Correlation between the Area of Increased Autofluorescence Surrounding Geographic Atrophy and Disease Progression in Patients with AMD

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PURPOSE. To test the hypothesis that the extension of areas with increased fundus autofluorescence (FAF) outside atrophic patches correlates with the rate of spread of geographic atrophy (GA) over time in eyes with age-related macular degeneration (AMD).

METHODS. The database of the multicenter longitudinal natural history Fundus Autofluorescence in AMD (FAM) Study was reviewed for patients with GA recruited through the end of August 2003, with follow-up examinations within at least 1 year. Only eyes with sufficient image quality and with diffuse patterns of increased FAF surrounding atrophy were chosen. In standardized digital FAF images (excitation, 488 nm; emission, >590 nm), total size and spread of GA was measured. The convex hull (CH) of increased FAF as the minimum polygon encompassing the entire area of increased FAF surrounding the central atrophic patches was quantified at baseline. Statistical analysis was performed with the Spearman’s rank correlation coefficient (ρ).

RESULTS. Thirty-nine eyes of 32 patients were included (median age, 75.0 years; interquartile range [IQR], 67.8–78.9); median follow-up, 1.87 years; IQR, 1.43–3.37). At baseline, the median total size of atrophy was 7.04 mm² (IQR, 4.20–9.88). The median size of the CH was 21.47 mm² (IQR, 15.19–28.26). The median rate of GA progression was 1.72 mm² per year (IQR, 1.10–2.83). The area of increased FAF around the atrophy (difference between the CH and the total GA size at baseline) showed a positive correlation with GA enlargement over time (ρ = 0.60; P = 0.0002).

CONCLUSIONS. FAF characteristics that are not identified by fundus photography or fluorescein angiography may serve as a prognostic determinant in advanced atrophic AMD. As the FAF signal originates from lipofuscin (LF) in postmitotic RPE cells and since increased FAF indicates excessive LF accumulation, these findings would underscore the pathophysiological role of RPE-LF in AMD pathogenesis. (Invest Ophthalmol Vis Sci. 2006;47:2648–2654) DOI:10.1167/iows.05-0892

Geographic atrophy (GA) of the retinal pigment epithelium (RPE) is responsible for irreversible severe visual loss in approximately 20% of all patients with age-related macular degeneration (AMD). The pathophysiological mechanisms underlying the atrophic process that involves the RPE, the outer neurosensory retina, and the choriocapillaris are poorly understood to date.2–5

The accumulation of lipofuscin (LF) in postmitotic human RPE cells and its harmful effects on normal cell function have been largely studied in vitro with fluorescence microscopic techniques.6–13 It has been shown that fundus autofluorescence (FAF) in vivo is mainly derived from LF in the RPE and that it can be imaged over large retinal areas with the scanning laser ophthalmoscope (SLO).14–18

Previous studies have been focused on the importance of increased FAF in the junctional zone of GA in patients with AMD. The development of new and the enlargement of existing atrophic areas over areas with previously increased FAF have been described.19 Different patterns of increased FAF have been shown.20 Variable degrees of loss of retinal sensitivity over areas with increased FAF have been identified.21 Furthermore, it has been shown that, in areas of increased FAF outside GA, the loss of dark-adapted retinal sensitivity of the rod system considerably exceeds the light-adapted sensitivity loss of the cone system.22

The present study was designed to test the hypothesis that the extension of areas with increased FAF surrounding atrophic patches is associated with the GA enlargement over time in patients with advanced atrophic AMD.

METHODS

Patients with GA secondary to AMD were included from the longitudinal natural history arm of the multicenter Fundus Autofluorescence in Age-Related Macular Degeneration Study (FAM). Only patients older than 55 years, with clear media to allow FAF imaging and with uni- or multifocal GA, were included. Exclusion criteria included any history of retinal surgery, laser photocoagulation, and radiation therapy or other retinal diseases in the study eye, including diabetic retinopathy, or hereditary retinal dystrophies. Fluorescein angiography was performed only if there were funduscopic signs present indicative of neovascular AMD in addition to patches of GA. Such eyes were ex-
The reflectance signal does not contribute to the obtained FAF image. For eyes previously characterized by other FAF patterns, all eyes were chosen. All eyes previously characterized by other FAF patterns were recruited through the end of August 2003, with follow-up examinations within at least 1 year from baseline. Only eyes with sufficient follow-up time, through July 2003, the present study looked at patients included from the study. Patients had regular follow-up visits at 6-month intervals. As part of the study protocol, each patient underwent a routine ophthalmic examination, including funduscopy and determination of best-corrected central visual acuity by Early Treatment Diabetic Retinopathy Study (ETDRS) charts. Pupils were dilated with 1% tropicamide before FAF examinations.

