

Progression of Age-Related Geographic Atrophy: Role of the Fellow Eye

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PURPOSE. To evaluate the role of fellow eye status in determining progression of geographic atrophy (GA) in patients with age-related macular degeneration (AMD).

METHODS. A total of 300 eyes with GA of 193 patients from the prospective, longitudinal, natural history FAM Study were classified into three groups according to the AMD manifestation in the fellow eye at baseline examination: (1) bilateral GA, (2) early/intermediate AMD, and (3) exudative AMD. GA areas were quantified based on fundus autofluorescence images using a semiautomated image-processing method, and progression rates (PR) were estimated using two-level, linear, mixed-effects models.

RESULTS. Crude GA-PR in the bilateral GA group (mean, 1.64 mm²/y; 95% CI, 1.478–1.803) was significantly higher than in the fellow eye early/intermediate group (0.74 mm²/y, 0.146–1.342). Although there was a significant difference in baseline GA size ($P = 0.0013$, t -test), and there was a significant increase in GA-PR by 0.11 mm²/y (0.05–0.17) per 1 disc area (DA; 2.54 mm²), an additional mean change of -0.79 (-1.43 to -0.15) was given to the PR beside the effect of baseline GA size. However, this difference was only significant when GA

size was ≥ 1 DA at baseline with a GA-PR of 1.70 mm²/y (1.54–1.85) in the bilateral and 0.95 mm²/y (0.37–1.54) in the early/intermediate group. There was no significant difference in PR compared with that in the fellow eye exudative group.

CONCLUSIONS. The results indicate that the AMD manifestation of the fellow eye at baseline serves as an indicator for disease progression in eyes with GA ≥ 1 DA. Predictive characteristics not only contribute to the understanding of pathophysiological mechanisms, but also are useful for the design of future interventional trials in GA patients. (ClinicalTrials.gov number, NCT00393692.) (*Invest Ophthalmol Vis Sci.* 2011; 52:6552–6557) DOI:10.1167/iovs.11-7298

Geographic atrophy (GA) represents the atrophic late-stage manifestation of dry age-related macular degeneration (AMD). It is responsible for approximately 35% of all cases of late AMD.^{1,2} Although the overall incidence of neovascular AMD is still higher, GA has recently been found to occur four times as often as neovascular AMD in individuals ≥ 85 years of age, reflecting its important impact on public health in aging populations.¹

As opposed to the recent breakthrough by anti-vascular endothelial growth factor (VEGF) therapy for the active neovascular form, there is to date no efficacious treatment for patients with GA, to prevent, halt, or slow the disease process.

GA is characterized by the development of well-defined areas of outer retinal atrophy which progressively enlarge over time at a mean rate of 1.3 to 2.6 mm²/y.^{3–9} Atrophic areas of the retina are associated with photoreceptor, RPE, and choriocapillaris dropout, and thus a corresponding absolute scotoma (i.e., complete loss of retinal sensitivity). Therefore, atrophy expansion is associated with progressive visual impairment.^{10,11}

A high interindividual variation of atrophy progression rates has been independently reported by various longitudinal natural history studies^{3,4,7–9,12,13} which cannot be explained by baseline atrophy or by any of the demographic factors analyzed so far. We have previously shown that distinct phenotypic perilesional patterns, identified by fundus autofluorescence (FAF) imaging, affect rates of GA spread,^{8,14} whereas known genetic risk variants relevant to the onset of AMD do not.¹⁵ To date, the underlying pathophysiological pathways triggering spread of atrophy are still poorly understood.

Most epidemiologic and natural history studies on progression of GA are based on color fundus (CF) photographs.^{6,7,9,16} However, this imaging technique has limitations with regard to identification of GA areas as well as precise outlining of lesion boundaries and therefore accurate quantification over time. Measurements of areas may be difficult due to interpatient variability of fundus pigmentation, media opacities, the presence of drusen, crystalline deposits, and small satellites in the

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presence of multifocal atrophy.^{17–19} With the advent of confocal scanning laser ophthalmoscopy, fundus autofluorescence (FAF) imaging has been brought forward as a new modality that has been shown to be suitable for precise and reproducible GA identification and measurements.^{20–22} FAF imaging has been used to observe GA progression in the Fundus Autofluorescence in Age-related Macular Degeneration Study (FAM), a multicenter study conducted in Germany,^{8,13,23} and in other natural history studies and ongoing interventional trials in patients with GA.^{24,25}

The purpose of this study was to investigate whether AMD manifestation in the fellow eye, determined at baseline examination, is associated with different growth rates over time in patients with GA secondary to age-related macular degeneration (AMD).

