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Natural History of Geographic Atrophy Progression Secondary to Age-Related Macular Degeneration (Geographic Atrophy Progression Study)

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Purpose: The Geographic Atrophy Progression (GAP) study was designed to assess the rate of geographic atrophy (GA) progression and to identify prognostic factors by measuring the enlargement of the atrophic lesions using fundus autofluorescence (FAF) and color fundus photography (CFP).

Design: Prospective, multicenter, noninterventional natural history study.

Participants: A total of 603 participants were enrolled in the study; 413 of those had gradable lesion data from FAF or CFP, and 321 had gradable lesion data from both FAF and CFP.

Methods: Atrophic lesion areas were measured by FAF and CFP to assess lesion progression over time. Lesion size assessments and best-corrected visual acuity (BCVA) were conducted at screening/baseline (day 0) and at 3 follow-up visits: month 6, month 12, and month 18 (or early exit).

Main Outcome Measures: The GA lesion progression rate in disease subgroups and mean change from baseline visual acuity.

Results: Mean (standard error) lesion size changes from baseline, determined by FAF and CFP, respectively, were 0.88 (0.1) and 0.78 (0.1) mm^2 at 6 months, 1.85 (0.1) and 1.57 (0.1) mm^2 at 12 months, and 3.14 (0.4) and 3.17 (0.5) mm^2 at 18 months. The mean change in lesion size from baseline to month 12 was significantly greater in participants who had eyes with multifocal atrophic spots compared with those with unifocal spots ($P < 0.001$) and those with extrafoveal lesions compared with those with foveal lesions ($P = 0.001$). The mean (standard deviation) decrease in visual acuity was 6.2 ± 15.6 letters for patients with image data available. Atrophic lesions with a diffuse (mean 0.95 mm^2) or banded (mean 1.01 mm^2) FAF pattern grew more rapidly by month 6 compared with those with the "none" (mean, 0.13 mm^2) and focal (mean, 0.36 mm^2) FAF patterns.

Conclusions: Although differences were observed in mean lesion size measurements using FAF imaging compared with CFP, the measurements were highly correlated with one another. Significant differences were found in lesion progression rates in participants stratified by hyperfluorescence pattern subtype. This large GA natural history study provides a strong foundation for future clinical trials. *Ophthalmology 2015;■:1–8 © 2015 by the American Academy of Ophthalmology.*

Age-related macular degeneration (AMD) is a multifactorial disease caused by both genetic and environmental factors. Geographic atrophy (GA) is a progressive form of dry AMD that is characterized by irreversible loss of macular retinal tissue, retinal pigment epithelium (RPE), and choriocapillaris. Geographic atrophy is a significant cause of central vision loss, which is irreversible and usually bilateral.[1,2] Geographic atrophy is responsible for severe vision loss in approximately 20% of all patients with AMD, and more than 8 million people are affected worldwide.[3] Oxidative stress, dysregulation of the complement system, and inflammation are thought to play pathophysiologic roles in the development and progression of AMD, although the relative contribution of each of these pathways and molecular mechanisms is not well established.[4–7] Clinical presentation of GA includes variable lesion topography that typically enlarges over time.[6,8] The lesions usually begin to appear in the extrafoveal area with expansion into the foveal center later in the disease course.[9] These lesions lead to progressive degenerative changes in the corresponding RPE cell monolayer, inner choroid, and photoreceptors.[4,8]

There remains a limited understanding of the underlying mechanisms and natural history of GA lesion progression. In clinical studies, mean lesion progression rates vary widely among individuals, ranging from 1.2 to 2.8 mm^2 per year.[4] The size of the lesion, as well as the topography and number of lesions, may affect progression rates.[4] Other risk factors identified include greater distance from the fovea, presence of epiretinal membrane, GA in the fellow eye, and treatment with anti-vascular endothelial growth

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factor medications.[10] However, specific reasons for the differences in progression rates are not well understood. Inconsistencies in study design, including imaging technology used, clinical protocols, and follow-up times, may account for differences in lesion progression rates among studies.[2,8] In previous investigations, color fundus photography (CFP) has been used to measure lesion progression.[11] More recently, fundus autofluorescence (FAF) was used in a multicenter natural history study to follow GA progression (Fundus Autofluorescence Imaging in Age-Related Macular Degeneration [FAM] study).[8,12] Fundus autofluorescence imaging of atrophic lesions in GA is primarily based on autofluorescence properties of RPE cells, with a marked reduction of the autofluorescence signal indicative of RPE loss due to the concomitant disappearance of intracellular dominant fluorophores.[13] The majority of eyes with GA also show abnormal FAF hyperfluorescence patterns that have recently been classified as banded, patchy, focal, and diffuse.[14]

The Natural History of Geographic Atrophy Progression (GAP) study was designed to assess disease progression in participants with GA secondary to AMD, by serial measurement of lesion size using CFP and FAF. Lesion progression was also assessed in participants segregated into disease subtypes that included baseline lesion size, location, and distribution, as well as FAF hyperfluorescence pattern. Previous reports from the GAP study have focused on characteristics of reticular drusen and lesion topography.[15–17] This report compares lesion progression between the 2 different imaging modalities and the relationship between changes in progression rate and changes in best-corrected visual acuity (BCVA). The large data set obtained in this study provides additional insights into natural history of GA and can help determine anatomic and functional outcome measures relevant for future clinical trials.