FAF was measured using a cSLO (Heidelberg Retina Angiograph, HRA classic and HRA 2; Heidelberg Engineering, Dossenheim, Germany), the optical and technical principles of which have been described previously. Briefly, an argon blue laser (HRA classic) or an optically pumped solid state laser (HRA 2) are used for excitation (both 488 nm) and the emitted light >500 nm is detected with a barrier filter. The reflectance of the blue argon laser light is suppressed by a factor of $10^{-6}$ with an interference filter. Consequently, it is assumed that the reflectance signal does not contribute to the obtained FAF image. For image acquisition, a standardized protocol for FAF image was used.

The database of the FAM Study was reviewed for eligible patients. Although the previous analysis of the FAM database by Bindewald et al. included patients with at least two examinations, regardless of the follow-up time, through July 2003, the present study looked at patients recruited through the end of August 2003, with follow-up examinations within at least 1 year from baseline. Only eyes with sufficient image quality to determine accurately the areas of increased FAF surrounding atrophy and only eyes with diffuse patterns of increased FAF surrounding atrophy (diffuse reticular, diffuse branching, diffuse fine granular or diffuse fine granular with peripheral punctuated spots) were chosen. All eyes previously characterized by other FAF patterns such as none FAF, focal FAF, banded FAF, and patchy FAF were excluded. At baseline and at all follow-up visits, the total size of atrophy was measured in each image by manual outlining with image-analysis software (Heidelberg Eye Explorer [HEE]; Heidelberg Engineering), and the rate of progression of atrophy over time was calculated. If there was more than one area of atrophy in one eye, the total size of atrophy would represent the sum of all atrophic areas. The differentiation of drusen and very small atrophic patches can sometimes be difficult. In this study, only eyes with advanced AMD with one or multifocal atrophic areas and only areas $\geq0.1$ mm$^2$ were delineated as atrophic areas. GA typically shows an extensive, dark FAF signal. In contrast, the FAF signal does not correspond very well with drusen. They are characterized by increased or normal FAF intensity. Lois et al. showed, for large foveal soft drusen, good correspondence with areas of increased FAF, whereas they observed over time the development of decreased FAF at the former site of drusen, consistent with the occurrence of GA. With the SLO imaging methods used, we did not see FAF signals that were much decreased over drusen.

For determining the extension of areas with increased FAF, the convex hull (CH) of increased FAF was outlined with the polygon tool of the HEE software at the baseline examination (Fig. 1). The CH was defined as the minimum polygon encompassing the entire area of increased FAF surrounding the central atrophic patches. This polygon had to be convex, requiring that all corners not have an angle over 180°. Measured data were manually transferred to computer (Excel spreadsheet; Microsoft, Redmond, WA).

The difference of the CH size and the total size of atrophy at the baseline image was calculated and represented the area with increased FAF surrounding the atrophic patches (Fig. 2). The relation between this difference and the progression of the total size of atrophy over time in each eye was determined by using the Spearman’s rank correlation coefficient ($\rho$). All statistical analyses were performed on computer (SAS, ver. 8.2; SAS Institute Inc., Cary, NC).

The maximum retinal irradiance of the lasers used for FAF imaging was well below the limits established by the American National Standards Institute (ANSI Z136.1,1993) and other international standards. The study adhered to the tenets of the Declaration of Helsinki and was approved by the locally appointed ethics committees of the participating study centers. Before inclusion, informed consent was obtained from each participating patient after explanation of the nature of the study.

