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# Growth of Geographic Atrophy in the Comparison of Age-related Macular Degeneration Treatments Trials

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***Purpose:*** To evaluate the growth of geographic atrophy (GA) during anti−vascular endothelial growth factor (VEGF) therapy.

***Design:*** Cohort within a clinical trial.

***Participants:*** Patients included in the Comparison of Age-related Macular Degeneration Treatments Trials (CATT).

***Methods:*** Participants were randomly assigned to injections of ranibizumab or bevacizumab and to a 2-year dosing regimen of monthly or pro re nata (PRN) or to monthly for 1 year and PRN the following year. Digital color photographs and fluorescein angiograms at baseline and 1 and 2 years were evaluated for GA, and the total area of GA was measured by 2 graders masked to treatment; differences were adjudicated. Multivariate linear mixed models of the annual change in the square root of the area included baseline demographic, treatment, and ocular characteristics on imaging as candidate risk factors.

***Main Outcome Measures:*** Geographic atrophy growth rate.

***Results:*** Among 1185 participants, 86 (7.3%) had GA at baseline, 120 (10.1%) developed GA during year 1, and 36 (3.0%) developed GA during year 2. Among 194 eyes evaluable for growth, the rate was 0.43 mm/yr (standard error [SE], ±0.03 mm/year). In multivariate analysis, the growth rate was 0.37 mm/year in eyes receiving bevacizumab and 0.49 mm/year in eyes receiving ranibizumab (difference, 0.11 mm/yr; 95% confidence interval [CI], 0.01−0.22; $P = 0.03$). Growth rate did not differ between eyes treated monthly and PRN ($P = 0.85$). Eyes with subfoveal choroidal neovascularization (CNV) lesions had a lower growth rate than eyes with nonsubfoveal CNV lesions (difference, 0.12; 95% CI, 0.01−0.22; $P = 0.03$). Eyes with GA farther from the fovea had higher growth rates by 0.14 (95% CI, 0.01−27) mm/year for every millimeter farther from the fovea. The growth rate was 0.58 mm/year for eyes with predominantly classic lesions, 0.41 mm/year for eyes with minimally classic lesions, and 0.30 mm/year for eyes with occult only lesions ($P < 0.01$). The growth rate in eyes having a fellow eye with GA was higher by 0.13 mm/year (95% CI, 0.01−0.24; $P = 0.03$) than in eyes without GA in the fellow eye. Eyes with epiretinal membrane had a higher growth rate than eyes without epiretinal membrane (difference, 0.16; 95% CI, 0.03−0.30; $P = 0.02$).

***Conclusions:*** Geographic atrophy growth depends on several ocular factors. Ranibizumab may accelerate GA growth. *Ophthalmology 2015;122:809-816 © 2015 by the American Academy of Ophthalmology.*

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

Age-related macular degeneration (AMD) is a leading cause of vision loss in elderly people in the United States.[1] Loss of vision from this disease is mostly due to the development of neovascular AMD or geographic atrophy (GA).

Intravitreal injections of anti-vascular endothelial growth factor (VEGF) agents are currently used for the treatment of neovascular AMD with excellent visual acuity response.[2−6] One of the findings observed during therapy is the development of atrophy of retinal pigment epithelium (RPE) and choriocapillaries that resembles the appearance of de novo GA.[7] Results from the Comparison of Age-related Macular Degeneration Treatments Trials (CATT) in which patients were treated for 2 years with the anti-VEGF agents ranibizumab or bevacizumab showed that the 2-year incidence of GA was approximately18%.[8] When GA was present at the fovea, the visual acuity was markedly decreased.[9,10] Eyes treated with ranibizumab had a higher risk than eyes treated with bevacizumab, and eyes treated monthly had a higher risk than eyes treated pro re nata (PRN).[11]

There are no long-term follow-up studies of these atrophic lesions, and it is not known whether their histology, growth patterns, and functional effects are similar to those of de novo GA lesions that develop in areas where no neovascularization was present previously. Because atrophic



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lesions associated with treated neovascularization are clinically indistinguishable from de novo GA, they will be referred to as GA throughout this article.

The purpose of this study was to evaluate GA growth during anti-VEGF therapy. We also assessed the association between GA growth and characteristics of the affected patients and eyes, including drug and dosing regimen. Finally, we investigated whether the growth of GA associated with the neovascular lesion is different from that of GA developing away from the neovascular lesion.