Methods

The GAP study (ClinicalTrials.gov identifier: NCT00599846) was a prospective, multicenter, noninterventional, observational study. It was originally designed to identify risk factors and to quantify atrophic lesion progression in participants with GA secondary to AMD. With the initiation of the Geographic Atrophy Treatment Evaluation (GATE) study, the GAP study was terminated, and participants were allowed to exit early from the GAP study and enroll in the interventional GATE study if inclusion criteria were met. Informed consent was obtained for all participants, and records were maintained in a Health Insurance Portability and Accountability Act–compliant manner. Institutional Review Board/Independent Ethics Committee approval was obtained, and the research was performed in compliance with the ethical principles of the Declaration of Helsinki and Good Clinical Practice.

The study included participants who were 55 years of age or older and diagnosed with GA secondary to AMD in at least 1 eye, with no evidence of choroidal neovascularization (CNV) in either eye. To be eligible for enrollment, the study eye needed a well-demarcated area of GA with the following lesion subtype characteristics: For unifocal lesions, the lesion had to be $\geq$1.25 mm^2 ($\geq$0.5 disc areas [DA]) and $\leq$17.5 mm^2 ($\leq$7 DA). For multifocal lesions, 1 lesion had to be $\geq$1.25 mm^2 ($\geq$0.5 DA) and all lesions combined (the total lesion size) could not exceed 17.5 mm^2 ($\leq$7 DA). Participants had to have BCVA of $\geq$35 letters in the study eye (i.e., 20/200 Snellen equivalent) and drusen $\geq$63 μm and/or GA in the fellow eye. Exclusion criteria also included ocular diseases that would confound assessments of the retina (e.g., diabetic retinopathy, uveitis); cataract or ocular surgery within 90 days of baseline visit; or any systemic disease with limited survival prognosis (e.g., cancer). To ensure that the study population was representative of all eligible participants, no participant was excluded because of gender, race, occupation, or socioeconomic status. The number and timing of study visits were preset by the study protocol as follows: visit 1, baseline (day 0); visit 2, day 180; visit 3, day 360; visit 4, day 540/exit. There were no interim analyses planned or conducted during the course of the study.

The BCVA was assessed on Early Treatment Diabetic Retinopathy Study charts at baseline and exit visits. Visual acuity data were expressed as the number of letters read on the Early Treatment Diabetic Retinopathy Study chart. The CFP and FAF images were collected at every visit, baseline, and every 6 months for up to 18 months. The CFP was performed with standard fundus cameras that had a minimum resolution of 2000 × 2000 pixels. Confocal scanning laser ophthalmoscopy FAF was performed with HRAc, HRA2, or Spectralis (Heidelberg Engineering, Heidelberg, Germany) using 488 nm blue light excitation. To minimize variability, study-site technicians and photographers were certified to perform the imaging procedures before any study eye image evaluation. The CFP and FAF images were transmitted to a central reading center, the Duke Reading Center, through a secure, web-based portal. Images were then assigned to trained Duke Reading Center or GRADE Reading Center readers who independently assessed the CFP and FAF images. The lesion progression rate was defined as the change in lesion size from baseline to months 6, 12, and 18.

For FAF imaging, comparative grading using 2 computer screens was applied. That is, all confocal scanning laser ophthalmoscopy image data (including blue reflectance and infrared) were available for the analysis of each single visit (whereas CFP and fluorescein angiograms were not available). For each visit, the status of the fovea with regard to any atrophy involvement within a circle of 300 μm in diameter centered on the fovea was classified as "foveal" or "extrafoveal" GA. For each visit, the total size of atrophy was measured by a semiautomatic procedure, which has been described in detail.[18,19] Briefly, the reader manually set a seeding point inside the atrophic region to start an automatic region-growing algorithm that detected well-demarcated areas of severely decreased FAF signal. The reader then manually adjusted the threshold of the algorithm. Holes within the detected GA area could be identified, and further GA areas in the same image could be integrated. Furthermore, a second "blood vessel detection" algorithm was used to exclude interfering blood vessels that had intensities similar to those of atrophic areas. In addition, a shadow correction tool was used when there was uneven illumination, and constraints were placed to improve lesion boundary discrimination of atrophic patches. The minimum size of atrophic areas was predefined as 0.05 mm^2. When there was confluent peripapillary atrophy in addition to central atrophy, a line constraint tool was used to draw a vertical line at the most narrow part (the "bridge") of the confluent atrophy. Any atrophy nasal to this line was disregarded for atrophy quantification. For scaling, the individual scaling factor that is registered by the Heidelberg Eye Explorer during image acquisition was used. All follow-up images were aligned to the baseline image, and the scaling factor of the baseline image was used to correct for variable focusing at different study visits.[19]

This study did not investigate a drug, product, or medical device as defined by the Food Drug and Cosmetic Act. Accordingly, it was not necessary to collect adverse event information. The majority of participants (86%, 317/368) did not complete the study, because the study was terminated when sufficient data were