**RESULTS**

Reviewing the database of the FAM Study until the end of August 2003, 150 eyes of 96 patients had follow-up examinations within at least 1 year from baseline. Of this sample, 39 eyes of 32 patients met the inclusion criteria and were chosen for further evaluation (Fig. 3). The median age was 75.0 years (interquartile range [IQR], 67.8 –78.9; Table 1). There were 17 women and 15 men. The overall median follow-up for all eyes was 1.87 years (IQR, 1.43–3.37).

**Figure 1.** Example of the determination of the CH in a FAF image of an 83-year-old woman (patient 6). The CH of increased FAF was outlined by using the mouse-driven arrow of the HEE. To clarify the border of the CH, arrows have been drawn secondarily.

**Figure 2.** Illustration of analysis strategy. The area of increased FAF (gray) was calculated for each eye by the difference between the convex hull of increased FAF (black) and the total size of atrophy (white).
FIGURE 3. Flow diagram showing the inclusion process. Reviewing the FAM Study database through the end of August 2003, 150 eyes of 96 patients had follow-up examinations within at least 1 year from baseline. Image quality was sufficient in 136 (90.7%) eyes for classification of FAF of which 79 (58.1%) eyes were divided into the diffuse pattern. Because of uneven image illumination, the delineation of the exact borders of the CH was not possible in 14 (17.7%) of 79 eyes. Furthermore, the GA area and FAF pattern exceed the $30°/H11003$ image frame in 26 (32.9%) eyes. The remaining 39 (49.4%) eyes were included in the study.

**Table 1. Characteristics of Study Eyes**

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In addition to characteristics of the study eyes, reasons for the exclusion of the fellow eyes (if applicable) are given. DS, disciform scar; drusen, early AMD; no diffuse, no diffuse FAF pattern around GA (e.g., banded pattern); quality, image quality not sufficient for delineation of CH (e.g., uneven illumination); image size, GA and FAF pattern exceed $30°/H11003$ image frame; no data, data for fellow eye missing. $n = 39$. 

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At baseline, multifocal atrophy with two or more atrophic patches was present in 30 eyes, but 9 eyes showed only a single area of atrophy. In 32 eyes atrophy was extrafoveal, whereas the GA area extended through the foveola in 7 eyes. Thirty-one eyes showed GA in the fellow eye. In case in which bilateral GA was present, the main reason for excluding the fellow eye most often (13/24 fellow eyes) was low image quality that did not permit accurate identification of the CH (Table 1). The FAF pattern was classified as diffuse reticular in 6 eyes, diffuse branching in 17 eyes, and diffuse fine granular in 16 eyes.

Visual acuity at baseline ranged from 5/200 to 20/20, with a median visual acuity of 20/60 (IQR 20/125–20/40). The GA progression rate ranged from 0.25 to 6.18 mm² per year, with a median rate of spread of 1.72 mm² per year (IQR, 1.10–2.83).

Figure 4 illustrates examples of FAF images and outlined atrophic areas as well as extension of the CH. Overall, eyes with larger areas of increased FAF outside atrophy were asso-
associated with higher rates of GA progression over time, compared with eyes with smaller areas of increased FAF outside atrophy at baseline. The area of increased FAF surrounding the atrophy (the difference between the CH and the total GA size) at baseline showed a positive correlation with the degree of spread of GA over time ($p = 0.60; P = 0.0002; \text{Fig. 5}$).

**DISCUSSION**

This is the first study to demonstrate that FAF imaging can be used to identify prognostic markers for progression of atrophy over time in patients with GA due to AMD. GA is an important cause of severe irreversible visual loss in patients with AMD. In natural history studies, it has been shown that GA gradually enlarges over time with interindividual variable rates of spread.2,3,5 The prevalence of AMD is increasing, largely because of demographic factors.29 Although the etiology of multifactorial complex AMD is still poorly understood, implicated risk factors include age, ethnicity, smoking, hypertension, obesity, diet, and genetic factors.30 Recently, the association of AMD and a complement factor H variant has been reported.31–33 Ocular risk factors encompass certain drusen characteristics as well as focal hyperpigmentation.5,34 The present study indicates that additional ocular risk factors can be identified based on FAF imaging. A large area of increased FAF surrounding atrophy obviously represents a high-risk factor for the rate of GA progression and, therefore, for additional visual loss with enlargement of the absolute scotoma associated with GA. This is functionally relevant for the patient in terms of need for low vision aids, ability to read and quality of life.