## Methods

The CATT cohort and methods have been described.[8–11] The CATT cohort consisted of 1185 patients with AMD and untreated choroidal/retinal neovascularization (CNV) with the CNV or its sequelae, such as intraretinal fluid, subretinal fluid, serous pigment epithelial detachment, hemorrhage, or blocked fluorescence, involving the foveal center. Patients were enrolled at 43 clinical centers in the United States between February 2008 and December 2009. Inclusion criteria included age ≥50 years and active untreated CNV secondary to AMD and visual acuity between 20/25 and 20/320 in the study eye. According to the CATT protocol, patients with foveal center GA were not eligible.[6] 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 patients provided written informed consent. The CATT study was registered at www.clinicaltrials.gov (NCT00593450). At enrollment, patients were randomly assigned to 1 of 4 treatment groups defined by drug (ranibizumab or bevacizumab) and dosing regimen (monthly or PRN). At 1 year, patients initially assigned to monthly treatment retained their drug assignment but were reassigned randomly, with equal probability, to monthly or PRN treatment. Patients initially assigned to PRN treatment had no change in assignment and retained both their drug assignment and their PRN dosing regimen for the second year.

At enrollment, patients provided a medical history and had bilateral color fundus photography, fluorescein angiography (FA), and time-domain optical coherence tomography (OCT). Follow-up examinations were scheduled every 28 days for 2 years. Color fundus photography and FA were performed again at 52 weeks and 104 weeks.

Morphologic features of the study eyes at baseline were evaluated.[8,9] Two trained and certified graders at the CATT Fundus Photograph Reading Center reviewed baseline and follow-up images for signs of GA in the study eye and the fellow eye. Discrepancies between the 2 graders were adjudicated.

Both color fundus photography and FA were used in assessing and characterizing GA. The diagnosis of GA required the presence within the macular vascular arcades of 1 or more patches ≥250 μ in the longest linear dimension of partial or complete depigmentation in the color fundus photography that had 1 or more of these additional characteristics: sharply demarcated borders seen in color fundus photography or FA, visibility of underlying choroidal vessels, excavated or punched-out appearance on stereoscopy of color fundus photography or FA, or uniform hyperfluorescence bounded by sharp borders on late-phase angiography. The OCT scans were not used for the determination of the presence of GA.

Geographic atrophy detected on color fundus photography or FA at baseline was considered prevalent GA. Geographic atrophy that was not detected at baseline but was present at year 1, 2, or both was considered incident GA. We excluded from the study all participants with ungradable photographs at baseline and those for whom all follow-up photographs were ungradable or missing.

ImageJ software[12] was used to measure the area of each individual GA lesion on a selected FA image. The drawing of GA was done manually on the same image by 2 independent graders. A scaling factor for this image was determined from 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 between graders in the GA area were greater than 50% or 2 $mm^2$, an open adjudication between the 2 graders was performed, a new single drawing was agreed on, and a new measurement was obtained. 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 edge of GA also was determined. Finally, for each individual GA lesion, we determined whether the location was clearly outside the area of the total CNV lesion apparent at any previous visit or the current visit. 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 or 2 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 studies.[8,11] There were 14 eyes that had GA in the original grading but were reassessed as not having GA at baseline, year 1, or year 2 visits in the new grading performed for the current study.

At the CATT OCT Reading Center, 2 certified readers independently analyzed all baseline scans for morphologic characteristics.[13] Readers evaluated the presence of intraretinal fluid, subretinal fluid, and fluid below the RPE. When fluid was present, readers noted the location of fluid relative to the foveal center. They also identified the presence of subretinal hyperreflective material, epiretinal membrane, and vitreomacular attachment. Readers measured the thickness of the (1) retina, (2) subretinal fluid, and (3) subretinal tissue complex (defined as the distance from the outer photoreceptor border of the retina to Bruch's membrane, excluding subretinal fluid) at the foveal center. A senior reader reconciled any grading disagreements between the reader pair.

Four single nucleotide polymorphisms previously associated with the risk of developing AMD were evaluated for association with growth of GA: (1) complement factor H Y402H (rs1061170), (2) age-related maculopathy susceptibility 2 (also called *LOC387715*) A69S (rs10490924), (3) high temperature requirement factor A1 (rs11200638); and (4) complement component 3 R80G (rs2230199).[14,15] One single nucleotide polymorphism previously associated with protection against GA, Toll-like receptor 3 (rs3775291), was also evaluated.[16]

### Statistical Methods

A number of risk factors for GA growth were assessed. These included (1) demographic factors: age, sex, smoking, hypertension, dietary supplements; (2) GA characteristics: area, number, location, distance from the fovea, presence of GA in the fellow eye; (3) study eye characteristics: visual acuity, total CNV lesion size, CNV type and location, retinal angiomatous proliferans lesion, hemorrhage; (4) OCT characteristics: intraretinal fluid, subretinal fluid, sub-RPE fluid, subretinal hyperreflective material, epiretinal membrane; and (5) treatment characteristics: drug (ranibizumab and bevacizumab) and regimen (monthly and PRN).

