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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 2016;■:1−8 © 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