

Combined Fundus Autofluorescence and Near Infrared Reflectance as Prognostic Biomarkers for Visual Acuity in Foveal-Sparing Geographic Atrophy

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PURPOSE. To identify predictors of best corrected visual acuity (BCVA) in eyes with foveal-sparing geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

METHODS. Best corrected visual acuity (Early Treatment Diabetic Retinopathy Study charts); serial fundus autofluorescence; and near-infrared reflectance images of patients participating in the FAM (NCT00393692) and DSGA (NCT02051998) studies were analyzed. The sizes of GA and spared fovea, and the minimal linear dimension of intact retinal pigment epithelium ("bridge") between the residual foveal island and the surrounding retina were quantified and associations with BCVA were assessed by local regression curves and mixed effects models.

RESULTS. A total of 65 eyes (51 patients, aged 75.68 ± 8.41 years) were included. Median time between baseline and last visit with detectable foveal sparing was 18 (quartiles: 12, 33) months. Median BCVA was 0.30 (0.20, 0.52) logMAR at baseline and 0.4 (0.3, 0.7) logMAR at follow-up. Local regression curves suggested no linear association of BCVA with GA size, sparing size or bridge size. Most contrasting values for BCVA were observed for $>1.5 \text{ mm}^2$ foveal-sparing size and for 400 μm bridge size. Employing these values as cutoff levels, mixed effects modeling revealed that both anatomic parameters, but not time, significantly impacted BCVA.

CONCLUSIONS. During the review period eyes with foveal-sparing GA were likely to maintain the baseline BCVA. There was no linear correlation of BCVA with foveal-sparing size. Yet, BCVA was worse if the spared foveal area was $<1.5 \text{ mm}^2$ or if the bridge was smaller than 400 μm in width. These findings add to the understanding of the natural history of foveal-sparing GA and may support future clinical trial designs.

Keywords: geographic atrophy, foveal sparing, age-related macular degeneration, AMD, natural history, visual function

Geographic atrophy (GA) represents the late-stage of non-exudative age-related macular degeneration (AMD).¹⁻⁵ GA has been estimated to be present in 3.5 % of people over 75 years,^{6,7} and has become the predominant type of late AMD in the population of 85 years and older.⁸ In industrial countries, late-stage neovascular or dry AMD is the leading cause of legal blindness in the elderly.^{9,10} While various pathways have been proposed to be involved in this atrophic disease phenotype, the exact underlying pathophysiological mechanisms are yet incompletely understood.⁵

Typically, patches of GA initially occur in the parafoveal retina. With enlargement over time, multifocal atrophic areas may coalesce, and new atrophic areas may occur. On clinical examination, the fovea typically remains uninvolved by the

atrophic process until late in the course of the disease. This phenomenon is referred to as foveal sparing.^{4,11-13}

With the advent of confocal scanning laser ophthalmoscopy (cSLO) fundus autofluorescence (FAF) imaging it is now possible to identify and quantify GA areas reliably.^{14,15} Due to the absence of fluorophores in areas of RPE atrophy, GA is associated with a severely reduced FAF signal resulting in high contrast between the atrophic and nonatrophic retina. Semi-automated image analysis software has been developed and validated to quantify the size of atrophic areas and the spread over time.^{16,17} Reliable quantification of atrophy borders in close proximity to the fovea based only on FAF is challenging due to luteal pigment absorbing blue-light FAF (excitation: 488 nm). Recently, a combinatorial analysis of FAF and near-infrared



(NIR) images was established and allowed to overcome this problem.¹⁸

Areas of GA are associated with a corresponding absolute scotoma.^{19,20} Thus, the foveal-sparing course of atrophy development goes along with a progressive visual impairment presumably initially characterized by reading difficulties or the impaired recognition of faces due to parafoveal scotomata while the central visual acuity is still preserved.^{4,19,21-24} Late on during the course of the disease, central visual acuity dramatically declines and eccentric fixation may ensue.¹¹ Yet, the precise determinants and characteristics of this decrease in visual acuity in eyes with the foveal-sparing GA remain unknown.