Linear mixed-effects models were used to estimate GA growth. In these mixed-effects models, the GA area was modeled as a

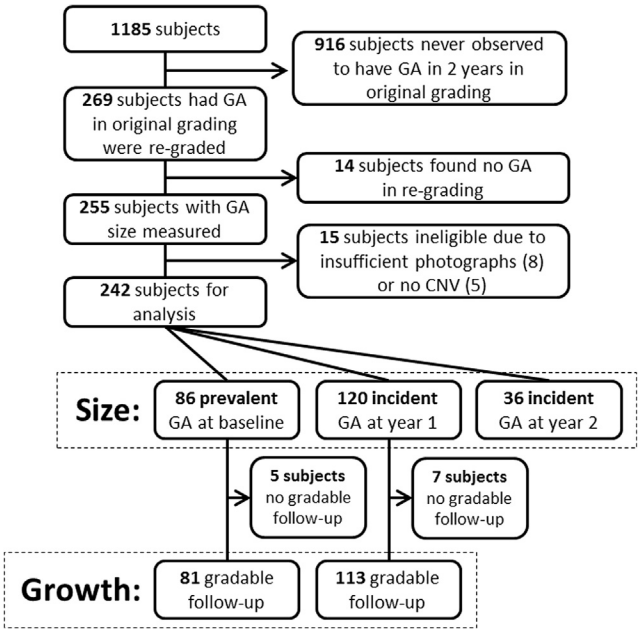


**Figure 1.** Flow chart describing the study patients. CNV = choroidal neovascularization; GA = geographic atrophy.

function of time (relative to its first observed GA), candidate risk factor(s), and interaction term(s) of risk factor(s) with time. Slopes and intercepts were modeled as random effects within subjects. We explored 3 approaches for modeling GA growth: (1) total GA area without transformation; (2) square root transformation[17]; and (3) log transformation. We found that use of the square root transformation decreased the dependency of GA growth on baseline GA size when compared with the total GA area; log transformation did not decrease the dependence further. Therefore, the square root transformation was used for all subsequent analyses. Similar analyses were performed for modeling the growth rate of individual GA lesions, except that additional random slopes and intercepts were nested within subjects.

Each risk factor was first evaluated by univariate analysis (without adjustment for other covariates), using mixed effect models for GA growth. Dosing regimen (monthly or PRN) was represented as a time-dependent covariate to accommodate the second randomization at 52 weeks for patients initially assigned monthly treatment. The risk factors with a $P$ value less than 0.20 in the univariate analysis were included in a multivariate analysis so that the independent effect of each predictor could be assessed. The final multivariate model was created by applying a backward selection procedure that retained only those predictors with a $P$ value less than 0.05, with the exception of drug and dosing regimen, which were included in all multivariate models. Adjusted mean growth rate and 95% confidence intervals (CIs) for the difference in mean growth rate between groups were calculated from the final multivariate linear models.

## Results

Among 1185 participants, 86 (7.3%) had GA at baseline, 120 (10.1%) developed GA during year 1, and 36 (3.0%) developed GA during year 2 (Fig 1). Among the participants with GA, growth of GA could be determined from 2 or more visits in 81 prevalent cases and in 113 cases in whom GA was detected in year 1. Among these patients, 151 had blood drawn for genetic analysis.

Characteristics of prevalent and incident GA were generally similar, as shown in Table 1. Mean number of GA lesions was 2.06 (standard deviation, 1.67) for prevalent cases and 1.53 (1.05) for incident cases. Distance to the fovea was 0.71 (0.44) mm for prevalent cases and 0.48 (0.41) mm for incident cases, including 5 (6%) prevalent and 25 (16%) incident cases of subfoveal GA (12% of all cases). Because subfoveal GA at baseline was an exclusion criterion in CATT, this value is artificially low. Mean

Table 1. Characteristics of Geographic Atrophy Cases at First Observed Appearance

