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Evaluation of Geographic Atrophy from Color Photographs and Fundus Autofluorescence Images

Age-Related Eye Disease Study 2 Report Number 11

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Purpose: To compare measurements of area of geographic atrophy (GA) and change in GA area from color photographs and fundus autofluorescence (FAF) images.

Design: The Age-Related Eye Disease Study 2 (AREDS2) was a prospective multicenter randomized clinical trial evaluating progression of dry age-related macular degeneration (AMD) using color photographs at annual visits over a 5-year study period. The FAF images were acquired in a subset of participants who joined the FAF ancillary study at any of the annual visits over the study period.

Participants: The AREDS2 FAF ancillary study included 8070 corresponding color and FAF visits of 2202 participants with variable follow-up.

Methods: Corresponding color and FAF images were independently evaluated at a central reading center for GA area measurement, lesion growth, and involvement of the macula center.

Main Outcome Measures: Presence, area, growth rate of GA, and involvement of center of macula from color and FAF images.

Results: Hypoautofluorescence was visible in 2048 visits (25.4%). Agreement for the presence of GA between the 2 modalities had a kappa of 0.79, with 23% of visits with hypoautofluorescence not presenting with GA on color photographs. Percentage agreement for GA presence ranged from 43% at baseline to 81% at year 5 with improving agreement over time. The mean difference in GA area between the 2 modalities was 0.5 mm^2, with larger areas on FAF. Growth rate of GA was 1.45 mm^2 from color photographs and 1.43 mm^2 from FAF images. The center of the macula was involved in 51% of color photographs and 56% with FAF images.

Conclusions: Geographic atrophy may be detected earlier by the use of FAF images, but over the course of the study, the 2 modalities become comparable. Progression of GA area is comparable between color photographs and FAF images, but evaluating involvement of the center of the macula may differ, probably because of macular pigmentation blocking autofluorescence. *Ophthalmology 2016;■:1–7 © 2016 by the American Academy of Ophthalmology.*

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Age-related macular degeneration (AMD) is the primary cause of blindness in the economically developed countries and the third leading cause worldwide.[1] In the United States, AMD affects 1.75 million individuals, and the number is predicted to reach 3 million by 2020.[2] Geographic atrophy (GA), the end stage of dry AMD, is a progressive disease that can cause substantial visual impairment; 2-year rate of visual acuity loss of ≥3 lines occurs in 40% of eyes with GA and baseline visual acuity of 20/50 or better.[3] The natural history of GA has been studied in detail, and currently there is no approved treatment available for GA.[4–10] Change in GA area has been used as an outcome measure for clinical trials evaluating treatments of the condition.[6,10–12] Historically, area measurements of GA were performed using stereoscopic color fundus photographs.[4,13] Fundus autofluorescence (FAF) imaging is a more recent modality from which GA location and extent can be accurately measured; GA typically is visualized as dark areas due to absence of autofluorescence.[14]

Several groups have evaluated the rate of GA enlargement by color photographs, FAF, or optical coherence tomography scans.[4,10,12,15,16] Sunness et al[8] reported a mean overall GA enlargement rate of 2.6 mm^2/year (median area enlargement rate of 2.1 mm^2/year) using film color photographs. The Age-Related Eye Disease Study Research Group evaluated change in GA area over a 4-year period with images digitized from film color photographs; mean change in area was 2.03 mm^2 in the first year, and

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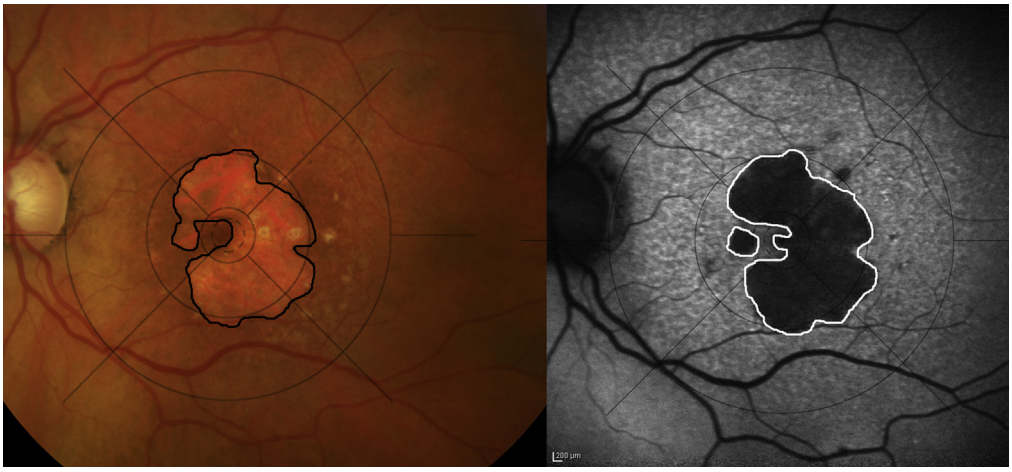