METHODS

Patients

Patients with (1) uni- and/or multifocal GA in at least one eye, (2) sufficient image quality to accurately determine the size of atrophy, and (3) clearly definable diagnosis of the fellow eye at each visit were included from the GA arm of the longitudinal natural history, multicenter FAM (Fundus Autofluorescence in Age-related Macular Degeneration) study. The study complied with the Declaration of Helsinki and was approved by the local Institutional Review Boards and the local Ethics Committees at the participating study centers: the Department of Ophthalmology, University of Aachen, Germany (A), the Department of Ophthalmology, University of Bonn, Germany (B), the Department of Ophthalmology, University of Heidelberg, Germany (H), the Department of Ophthalmology, University of Leipzig, Germany (L), St. Franziskus Hospital Münster, Germany (M), and the Department of Ophthalmology, University of Würzburg, Germany (W).

Informed consent was obtained from each patient after explanation of the nature and possible consequences of the study.

Exclusion criteria included any history of retinal surgery, laser photocoagulation, radiation therapy, or other retinal diseases in either eye. (For a more detailed description of inclusion and exclusion criteria, see Holz et al.⁸)

Follow-up visits were scheduled every 12 months. At each visit, patients underwent a routine ophthalmic examination, including determination of best corrected visual acuity using Early Treatment Diabetic Retinopathy Study (ETDRS) charts. Pupils were dilated with 1.0% tropicamide and 2.5% phenylephrine. A standardized case report form (CRF), including ophthalmic history, possible risk factors, and family history, was completed for each patient.^{8,11,23,26}

FAF Imaging

At each visit, FAF was recorded with a confocal scanning laser ophthalmoscope (cSLO, Heidelberg Retina Angiograph, HRA classic and HRA 2; Heidelberg Engineering, Germany), the optical and technical principles of which have been published.^{27,28} Images were recorded in accordance with a standard operation procedure (SOP), including focusing in the red-free reflectance mode ($\lambda = 514$ nm for HRA classic, $\lambda = 488$ nm for HRA 2), acquiring a series of $30^\circ \times 30^\circ$ images (488

nm), and calculating mean images after automated alignment (of nine single images) to amplify signal-to-noise ratio using image-analysis software (Heidelberg Eye Explorer; Heidelberg Engineering).²⁰ The image resolution was 512×512 pixels for the HRA classic and 768×768 pixels for the HRA 2.

The study centers A, H, L, M, and W started image acquisition with the HRA classic (first patients were enrolled in 1996) while study center B (patient recruitment started in 2004) used the HRA2 from the beginning.

A, H, L, and M upgraded the FAF imaging device from the HRA classic to the HRA2; therefore, in these study centers, eyes may have changed the imaging device during follow-up (see below). Study center W used the HRA classic throughout.

Altogether, 1064 single FAF images were analyzed; of these, 719 images were acquired with the HRA classic and 345 images with the HRA2. A total of 163 eyes were imaged only with the HRA classic over time, whereas 80 eyes were imaged solely with the HRA2. In 57 eyes, there was a change in the FAF acquisition device (from HRA classic to HRA2) during the follow-up period (Table 1).

Definition of GA due to AMD

The fundusoscopic appearance of GA is characterized by one or more well-defined, usually more or less circular, patches of partial or complete depigmentation of the retinal pigment epithelium, typically with exposure of underlying large choroidal blood vessels.³

In the FAM study, GA due to AMD is further defined as a sharply demarcated lesion with clearly reduced FAF of ≥ 0.05 mm² (~ 178 μ m in diameter) that does not correspond to exudative retinal changes (e.g., bleeding, exudates, fibrous scar) in an eye with funduscopically visible soft drusen and/or retinal pigment abnormalities consistent with AMD.