| Characteristic | Group | Prevalent Cases (N = 86) | | | Incident Cases (N = 156) | | |
|---|---|---|---|---|---|---|---|
| | | *n* | *Mean (SD)* | *P Value** | *n* | *Mean (SD)* | *P Value** |
| No. of GA cases | | | | | | | |
| All | All | 86 | 2.06 (1.67) | | 156 | 1.53 (1.05) | |
| Drug | Ranibizumab | 49 | 1.88 (1.35) | 0.31 | 84 | 1.70 (1.26) | 0.04 |
| | Bevacizumab | 37 | 2.30 (2.01) | | 72 | 1.32 (0.69) | |
| Regimen[†] | Monthly | 41 | 1.95 (1.28) | 0.73 | 81 | 1.56 (1.00) | 0.37 |
| | PRN | 45 | 2.16 (1.97) | | 75 | 1.49 (1.11) | |
| Distance to fovea (mm) | | | | | | | |
| All | All | 86 | 0.71 (0.44) | | 156 | 0.48 (0.41) | |
| Drug | Ranibizumab | 49 | 0.73 (0.46) | 0.50 | 84 | 0.47 (0.38) | 0.87 |
| | Bevacizumab | 37 | 0.69 (0.42) | | 72 | 0.50 (0.43) | |
| Regimen[†] | Monthly | 41 | 0.63 (0.36) | 0.26 | 81 | 0.53 (0.43) | 0.14 |
| | PRN | 45 | 0.79 (0.49) | | 75 | 0.43 (0.37) | |
| Total area of GA ($mm^2$) | | | | | | | |
| All | All | 86 | 2.58 (5.96) | | 156 | 2.39 (3.27) | |
| Drug | Ranibizumab | 49 | 3.31 (7.64) | 0.06 | 84 | 2.65 (3.46) | 0.09 |
| | Bevacizumab | 37 | 1.60 (2.08) | | 72 | 2.09 (3.03) | |
| Regimen[†] | Monthly | 41 | 3.14 (8.07) | 0.68 | 81 | 2.33 (3.29) | 0.53 |
| | PRN | 45 | 2.06 (2.98) | | 75 | 2.45 (3.27) | |

GA = geographic atrophy; PRN = pro re nata; SD = standard deviation.
*Wilcoxon rank-sum test.
[†]For incident GA, dosing regimen was based on the treatment regimen when GA was first observed.

Table 2. Univariate Analysis for the Association between Baseline Factors and Geographic Atrophy Growth Rate (mm/yr) within 2 Years

| Baseline Characteristics | n | Mean (SE) mm/yr | P Value |
|---|---|---|---|
| Overall growth rate | 194 | 0.43 (0.03) | |
| Drug | | | 0.02 |
| Ranibizumab | 106 | 0.49 (0.04) | |
| Bevacizumab | 88 | 0.36 (0.04) | |
| Regimen* | | | 0.68 |
| Monthly | 104 | 0.45 (0.04) | |
| PRN | 90 | 0.43 (0.04) | |
| Age (yrs) | | | 0.17 |
| <75 | 32 | 0.32 (0.07) | |
| 75–85 | 123 | 0.44 (0.03) | |
| >85 | 39 | 0.48 (0.06) | |
| Per 10-yr increase | | 0.06 (0.04) | 0.13 |
| Sex | | | 0.16 |
| Female | 123 | 0.46 (0.03) | |
| Male | 71 | 0.38 (0.05) | |
| Cigarette smoking | | | 0.39 |
| Never | 85 | 0.46 (0.04) | |
| Quit/current | 109 | 0.41 (0.04) | |
| Hypertension | | | 0.17 |
| No | 66 | 0.38 (0.05) | |
| Yes | 128 | 0.46 (0.03) | |
| Use of dietary supplements (ß-carotene, vitamins C, E, and/or zinc) | | | 0.78 |
| No | 65 | 0.44 (0.05) | |
| Yes | 129 | 0.42 (0.03) | |
| GA in fellow eye | | | 0.02 |
| No | 135 | 0.38 (0.03) | |
| Yes | 58 | 0.52 (0.05) | |
| Prevalent/incident GA | | | 0.54 |
| Prevalent | 81 | 0.45 (0.04) | |
| Incident | 113 | 0.41 (0.04) | |
| No. of distinct GA lesions | | | 0.19 |
| 1 | 124 | 0.39 (0.04) | |
| 2 | 35 | 0.45 (0.07) | |
| >2 | 35 | 0.52 (0.06) | |
| Per GA increase | | 0.03 (0.02) | 0.18 |
| First observed GA area ($mm^2$) | | | <0.01 |
| <1 | 86 | 0.31 (0.04) | |
| 1–2 | 47 | 0.58 (0.05) | |
| >2–5 | 37 | 0.46 (0.06) | |
| >5 | 24 | 0.47 (0.08) | |
| Per $mm^2$ | | 0.00 (0.01) | 0.86 |
| Distance to fovea (mm) | | | 0.18 |
| Subfoveal | 21 | 0.32 (0.09) | |
| <0.5 mm | 73 | 0.39 (0.05) | |
| ≥0.5 mm | 100 | 0.47 (0.04) | |
| Per millimeter increase | | 0.13 (0.07) | 0.06 |
| GA completely outside the lesion | | | 0.85 |
| No | 167 | 0.43 (0.03) | |
| Yes | 27 | 0.42 (0.07) | |
| Visual acuity | | | 0.09 |
| ≥20/40 | 56 | 0.41 (0.05) | |
| 20/50–80 | 79 | 0.49 (0.04) | |
| 20/100–160 | 41 | 0.31 (0.06) | |
| ≤20/200 | 18 | 0.48 (0.09) | |
| Total area of CNV lesion (disc area) | | | 0.22 |
| ≤1 | 70 | 0.48 (0.05) | |
| >1–≤2 | 36 | 0.33 (0.07) | |
| >2–≤4 | 41 | 0.46 (0.06) | |
| >4 | 43 | 0.38 (0.06) | |
| Per disc area increase | 190 | −0.00 (0.01) | 0.77 |
| Location of CNV lesion | | | 0.02 |
| Subfoveal | 117 | 0.37 (0.04) | |
| Not subfoveal | 77 | 0.51 (0.04) | |
| CNV lesion type | | | <0.001 |
| Predominantly classic | 26 | 0.68 (0.07) | |
| Minimally classic | 33 | 0.50 (0.07) | |
| Occult only | 134 | 0.36 (0.03) | |
| RAP lesion | | | 0.99 |
| No | 158 | 0.43 (0.03) | |
| Yes | 35 | 0.43 (0.07) | |
| Hemorrhage (associated with lesion) | | | 0.21 |
| No | 55 | 0.37 (0.05) | |
| Yes | 139 | 0.45 (0.03) | |
| Intraretinal fluid | | | 0.65 |
| None | 19 | 0.34 (0.10) | |
| Not subfoveal | 61 | 0.44 (0.05) | |
| Subfoveal | 110 | 0.43 (0.04) | |
| Subretinal fluid | | | 0.59 |
| None | 55 | 0.46 (0.05) | |
| Not subfoveal | 84 | 0.43 (0.04) | |
| Subfoveal | 52 | 0.38 (0.05) | |
| Sub-RPE fluid | | | 0.08 |
| None | 80 | 0.48 (0.04) | |
| Not subfoveal | 42 | 0.43 (0.06) | |
| Subfoveal | 57 | 0.33 (0.05) | |
| Subretinal hyperreflective material | | | 0.39 |
| No | 42 | 0.38 (0.06) | |
| Yes | 149 | 0.44 (0.03) | |
| Epiretinal membrane | | | 0.04 |
| No | 155 | 0.40 (0.03) | |
| Yes | 34 | 0.55 (0.07) | |

