<0.001
No	859	1.00	
Yes	107	2.02 (1.36–3.00)	
GA in fellow eye			<0.001
None/questionable	883	1.00	
Present	83	2.31 (1.51–3.54)	
Subretinal tissue complex thickness at foveal center (mm)			<0.001
>0–≤75	231	1.00	
>75–≤160	223	0.69 (0.46–1.04)	
>160–≤275	248	0.60 (0.39–0.91)	
>275	264	0.29 (0.18–0.47)	
Intraretinal fluid			<0.001
No fluid	257	1.00	
Fluid not in foveal center	253	1.83 (1.17–2.87)	
Fluid in foveal center	456	2.27 (1.49–3.44)	
Subretinal fluid			<0.001
No fluid	152	1.00	
Fluid not in foveal center	463	0.61 (0.42–0.89)	
Fluid in foveal center	351	0.37 (0.24–0.56)	

CI = confidence interval; CNV = choroid neovascularization; DA = disc area; GA = geographic atrophy; PRN = pro re nata; RAP = retinal angiomatous proliferation.
*P value from Cox proportional hazard model.

2 years, was 1.38 (95% CI, 0.98–1.93), although there was no significant difference across the 3 regimen groups ($P = 0.17$).[2]

Among the SNPs investigated, genotype TT of age-related maculopathy susceptibility 2 (aHR, 1.82; 95% CI, 1.24–2.68) was associated with higher incidence of GA, and genotype TT of Toll-like receptor 3 (aHR, 0.51; 95% CI, 0.28–0.93) was associated with a lower incidence of GA (Table 6).

Geographic Atrophy Growth

The GA growth analysis including all trial participants identified 81 prevalent GA cases that had at least 1 follow-up visit for GA size measurement and 133 incident cases of GA (114 at year 1, 19 at year 2) that had at least 1 additional GA measurement at a later time (any following visit), allowing the assessment of GA growth (Fig 1). The overall growth of GA was 0.33 mm/year (standard error [SE], 0.02 mm/year) for all trial participants with GA growth evaluation (N = 214) and 0.29 mm/year (SE, 0.02 mm/year) among participants who completed the 5-year follow-up (N = 112). The prevalent cases had more GA growth (0.57 [0.03] mm/year) than incident cases (0.30 [0.02] mm/year) ($P = 0.06$).

In the univariate analysis, when prevalent and incident GA cases were considered together, ranibizumab treatment during the first 2 years of the study ($P = 0.03$), GA in the fellow eye ($P = 0.02$), larger area of GA when first observed ($P = 0.04$), larger distance from the foveal center ($P < 0.001$), worse baseline visual acuity in the fellow eye ($P = 0.02$), classic CNV lesion type at baseline ($P = 0.003$), hemorrhage at baseline associated with the CNV lesion ($P = 0.02$), absence of sub-RPE fluid ($P < 0.001$), and presence of epiretinal membrane ($P = 0.04$) were significantly associated with faster growth (Table S7, available at www.aaojournal.org).

Upon multivariate analysis, (Table 8), eyes treated with ranibizumab in the first 2 years of the clinical trial had a higher growth rate than eyes treated with bevacizumab (adjusted growth rate, 0.38 vs. 0.28 mm/year; $P = 0.009$). In a separate multivariate analysis of GA growth including only the cohort of participants who completed the 5-year follow-up visit (N = 112), the difference between eyes treated with ranibizumab for the first 2 years and eyes treated with bevacizumab during the first 2 years was 0.32 versus 0.26 mm/year, respectively ($P = 0.12$). Eyes with GA in the fellow eye had a higher growth rate in the study eye (0.37 mm/year) than those with no GA in the fellow eye (0.28 mm/year; $P = 0.03$). Eyes with hemorrhage associated with the CNV lesion had a higher GA growth (0.37 mm/year) than eyes without hemorrhage (0.29 mm/year; $P = 0.049$). Eyes without sub-RPE fluid had higher GA growth rate than eyes with sub-RPE fluid away from the fovea or subfoveal fluid (0.40, 0.32, and 0.26 mm/year, respectively; $P = 0.003$). There was no difference in GA growth among the 3 dosing regimens ($P = 0.84$) that participants received during the first 2 years of the study (Table 8). We found that the associations between these risk factors and GA growth rates were all similar among prevalent and incident cases ($P > 0.19$).

We assessed GA growth rate for individual GA lesions that were associated with the CNV lesion (N = 236) and those that were completely away from the CNV lesion when first observed (N = 97). Mean growth rate for GA that was associated with CNV was significantly higher (0.33 [0.03] mm/year) than that observed for GA that was away from CNV (0.19 [0.04] mm/year; $P = 0.001$).

Among 214 participants available for GA growth analysis, 168 (78.5%) had blood drawn for genetic analysis. No significant associations were observed between genotype and GA growth rate (Table S9, available at www.aaojournal.org).