Image Processing and Quantification of Total Size of Atrophy

Serial FAF images of the same eye were processed by using image-analysis software (Picture Window Pro 4.0.1.2 analysis software; Digital Light & Color, Cambridge, MA). Four points—anatomic landmarks surrounding the atrophic area, such as bifurcations of blood vessel—were selected in each serial image of an eye, and the four-point alignment function was applied, whereby the respective overlay image was shifted, rotated, scaled, and warped so that all four corresponding points were congruent in serial images. This image processing resulted in an adjustment of variable focusing and different image resolution between serial examinations of the same eye.

As previously described, the total size of GA was then measured in the processed FAF images by automated imaging analysis software that uses region-growing algorithms to segment GA areas.^{20,21} To ensure an accurate conversion from pixel values to millimeters during the measurement and therefore to allow for comparison of the GA lesion size between images, we used the image-specific scale factor given by the instrument (HRA classic or HRA2). This factor is based on the Gullstrand eye, assuming standard corneal radii and taking into account the individual spherical refraction as adjusted by the operator during image acquisition and image resolution. As all serial images of one eye were aligned to the baseline image, the scale factor of the baseline FAF image was

TABLE 1. Application of the HRA Classic and HRA 2, for Fundus Autofluorescence Imaging in Patients/Eyes Sorted by Diagnosis

Diagnosis Fellow Eye	Patients (n)	Eyes (n)	Eyes Imaged by HRA Classic n (%)	Eyes Imaged by HRA2 n (%)	Eyes with Change from HRA Classic to HRA2 n (%)
Bilateral GA	148	255	142 (55.7)	67 (26.3)	46 (18)
Early AMD	16	16	8 (50)	5 (31.3)	3 (18.8)
CNV	29	29	13 (44.8)	8 (27.6)	8 (27.6)
Total	193	300	163 (54.3)	80 (26.7)	57 (19)

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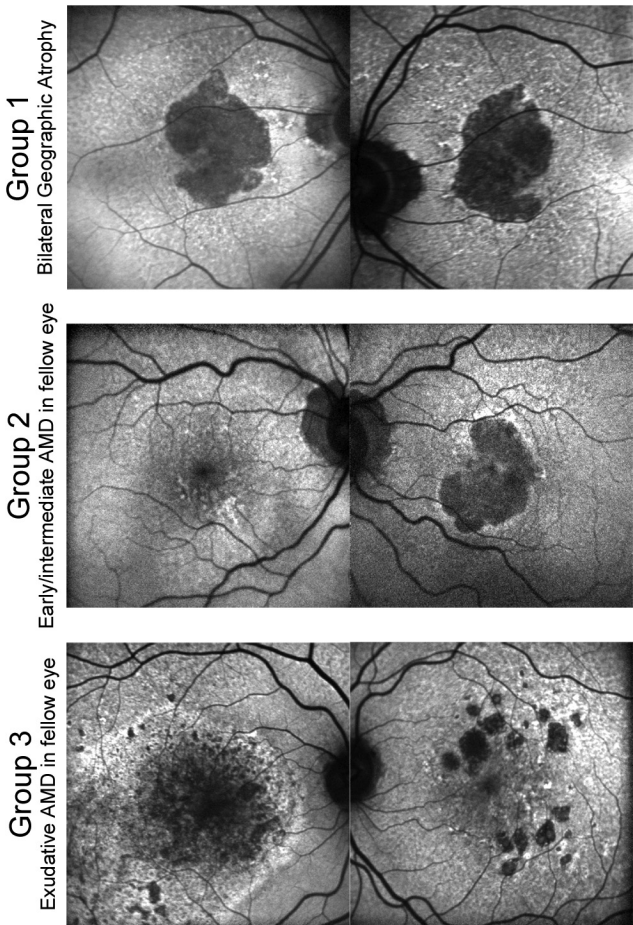


FIGURE 1. For each of the three groups, bilateral fundus autofluorescence images for one representative patient are shown.

used for all serial images of the same eye. The minimum size of a single atrophic patch was arbitrarily set at 0.05 mm². If there was more than one area of atrophy ≥ 0.05 mm² in one eye, the total size of atrophy would represent the sum of all atrophic areas.