CNV = choroidal neovascularization; GA = geographic atrophy; PRN = pro re nata; RAP = retinal angiomatous proliferans; RPE = retinal pigment epithelium; SE = standard error.
*Regimen group was modeled as a time-dependent variable with values of PRN or monthly (for switched group, monthly in year 1 and PRN in year 2).

of total area of GA was 2.58 (5.96) $mm^2$ for prevalent cases and 2.39 (3.27) $mm^2$ for incident cases at the time of first GA detection.

Using the model for square root transformed total GA area, GA growth rate was 0.45 (standard error [SE], 0.04) mm/year for prevalent cases and 0.41 (0.04) mm/year for incident cases, with an overall growth of 0.43 (0.03) mm/year (Table 2). Risk factors for faster GA growth were assessed by univariate analysis of data from combined prevalent cases and incident cases; the results are summarized in Table 2.

When prevalent and incident GA cases were considered together, ranibizumab treatment ($P = 0.02$), GA in the fellow eye ($P = 0.02$), and area of GA when first observed ($P < 0.01$), but not subfoveal location of CNV, classic CNV lesion type ($P < 0.001$), and presence of epiretinal membrane ($P = 0.04$), were significantly associated with faster growth. No significant associations were observed between genotype and GA growth rate (Table 3, available at www.aaojournal.org).

Table 4 summarizes the results of the multivariate analysis. When all prevalent and incident cases were analyzed together, the mean growth was 0.37 (0.06) mm/year in eyes receiving bevacizumab and 0.49 (0.06) mm/year in eyes receiving ranibizumab, and this difference of 0.11 mm/year (95% CI, 0.01–0.22) was statistically significant ($P = 0.03$). Because the