Discussion

Our study identified a number of risk factors for the development of GA in exudative AMD treated with anti–vascular endothelial growth factor (VEGF) therapy for up to 5 years. Among them are age, elevated cholesterol, ranibizumab treatment, poor vision, large total CNV lesion, RAP lesions, fellow

Table 6. Associations of Genotype with Development of Geographic Atrophy by 5 Years among Trial Participants

SNP*	Genotype	Patients at Risk, N	Cumulative Incidence at Year 5	Hazard Ratio (95% CI)
CFH	TT	157	0.34	1.0
	TC	355	0.37	0.98 (0.68–1.42)
	CC	248	0.33	1.00 (0.67–1.50)
	Adjusted *P* value†			0.97
ARMS2	GG	237	0.32	1.0
	GT	371	0.33	1.07 (0.77–1.50)
	TT	152	0.47	1.82 (1.24–2.68)
	Adjusted *P* value†			0.01
C3	CC	423	0.37	1.0
	CG	287	0.36	1.00 (0.75–1.34)
	GG	50	0.28	0.72 (0.38–1.35)
	Adjusted *P* value†			0.61
TLR3	CC	375	0.40	1.0
	TC	313	0.33	0.78 (0.58–1.04)
	TT	72	0.23	0.51 (0.28–0.93)
	Adjusted *P* value†			0.02

ARMS2 = age-related maculopathy susceptibility 2; CFH = complement factor H; CI = confidence interval; C3 = complement component 3; GA = geographic atrophy; SNP = single nucleotide polymorphism; TLR3 = Toll-like receptor 3.
*The risk alleles are C for CFH, T for ARMS2, G for C3, and C for TLR3.
†The multiple linear trend *P* values were calculated using the approach of false discovery rate, adjusted by age, gender, and smoking status.

eye GA, thinner subretinal tissue complex at the fovea and intraretinal fluid, especially in the fovea, and absence of subretinal fluid. Most of these factors had been identified in our previous report after 2 years of anti-VEGF treatment. Other factors, such as hypercholesterolemia, became statistically significant after 5 years of follow-up, supporting a previous study showing an association between elevated cholesterol and GA.[15] Conversely, blocked fluorescence on FA and vitreomacular attachment, which were associated with decreased risk of GA development at 2 years of follow-up, are now not statistically significantly associated with risk of GA.

At the end of the 2-year clinical trial, ranibizumab treatment was associated with increased risk of GA compared with bevacizumab.[2] After 2 years in the clinical trial, participants were allowed to receive any treatment and few eyes were treated exclusively with their originally assigned treatment during the next 3 years.[16] Eighty percent of the eyes originally assigned to ranibizumab treatment and 70% of the eyes originally assigned to bevacizumab received other anti-VEGF treatment or no treatment in the ensuing 3 years. Because of the large variability in the treatments that participants received in the last 3 years of follow-up, it is difficult to assess the effects of each type of treatment on GA development and growth. Notwithstanding this variable treatment after the clinical trial, ranibizumab treatment within the first 2 years remained associated with increased risk of GA throughout 5 years of follow-up, although the association was of borderline significance ($P = 0.06$). In contrast to our study, the Inhibit VEGF in Age-Related Choroidal Neovascularization 2-year trial did not find a significant difference in the development of GA between ranibizumab and bevacizumab (28% and 31%, respectively; $P = 0.46$).[17]

Similar to our previous 2-year report showing that ranibizumab was associated with a significantly higher GA growth rate than bevacizumab,[3] our current 5-year follow-up report shows a similar and significant difference 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.[16] When only the cohort of participants who completed the 5-year follow-up were assessed separately, a similar magnitude of difference in GA growth was observed between ranibizumab and bevacizumab, although the difference was not statistically significant, perhaps because the sample that completed the 5-year follow-up was smaller than the sample that completed the 2-year follow-up.

At 5 years of follow-up treatment, although the monthly regimen treatment showed a higher risk of GA incidence than the PRN regimen, the difference was not statistically significant (aHR, 1.39; 95% CI, 0.98–1.93). These results are somewhat different from the significant association found at the end of the 2 years of the trial.[3] This could be because at the end of the trial none of the participants continued on a monthly regimen for the ensuing 3 years.[16] In addition, the number of participants who completed the 5-year follow-up was smaller than the participants who completed 2 years of follow-up, and this decreased our power to detect differences.

Table 8. Multivariate Analysis for Risk Factors of Geographic Atrophy Growth by 5 Years among All Trial Participants

	N	Mean Growth Rate (mm/yr) (95% CI)	Mean Difference (mm/yr) (95% CI)	*P* Value
Drug in first 2 yrs				
Ranibizumab	108	0.38 (0.32–0.43)	0.09 (0.02 to 0.17)	0.009
Bevacizumab	87	0.28 (0.22–0.34)	0	
Regimen in first 2 yrs				
Monthly	55	0.32 (0.25–0.40)	0.00 (−0.09 to 0.10)	0.94
Switch	48	0.32 (0.25–0.40)	0	
PRN	92	0.34 (0.28–0.39)	0.01 (−0.07 to 0.10)	
Baseline GA in fellow eye				
No	139	0.28 (0.24–0.33)	0	0.03
Yes	56	0.37 (0.30–0.44)	0.09 (0.01 to 0.17)	
Hemorrhage associated with CNV				
No	56	0.29 (0.22–0.36)	0	0.049
Yes	139	0.37 (0.32–0.41)	0.08 (0.00 to 0.16)	
Sub-RPE fluid				
None	90	0.40 (0.35–0.46)	0.14 (0.06 to 0.23)	0.003
Not subfoveal	46	0.32 (0.25–0.39)	0.06 (−0.04 to 0.16)	
Subfoveal	59	0.26 (0.19–0.33)	0	

CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; N = number of eyes; PRN = pro re nata; RPE = retinal pigment epithelium.