Classification

To determine whether the growth rate of GA over time is associated with the AMD manifestation in the fellow eye determined at the baseline visit, patients were classified into three groups: (1) bilateral GA (one or both eyes considered as study eye), (2) early/intermediate AMD in the fellow eye (drusen and pigmentations, no GA ≥ 0.05 mm²), and (3) exudative AMD in the fellow eye (Fig. 1). For the latter, the diagnosis of exudative AMD was based on the CRF documented by the investigator. Fluorescein angiography was performed at the discretion of the investigator when signs or symptoms were suggestive of exudative disease, including exudates, hemorrhages, and fibrosis, were identified. In addition, recorded images were scrutinized for such changes in the reading center. This included FAF and fluorescein

angiography images, if available, as well as red-free, infrared reflectance, and color fundus photographs that were additionally acquired in FAM study patients. Optical coherence tomography (OCT), which becomes increasingly important in noninvasive differentiation between exudative and nonexudative AMD²⁹ was not available when the FAM study was initiated. Meanwhile, the study protocol has been amended to include spectral-domain OCT imaging, but it was not included in the current analysis.

Statistical Analysis

To assess the difference between growth rates of the three groups a two-level, linear, mixed-effects model, with patient-specific and eye-specific random intercepts and slopes, was applied using all of the available data. Random effects adjust for unobserved heterogeneity and help to handle correlated observations that occur in two levels within patients: related observations over follow-up time and those between the two eyes of a patient with bilateral GA (i.e., group 1). On eye level, the regression lines belonging to both eyes of an individual patient will vary, but less extensively than the regression lines between two different individuals.

A more detailed description of the modeling strategy is given elsewhere.³⁰ Two statistical software packages (SAS, ver. 9.2; SAS Institute Inc., Cary, NC, and R version 2.11.1, www.r-project.org) were used for analyzing the data.

RESULTS

Characteristics of Study Eyes and Patients

A total of 300 GA eyes of 193 patients met the inclusion criteria and were included in the analysis. Overall, 76.7% of the patients had bilateral GA without evidence of CNV, 8% had GA in one eye and drusen or pigmentary changes without advanced AMD in the fellow eye, and 15% had GA without CNV in one eye and CNV or disciform scar in the fellow eye. Table 2 shows the frequency and major baseline demographics for all three strata. In seven patients, the diagnosis of the fellow eye changed during the observation period; only data before this transition were used for statistical analysis.

For 95.4% of study eyes, longitudinal data were available. Also data of eyes with only one measurement were considered for hierarchical modeling, as these single observations do contribute information to the estimation of variances and between-subject effects.

GA Progression Rates in the Different Diagnosis Groups

The two-level, linear, mixed-effects model revealed a mean population-specific progression rate of 1.640 mm²/y (95% CI, 1.478–1.803) for group 1 (bilateral GA), 0.744 mm²/y (0.146–1.342) for group 2 (early/intermediate AMD in the fellow eye), and 1.362 mm²/y (0.937–1.787) for group 3 (CNV in the fellow eye; Fig. 2).

Influence of Baseline GA Size on GA Progression Rate

To assess whether there was any difference between the three diagnosis groups, a closed-testing principle based on the

TABLE 2. Data for the Study Groups

	Patients (Eyes) (n)	Mean Age (y)	Male/Female (n)	Mean Size of Baseline Atrophy (mm ²)	Mean Follow-up Period (y)
Group 1 Bilateral GA	148 (255)	73.43 (72.10–74.75)	57/91	7.08 (6.38–7.78)	2.80 (2.54–3.07)
Group 2 Early/intermediate AMD in fellow-eye	16 (16)	70.25 (67.56–72.93)	7/9	3.50 (1.59–5.41)	3.47 (2.23–4.72)
Group 3 Exudative AMD in fellow eye	29 (29)	74.96 (72.36–77.57)	11/18	6.74 (4.12–9.36)	2.56 (1.77–3.35)

For quantitative data, mean (95% CI) are displayed.