In a natural history study in patients with GA due to AMD, Sunness et al.2 have calculated a mean atrophy enlargement of 2.2 disc areas over 2 years using fundus photography for measuring sizes of atrophic patches. Applying their calculation factor adjusted for magnification alterations (disc area = 2.54 mm$^2$), the mean progression rate with 2.79 mm$^2$ per year would be in the same range compared with the rate of 2.10 mm$^2$ found here. However, limitations in this comparison have to be considered, because we have calculated the average GA progression rate for a certain time frame assuming linear progression instead of observing GA enlargement over a fixed period of 2 years.

The CH encompasses the area of increased FAF around the atrophic patches. As these areas of increased FAF consist sometimes only of small isolated spots of some micrometers or may be largely distributed around atrophic patches or irregularly shaped, the CH as the minimum polygon encompassing all areas of increased FAF is a relatively easy and reasonable way to determine the extension of increased FAF around atrophy. In contrast, the CH does not encompass the extension of increased FAF in GA eyes with localized, single areas of FAF only directly adjacent to atrophy and is therefore not a suitable method for these eyes (e.g., the previously described eyes with focal or banded pattern). For this reason, only eyes with a diffuse pattern of increased FAF surrounding atrophy were included. Reviewing the FAM database, a total of 136 of 150 eyes (90.7%) had sufficient image quality to classify the FAF pattern in the junctional zone, of which 79 (58.1%) eyes were divided into the diffuse pattern. This relative distribution of FAF patterns is in accordance with the previous reports of the FAM study.20

Although areas of increased FAF can be detected on most FAF images and allow the classification of the FAF pattern, the accurate identification of areas of increased FAF in the whole junctional zone of GA and the accurate identification of the borders of the CH require very good image quality with even illumination of the FAF image and a CH size not larger than the image size. To guarantee high standards for the analysis of the extension of increased FAF around GA, the present study excluded 14 (17.7%) eyes from the primarily identified 79 eyes with diffuse pattern because of insufficient image quality, and 26 (32.9%) eyes because the GA and CH size extended the image frame. These requirements for the inclusion of patients may have to be considered in future clinical trials. In this study, the CH was measured at the baseline examination. Although preliminary observations indicate that the CH also enlarges over time, the rate of progression appears to be slower than the GA enlargement. This issue is explored in ongoing studies.

The progression rate was not plotted against the CH, but against the difference between the CH and the total size of atrophy at baseline. This difference was chosen to quantify the magnitude of areas with increased FAF surrounding atrophy independent of atrophy areas. Assuming that areas with increased FAF represent incipient atrophy, one would expect...
that two different eyes with the same CH size, but different sizes of total atrophy at baseline would show different rates of atrophy enlargement in the way that the eye with the smaller GA size at baseline would progress faster than the other eye. In fact, the CH size—without subtracting the GA area at baseline—and the progression rate are also significantly correlated in the studied eyes ($\rho = 0.45; P = 0.0052$) but not as high when using the difference between the CH and the GA size at baseline ($\rho = 0.60; P = 0.0002$).

In summary, this longitudinal natural history study indicates that atrophy enlargement over time significantly correlates with the extension of increased FAF at the posterior pole surrounding the atrophic patches. The findings underscore the potential pathophysiological relevance of LF in the context of atrophic AMD and are in accordance with previous experimental and clinical observations that could link accumulation of LF to impaired lysosomal function and to development of atrophy as well as reduced retinal sensitivity.\(^{12,19,20,35,36}\) FAF imaging gives information over and above fundus photography or fluorescein angiography and may serve as a tool to identify prognostic determinants and high-risk characteristics in advanced atrophic AMD beyond those previously identified. This may also be useful in the design of future interventional studies testing strategies to slow down spread of atrophy and absolute scotoma in a so far untreatable cause of irreversible visual loss.

References

APPENDIX

Centers and members participating in the FAM Study:

Almut Bindewald-Wittich, Monika Fleckenstein, Felix Roth, Steffen Schmitz-Valckenberg, Hendrik P. N. Scholl, Johannes N. Witten, and Frank G. Holz, investigators; Martina Hofmann and Gabriele Wessling, study nurses, Department of Ophthalmology, University of Bonn, Germany.

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