Figure 1. Color photograph and corresponding fundus autofluorescence (FAF) image with Age-Related Eye Disease Study (AREDS) grid overlay and planimetry outline of geographic atrophy (GA). The center of the macula is just involved in the color photograph, whereas the hypoautofluorescence merges with the darkness of the fovea in the FAF image. The area of GA is 7.43 mm^2 with the color photograph and 7.36 mm^2 with the FAF image.

enlargement rate thereafter was 1.71 mm^2/year.[10] Holz et al[17] found a mean growth rate of 1.74 mm^2/year (median area 1.52 mm^2/year) using FAF images. The Geographic Atrophy Progression (GAP) study reported a growth of 1.85 mm^2 with FAF and 1.57 mm^2 with color photographs in 1 year.[15] Fundus autofluorescence offers the advantage of improved contrast resulting in more precise delineation of GA borders, which enables semiautomated delineation of GA area and has been more widely used in GA imaging over recent years.[18]

The Age-Related Eye Disease Study 2 (AREDS2) was a multicenter phase III randomized controlled clinical trial designed to assess the effects of nutritional supplements on the course of AMD in people at moderate to high risk of progression to late AMD. Eligibility included participants with bilateral intermediate AMD or advanced AMD in 1 eye.[19] The primary outcome of the study was development of late AMD, defined as center-involved GA or neovascularization. Digital color fundus photographs taken at baseline and annual visits were sent to the AREDS2 Reading Center (University of Wisconsin Fundus Photograph Reading Center, Madison, WI) for evaluation. During the second year of the study, an FAF ancillary study was added and FAF images were submitted by a subset of clinical sites at annual visits along with the color photographs. Sites were permitted to join the FAF ancillary study over the course of the study period. This report compares results from the AREDS2 FAF ancillary study with temporally coincident stereoscopic color fundus photographs in eyes with GA. We report findings on cross-sectional and longitudinal comparisons of GA area measurements from color photographs and corresponding FAF images.

Methods

The study design and subject characteristics are detailed in AREDS2 Report Number 1.[19] The study was conducted under the Declaration of Helsinki and approved by institutional review boards at all participating clinics. Written informed consent was obtained from all study participants.

Digital stereoscopic color photographs of AREDS2 participants were obtained by certified photographers and sent to the AREDS2 Reading Center for evaluation. Evaluation of color photographs was performed by certified and trained graders with no access to any other visits, imaging modalities including FAF images, visual acuity scores, or other medical data. The details of the imaging protocol and evaluation methods using color photographs have been described.[20] In brief, calibrated stereoscopic images were viewed in a standardized digital viewing platform (ImageNet 2000, Topcon Corp, Tokyo, Japan) after color contrast and illumination adjustment.[21] Geographic atrophy from color photographs was defined as a lesion equal to or larger than drusen circle I-2 (diameter 430 μ, area 0.15 mm^2) in its widest diameter with at least 2 of the following features present: circular shape, sharp (well-demarcated) edges, and loss of the retinal pigment epithelium (partial or complete depigmentation of the retinal pigment epithelium, typically with exposure of underlying choroidal vessels). Planimetry tools were used to demarcate the area of GA within the Age-Related Eye Disease Study grid. If noncentral, distance of the proximity of the atrophy border closest to the center was documented.

Fundus autofluorescence images were obtained from Heidelberg Retina Angiograph (Heidelberg Engineering, Heidelberg, Germany) instruments or fundus cameras with FAF capability (outfitted with the appropriate excitation and barrier filters) by certified operators. A single image was acquired at 30° centered on the macula (Field 2). The images from Heidelberg Retina Angiograph were captured in high-speed mode (768×768 pixels) using the Automatic Real Time Mean function set at 14. Colors were taken before FAF images to precipitate photoreceptor pigment bleaching.[22] All images were viewed in the same software to standardize the evaluation for color photographs, fundus camera–based FAF images, and Heidelberg Retina Angiograph–based FAF images. Hypoautofluorescence was classified as well-defined, homogenously black areas with a minimum size of drusen circle I-2 in its widest diameter. Areas of hypoautofluorescence were demarcated using software planimetry tools. Areas were summed for eyes with multifocal GA to yield a single value for analysis. Involvement of macula by the hypoautofluorescent lesion also was noted. The macula was considered