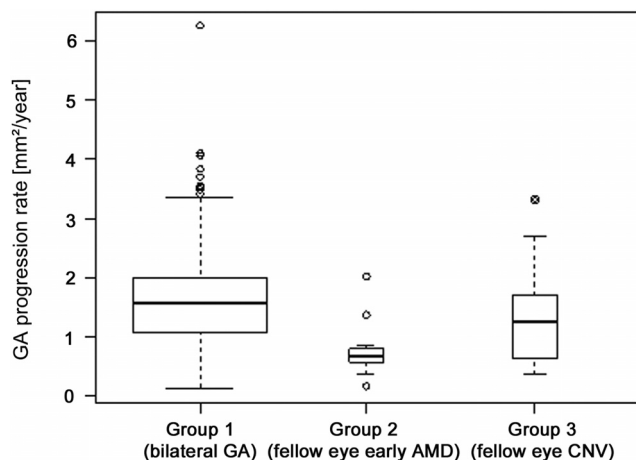


FIGURE 2. Boxplot displaying the distribution of estimated GA progression rates for all 300 eyes classified by disease status of their fellow eyes. Shown are the median (*horizontal bar*) and the 25% and 75% percentiles (*top and bottom boundaries* of the box). Values beyond the box but within $Q1 - 1.5 \times IQR$ to $Q3 + 1.5 \times IQR$ are depicted by the whiskers. Boxes are drawn with widths proportional to the square-roots of the number of eyes within the groups. Group 1 (bilateral GA), 1.640 mm²/y (95% CI, 1.478–1.803); group 2 (early AMD in the fellow eye), 0.744 mm²/y (0.146–1.342); group 3 (choroidal neovascularization in the fellow eye), 1.362 mm²/y (0.937–1.787).

Kruskal-Wallis test was applied. The results revealed a substantial difference in baseline GA size, which significantly differed between groups 1 and 2 ($P = 0.0013$, *t*-test), as well as between groups 2 and 3 ($P = 0.044$, *t*-test). Groups 1 and 3 did not differ significantly in GA size quantified at first measurement ($P = 0.799$, *t*-test). Figure 3 illustrates these findings.

Analysis of the GA progression rate, without considering the three fellow eye groups, revealed a significant influence of the baseline GA size on the GA progression rate in the current GA cohort. For each increase in GA size of 1 disc area (DA) there was a significant increase in the progression rate (0.11 mm²/y; 95% CI, 0.05–0.17; Fig. 4, solid regression line).

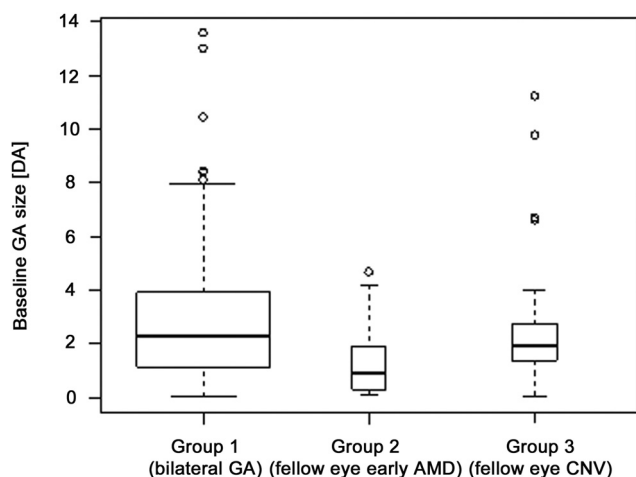


FIGURE 3. Boxplot for size (quantified by DA = 2.54 mm²) of GA at baseline in the three different diagnosis groups. There was a significant difference between group 1 (bilateral GA) and group 2 (early AMD in the fellow eye; $P = 0.001$), as well as between groups 2 and 3 (CNV in the fellow eye; $P = 0.044$). Between groups 1 and 3, there was no significant difference with respect to baseline GA size ($P = 0.799$, *t*-test).

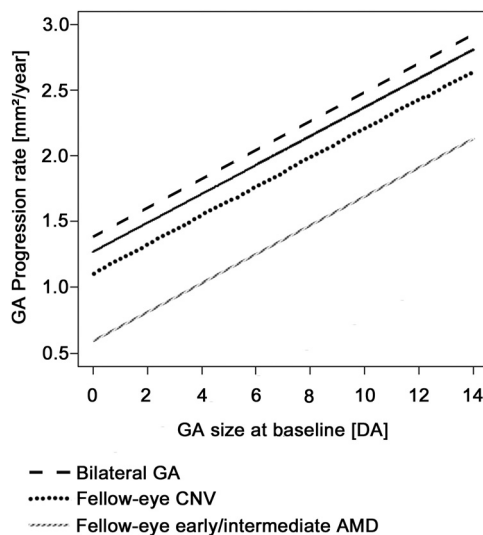


FIGURE 4. Association between estimated decay rate and GA baseline size. *Solid line*: regression model which adjusts only the progression rate with respect to baseline GA size. *Patterned lines*: extended regression model with interaction effects between fellow eye groups and time. For early AMD group (*bottom dashed line*), the negative shift in comparison to overall progression rate becomes most obvious (DA = 2.54 mm²).

