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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