Two other studies have compared the long-term effects of monthly versus PRN regimens of anti-VEGF therapy on incident GA and reported results similar to ours. The Inhibit VEGF in Age-Related Choroidal Neovascularization trial showed an increased risk of GA in eyes treated for 2 years with a monthly regimen (34%) compared with a PRN regimen (26%) (odds ratio, 1.45; 9% CI, 1.02−2.06).[17] Likewise, the HARBOR trial reported that eyes that received monthly ranibizumab had a higher incidence of GA when compared with PRN treatment (hazard ratio, 1.3; 95% CI, 1.0−1.7).[18]

Our study shows GA development in 266 study eyes of a group of 1011 participants (cumulative incidence rate, 38%; 95% CI, 34−42) during the 5 years of the study. Our GA incidence is lower than the 98% macular atrophy reported by the SEVEN UP study[19] that followed participants for up to 8 years. This large difference may be due to differences in the definition and assessment of atrophy. Ours was based on the detection of well-demarcated GA lesions on CP and FA, whereas theirs was based on the presence of a decreased signal on autofluorescence photographs.

Absence of sub-RPE fluid was a significant risk factor for rapid GA growth during anti-VEGF therapy. Sub-RPE fluid was not a significant risk factor in our previous 2-year follow-up report. Fluid under the RPE may provide a barrier to the diffusion of metabolites that may cause the development of GA. Consequently, absence of this type of fluid barrier may enhance the development of GA. Finally, the presence of hemorrhage associated with CNV lesion and the presence of GA in the fellow eye also were associated with more GA growth.

Our overall growth rate in the cohort that completed the 5 year follow-up was 0.33 mm/year, a value that is lower than the 0.43 mm/year that we reported for the full cohort after 2 years of the clinical trial. This difference may be due to a decreased growth rate during the 3 years after the end of the clinical trial or perhaps differences between the participants who completed the 5-year follow-up and those who did not.[16] The growth rate of 0.33 mm/year observed in our study is within the range of growth rates reported previously.[20,21] Several articles have expressed growth of GA in millimeters squared per year and have reported growth rates ranging from 1.28 to 2.6 mm^2/year.[22−29] If we calculate our results in millimeters squared, the mean GA growth in our study is 1.52 mm^2/year (0.12 mm^2/year), a value that is within that range. In contrast to our study, all these studies looked at GA growth that was not associated with exudative CNV.

Our previous report at 2 years of follow-up showed that classic CNV lesions at baseline were associated with a GA growth rate that was almost double the rate of GA growth associated with occult lesions.[3] In our current report, although the univariate analysis shows that predominantly classic lesions have a growth rate that is significantly higher (0.46 [0.05] mm/year) than that of occult-only lesions (0.29 [0.02] mm/year; $P = 0.003$; Table S3, available at www.aaojournal.org), the multivariate analysis does not demonstrate a significant difference, suggesting that the baseline type of CNV may not have a persistent independent effect on GA growth.

Because GA that develops de novo and is not associated with CNV may be different from GA that is associated with CNV, we assessed their growth rates. Indeed, we found that GA that develops away from the CNV had approximately half of the growth rate, suggesting that there may be significant differences between these 2 types of GA. McLeod et al[30] showed that dropout of the choriocapillaris in areas surrounding CNV may explain the higher growth of GA in close proximity to CNV.

In summary, our study describes a number of risk factors associated with increased GA incidence or faster GA growth in AMD participants treated with anti-VEGF medications for 5 years. Of note, the presence of subretinal fluid is associated with a lower incidence of GA, and the presence of sub-RPE fluid is associated with slower growth of GA. Further studies are needed to assess whether complete eradication of fluid under the retina should or should not be a goal for anti-VEGF therapy.

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Abbreviations and Acronyms:
aHR = adjusted hazard ratio; **AMD** = age-related macular degeneration; **CATT** = Comparison of AMD Treatments Trials; **CI** = confidence interval; **CNV** = choroidal neovascularization; **CP** = color photograph; **DA** = disc area; **FA** = fluorescein angiography; **GA** = geographic atrophy; **OCT** = optical coherence tomography; **PRN** = pro re nata; **RAP** = retinal angiomatous proliferation; **RPE** = retinal pigment epithelium; **SE** = standard error; **SNP** = single nucleotide polymorphism; **VEGF** = vascular endothelial growth factor.

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