Table 4. Multivariate Analysis for Factors Associated with Geographic Atrophy Growth within 2 Years

| Baseline Characteristics | n* | Mean (SE) mm/yr | Mean Difference (95% CI), mm/yr | P Value |
|---|---|---|---|---|
| Drug | | | | 0.03 |
| Bevacizumab | 83 | 0.37 (0.06) | Reference | |
| Ranibizumab | 104 | 0.49 (0.06) | 0.11 (0.01–0.22) | |
| Regimen† | | | | 0.85 |
| PRN | 86 | 0.43 (0.06) | Reference | |
| Monthly | 101 | 0.44 (0.06) | 0.01 (−0.09 to 0.11) | |
| Distance to fovea (mm) | | | | 0.03 |
| Per mm increase | | 0.14 (0.06) | 0.14 (0.01–0.27) | |
| Location of CNV lesion | | | | 0.03 |
| Subfoveal | 112 | 0.37 (0.06) | Reference | |
| Not subfoveal | 75 | 0.49 (0.06) | 0.12 (0.01–0.22) | |
| CNV lesion type | | | | <0.01 |
| Occult only | 129 | 0.30 (0.05) | Reference | |
| Minimally classic | 32 | 0.41 (0.08) | 0.11 (−0.03 to 0.26) | |
| Predominantly classic | 26 | 0.58 (0.08) | 0.28 (0.13–0.43) | |
| GA in fellow eye | | | | 0.03 |
| No | 133 | 0.37 (0.06) | Reference | |
| Yes | 54 | 0.49 (0.06) | 0.13 (0.01–0.24) | |
| Epiretinal membrane | | | | 0.02 |
| No | 153 | 0.35 (0.06) | Reference | |
| Yes | 34 | 0.51 (0.07) | 0.16 (0.03–0.30) | |

CI = confidence interval; CNV = choroidal neovascularization; GA = geographic atrophy; PRN = pro re nata; SE = standard error.
*Because of missing data in risk factors, the total number of cases included for multivariate analysis was not equal to the sum of prevalent cases and incident cases.
†Regimen group was modeled as a time-dependent variable.

area of GA was marginally larger in eyes treated with ranibizumab (Table 1) and there were concerns about the dependence of growth rate on initial area, we included the initial area in the model and found that the initial area was not associated with the growth rate ($P = 0.56$), and the estimated difference in growth rates remained 0.11 mm/year.

No significant difference in mean growth rate was detected between eyes treated monthly and eyes treated on a PRN regimen. Subfoveal location of CNV lesion was associated with slower growth of GA (0.37 [0.06] mm/year) than that of eyes in which the CNV was not located in the subfoveal area (0.49 [0.06] mm/year; $P = 0.03$).

The CNV lesion type was significantly associated with mean growth rate ($P < 0.01$; Table 4). Mean growth rates for all cases together were 0.58 (0.08) mm/year for predominantly classic CNV lesions, 0.41 (0.08) mm/year for minimally classic lesions, and 0.30 (0.05) mm/year for occult-only lesions.

Participants with GA in the fellow eye showed a significantly higher mean growth rate, 0.49 (0.06) mm/year, than participants without GA in the fellow eye, 0.37 (0.06) mm/year ($P = 0.03$). Finally, eyes with epiretinal membrane had a higher mean growth rate, 0.51 (0.07) mm/year, than eyes without epiretinal membrane, 0.35 (0.06) mm/year ($P = 0.02$).

We observed no significant association between the number of injections given and the GA growth rate. Greater distance from the GA lesion to the fovea was associated with a significantly higher GA growth rate ($P = 0.03$; Table 4).

Figure 2 shows a study eye in which GA lesions developed both in the area of the total CNV lesion and outside of the total CNV lesion. There were 40 cases (47%) of prevalent GA and 15 cases (10%) of incident GA in which at least 1 individual GA lesion was outside of the total CNV lesion. Furthermore, 26 of the 40 prevalent cases (65%) and only 2 of the 15 incident cases (13%) did not have GA contiguous with the total CNV lesion.

Individual GA lesions first observed outside the total CNV lesion were smaller (n = 94 lesions; mean, 0.70 $mm^2$) than those associated with the total CNV lesion (n = 214 lesions; 1.07 $mm^2$; $P < 0.001$). The growth rate of individual GA lesions outside of the total CNV lesion was 0.20 (0.05) mm/year, whereas growth of the 214 lesions associated with the total CNV lesion was 0.29 (0.04) mm/year. The difference between these 2 types of GA was of borderline statistical significance ($P = 0.06$).

## Discussion

The overall GA growth rate in CATT, expressed as a square root transformation, was 0.43 (0.03) mm/year. This was similar to the square root transformed rate in 2 recent studies of dry AMD. Domalpally et al[18] reported a growth rate of 0.4 mm/year in 593 Age-Related Eye Disease Study eyes with GA (mean baseline area, 3.17 $mm^2$ [SE, 0.19]), and Yehoshua et al[19] reported a growth rate of 0.37 mm/year in a small clinical trial of 30 patients with AMD (mean baseline area of 4.4 $mm^2$ [SE, 0.81]). Previous methods of calculating GA growth rates, expressed in millimeters squared, reported rates ranging from 1.28 to 2.6 $mm^2$/year.[20–26] If we model the GA growth in CATT in millimeters squared, the mean GA growth rate in our study is 1.65 $mm^2$/year (SE, 0.15; 95% CI, 1.36–1.94), similar to previous reports.