Impact of the Diagnosis of the Fellow Eye on the GA Progression Rate

To analyze the additional impact of the diagnosis of the fellow eye on the GA progression rate, we extended the regression model by introducing interaction effects between fellow eye groups and time. This method revealed for the early/intermediate AMD group, compared with the bilateral GA group, that a mean change of -0.79 (95% CI, -1.43 to -0.15) occurred in the progression rate, besides the effect of the baseline atrophy size (Fig. 4, top dashed line versus bottom dashed line). There was also a slight decrease in the CNV group compared with the bilateral GA group, but without significance (-0.29 ; -0.75 – 0.17 ; Fig. 4, top dashed line versus dotted line).

Impact of the Diagnosis of the Fellow Eye on the GA Progression Rate in Different Baseline GA Size Groups

There was no significant difference in GA progression rate in the subgroup of eyes with GA size of <1 DA at baseline between all three groups.

In the case of GA size ≥ 1 DA at baseline, growth rate was significantly higher in the bilateral GA group (1.7 mm²/y; 95% CI, 1.542–1.859) compared with the fellow eye early/intermediate AMD group (0.955 mm²/y; 0.369–1.542; Table 3, Fig. 5).

DISCUSSION

This study suggests that the disease stage and phenotypic manifestation of the fellow eye serves as an indicator of the pace of atrophy enlargement and thus the expansion of corresponding absolute scotoma over time. There was a significantly faster GA progression rate in bilateral GA compared with that in the fellow eye early/intermediate AMD group, at least in eyes with a baseline GA size equal to or larger than 1 DA. The present study is in accordance with recent analyses in the context of other prospective natural history studies on GA showing a significant influence of baseline lesion size on the GA progression rate.⁷ (Holz et al. *IOVS* 2010;51:ARVO E-Ab-

TABLE 3. Estimates for Population-Averaged Mean Progression Rates

	Baseline GA Size <1 DA	Baseline GA Size ≥1 DA
Group 1: bilateral GA	0.996 (0.638–1.354) <i>n</i> = 23 eyes	1.700 (1.542–1.859) <i>n</i> = 232 eyes
Group 2: early/intermediate AMD in the fellow eye	0.251 (–0.374–0.877) <i>n</i> = 5 eyes	0.955 (0.369–1.542) <i>n</i> = 11 eyes
Group 3: exudative AMD in the fellow eye	0.743 (0.232–1.255) <i>n</i> = 4 eyes	1.447 (1.036–1.858) <i>n</i> = 25 eyes

Data show GA progression (mm²/y) with 95% CI for all six strata. Results are those of a mixed-effects model, adjusted for both disease status of the fellow eye and baseline GA size (DA = 2.54 mm²).

strat 94). However, this parameter alone does not entirely explain the differences in the progression rates between different fellow eye groups.^{7,8}

Here, we demonstrate that there is a baseline–decay rate interaction as well as a diagnosis group–decay rate interaction and that, even after adjustment for the GA baseline size, the diagnosis group affects the decay rate.

The mechanisms responsible for the association between the disease status of the fellow eye and GA progression are not yet understood. It may be speculated that the status of the fellow eye reflects the individual disease activity for both eyes. The longer a late-stage AMD manifestation is present in the fellow eye, the more the probability increases that in the other eye the cell structures are severely diseased and thus GA will tend to progress faster.

Hence, the disease stage of the fellow eye appears to serve as a surrogate parameter for the severity of GA in the other eye. This assumption would encompass a change in GA progression rate in an individual eye with change of the diagnosis of the fellow eye over time and, therefore, indicates that a nonlinear growth curve model may be more appropriate in a longer follow-up of a given patient. In contrast, the growth of GA in a short period can be described well with a linear model.^{3,7,8,30}

In the present study population, there were only seven patients with a conversion in the disease manifestation of the fellow eye. Analysis of a possible increase in GA progression with change in the fellow eye from early- to late-stage AMD will be addressed in the ongoing study with a longer follow-up period.