It is of considerable interest that these growth rates, no matter how they are calculated, are similar to those in previous studies. All of these studies included patients with non-neovascular (dry) AMD, whereas in CATT the GA was in neovascular AMD and in most cases in the bed of

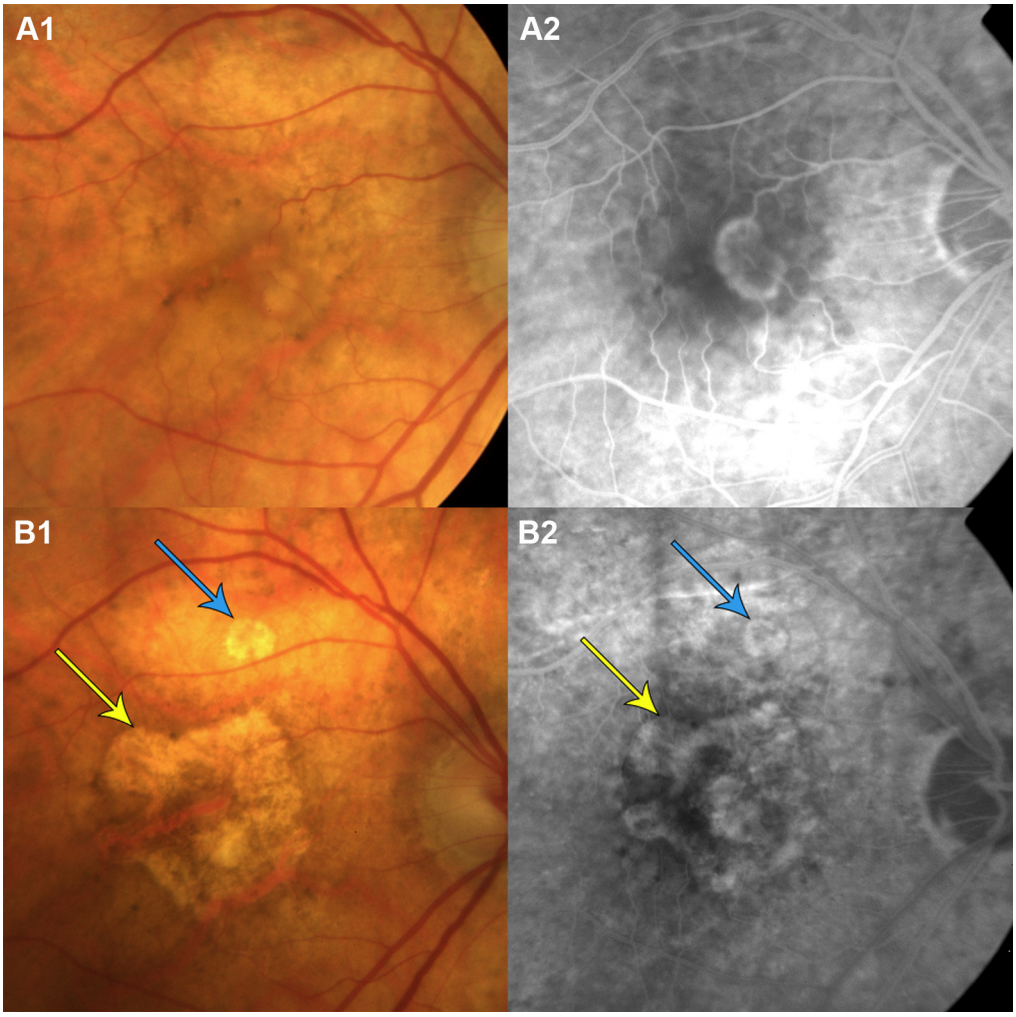


**Figure 2.** Color and fluorescein angiography (FA) photographs at baseline (**A1** and **A2**) and 2 years (**B1** and **B2**). This eye with a classic neovascular choroidal neovascularization (CNV) at baseline shows at 2 years geographic atrophy (GA) lesions associated with the total CNV lesion (**B1** and **B2**, *yellow arrows*) and outside of the area of total CNV lesion (**B1** and **B2**, *blue arrows*).

previous CNV. At the beginning of the study, we debated whether to name the atrophy observed as "GA" when we knew that neovascularization had previously resided in the same location. We elected to use the term "GA" because at the end of 2 years, the clinical appearance was indistinguishable from the GA that most clinicians historically think of as arising in dry AMD. The fact that the growth rate in our patients with neovascular AMD was so similar to that reported in non-neovascular AMD suggests that there may be some commonality between these lesions.