Other factors that have been shown to have an impact on GA progression rate include the configuration of GA. Klein et al.⁹ reported that eyes with multifocal atrophic lesions were

more likely to have higher enlargement rates than those with unifocal lesions. Furthermore, a relevant impact of phenotypic features of FAF abnormalities in the junctional zone of GA on atrophy progression has been demonstrated.^{8,14} In addition, Sunness et al.⁷ reported that knowledge of prior enlargement rates is indicative of subsequent enlargement rates. Another striking observation is the high degree of concordance/symmetry of progression rates between eyes in bilateral GA.^{3,7,9,13} This would indicate that multiple factors may influence GA progression rate or, more precisely, may serve as a surrogate parameter for disease progression in an individual eye.

The identification of predictive factors for atrophy progression may not only add to our understanding of underlying pathophysiological mechanisms, but also aid in the design of future interventional trials in GA patients. Employing enrichment criteria for the recruitment of fast progressors would reduce time scales for interventional clinical trials and costs and might facilitate the detection of a therapeutic signal (i.e., slowing progression of GA). Based on the results of the present study, the preferential inclusion of eyes with baseline GA larger than 1 DA and late-stage AMD in the fellow eye seems prudent. As patients with GA in one eye who have CNV or disciform scar in the fellow eye are at the highest risk for developing CNV in the GA eye,³¹ inclusion of patients with bilateral GA appears to be most reasonable.

Limitations of this study include the differences in the number of eyes in the different diagnosis groups, with a small number with CNV and early/intermediate AMD in the fellow eye. This is not only a result of a selection bias in the recruitment process of the FAM study, but also of referral patterns and perhaps symmetry in disease onset with regard to advanced atrophic AMD. Overall, 77% of patients in the present study had bilateral GA. Sunness et al.⁷ reported 63% with bilateral GA when analyzing the diagnosis in the fellow eye and, as in our cohort, there were only 8% of patients with early AMD in the fellow eye. Hence, the power of the current data is too low to discover any differences in eyes with baseline GA size smaller than 1 DA. Because of the limited follow-up period and limited number of patients so far with a conversion in the diagnosis in the fellow eye, we were unable to investigate whether a change in the disease status of the fellow eye leads to an acceleration of the enlargement rate that would be expected on the basis of the current analysis.

A further limitation may be the use of two different cSLO systems for longitudinal acquisition of FAF images that differ in the digital image resolution (512 × 512 pixel for HRA and 768 × 768 pixels for HRA2). In this study, a possible confounding factor was minimized by image alignment of all follow-up images to the corresponding baseline image and by considering the image-specific scaling factor for the measurement process, which takes into account the image resolution and the focus setting during the recording of FAF. The image-alignment process herein was performed after acquisition, as a software

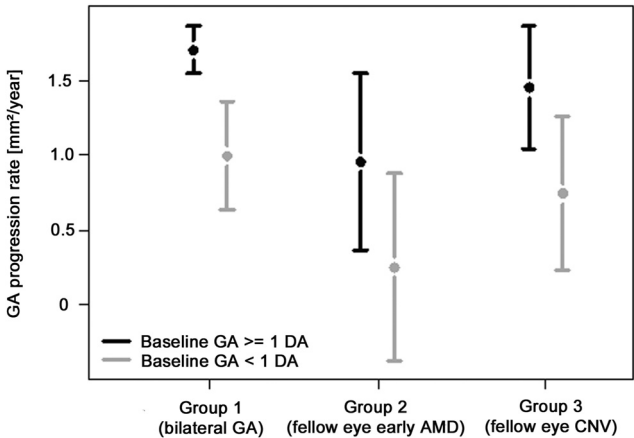


FIGURE 5. GA progression rates (mean and 95% CI) for the three different diagnosis groups stratified for baseline GA size ≥1 versus <1 DA (DA = 2.54 mm²).

tool for automated alignment of serial FAF images during image acquisition was not available for the HRA classic or HRA2. Meanwhile, further developments of Heidelberg Engineering systems (Spectralis) now allow for automated real-time alignment of serial images.

In conclusion, this study shows that even after adjustment for GA baseline size, the diagnosis of the fellow eye indicates the GA progression rate in patients with AMD. The data of the FAM study may further contribute to our understanding of the disease process and to the design of future interventional trials in GA aimed at slowing GA progression.

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