Most of the incident GA in CATT developed within or in close proximity to the total CNV lesion. Only 15 cases of incident GA had individual GA lesions that were clearly outside of the total CNV lesion. Whether GA that develops within or in close proximity to the total CNV lesion may be histologically different from GA that develops away from the total CNV lesion is not known. We measured whether these 2 types of GA have different growth rates and found that GA developing within or in close proximity to the total CNV lesion grows at a faster rate (0.29 mm/year) than GA that is clearly away from the total CNV lesion (0.20 mm/year), but the difference was of borderline significance ($P = 0.06$); therefore, no strong conclusions can be reached. A report by McLeod et al[27] showing dropout of choriocapillaries in areas adjacent to CNV could explain a higher yearly growth of GA associated or in close proximity to CNV.

Because the CATT study did not include a placebo treatment arm, we cannot determine whether anti-VEGF therapy has an effect on GA growth that is different from the natural history of GA developing in eyes with exudative AMD. However, there did seem to be a relative difference between drugs with a higher rate of GA growth observed in eyes treated with ranibizumab compared with bevacizumab. This evidence, together with our previous finding that ranibizumab is associated with a 43% increased risk of GA development in comparison with bevacizumab,[11] suggests that ranibizumab may have a stronger effect on GA formation. Studies performed in mice have shown that anti-VEGF treatment can interfere with the maintenance of the ocular vasculature[28] and may be associated with retinal

pigment epithelial and choroidal atrophy.[29,30] Therefore, it is possible that these medications that block the effects of VEGF may play a role in the development of GA. The differences in the incidence of GA between the 2 medications could be due to differences in their effects on the RPE and choroid or to the fact that eyes treated with ranibizumab had more complete resolution of fluid.[6,8]

Somewhat surprisingly, our results did not show any significant difference in GA growth between subjects treated monthly and subjects treated PRN. In our previous report, we found that 2 years of monthly treatment was associated with a 59% increase in GA incidence compared with PRN treatment.[11] Monthly treatment may be associated with higher GA incidence, but once the GA develops, the growth rate is not significantly different from that observed in the PRN group. Two genetic studies that have recently shown that certain single nucleotide polymorphisms can affect the incidence of AMD pathologic features but do not necessarily affect the progression of these features[23,24] are consistent with our findings.

The number of injections shows a similar pattern. Although a higher number of injections was associated with increased risk of GA development in our previous report,[11] once the GA developed, the growth rate was not significantly associated with number of injections.

In our previous report on the incidence of GA in CATT, we found no significant association between the type of CNV and newly occurring GA.[11] However, our current analyses show that once GA develops, eyes that were enrolled with predominantly classic CNV lesions had an almost doubled GA growth rate when compared with eyes with occult CNV lesions. This may be related to the anatomic position of the CNV in relation to the RPE, or perhaps to a more deleterious effect of classic CNV on the anatomy and function of the retina.

Although epiretinal membrane at baseline was not a significant risk factor for the incidence of GA, as shown in our previous report,[11] the presence of epiretinal membrane in our current study was significantly associated with faster GA growth once GA developed. The significance of this finding is not clear, but it is possible that epiretinal membranes may alter the anatomy of the retina in a way that may affect the diffusion of substances through the retina, resulting in a faster growth of GA.

In summary, our study describes a number of risk factors associated with faster GA growth in patients with AMD treated with anti-VEGF medications for 2 years. These factors were treatment with ranibizumab, female sex, greater distance from the fovea, extrafoveal location of CNV, predominantly classic CNV, GA in the fellow eye, and epiretinal membrane. Although at 2 years the effects of ranibizumab and bevacizumab on visual acuity are similar, the longer-term effects of these treatments on vision need to be studied. In our study, only 12% of GA was located in the foveal center, and this may partly explain why visual acuity is not greatly affected. However, because GA lesions grow over time, the long-term effect of these treatments on central visual acuity needs to be ascertained beyond 2 years.

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## Footnotes and Financial Disclosures

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Abbreviations and Acronyms:
**AMD** = age-related macular degeneration; **CATT** = Comparison of Age-related Macular Degeneration Treatments Trials; **CI** = confidence interval; **CNV** = choroidal neovascularization; **FA** = fluorescein angiography; **GA** = geographic atrophy; **OCT** = optical coherence tomography; **PRN** = pro re nata; **RPE** = retinal pigment epithelium; **SE** = standard error; **VEGF** = vascular endothelial growth factor.

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