Quantification of disease progression in both routine patient management and clinical research in ophthalmology still strongly relies on best corrected visual acuity (BCVA) as assessment for visual function and an outcome measure. In clinical trials, progression of the atrophic area is additionally employed as an anatomic surrogate outcome parameter.²⁵ In such trials, patients with foveal sparing are preferred candidates for inclusion, since these patients often exhibit a good to moderate BCVA and, therefore, would have the highest potential of functional loss over time. Furthermore, the higher fixation stability in this group of patients facilitates retinal imaging, making them even more attractive trial participants. Current evidence from a limited number of patients with foveal sparing suggests that the correlation between atrophy progression and BCVA loss is poor.²⁴ Therefore, a more detailed analysis of the relationship of BCVA with possible influencing factors appears prudent. In the present study, we hypothesize that the size of the spared fovea and the minimal linear dimension of intact retinal pigment epithelium between the residual foveal island and the surrounding retina (bridge) are key effectors of BCVA. Thus, herein we determine the relevance of those morphologic markers for vision loss in eyes with foveal-sparing GA due to AMD.

METHODS

Ethics Statement

The study followed the tenets of the Declaration of Helsinki and was approved by the local institutional review boards and the local ethics committees at the participating study centers. Informed consent was obtained from each patient after explanation of the nature and possible consequences of the study.

Definitions

Eyes were defined as having foveal sparing in GA if an intact residual foveal island was more than 270° encircled by well-demarcated areas of GA, in accordance with the previous description.¹⁸ An eye was classified as having a complete encirclement if GA surrounded the fovea in ring configuration. If there were bridges of intact RPE between the residual foveal island and the surrounding retina, an eye was classified as having incomplete encirclement (Fig. 1). The definition and classification of foveal sparing were based on FAF and NIR reflectance images.

Patients

All subjects presented in this study were recruited in two prospective multicenter, longitudinal, natural history studies (i.e., the Fundus Autofluorescence in Age-related Macular Degeneration [FAM] and the Directional Spread in Geographic Atrophy [DSGA]; ClinicalTrials.gov numbers, NCT00393692, NCT02051998). The inclusion and exclusion criteria for this

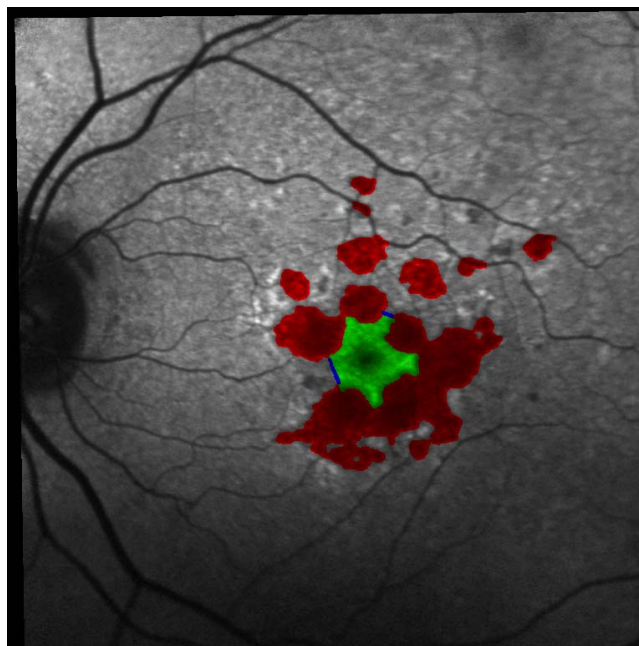


FIGURE 1. Representative left eye of an 80-year-old male patient with GA and foveal sparing as included in this study. The relevant structures, as quantified using the RegionFinder software and the Heidelberg Eye Explorer, respectively, were highlighted here for illustration purposes. *Green*: area of the spared fovea. *Red*: area of surrounding GA. *Blue*: width of the largest bridge of intact RPE between foveal retina and the retina surrounding the atrophy.

study have been described previously.^{13,26,27} Briefly, patients had to exhibit either uni- or multifocal GA and clear ocular media that allowed for good-quality FAF and NIR imaging in at least one eye. Exclusion criteria included any sign of present or previous neovascular activity, any current or previous treatment with anti-VEGF agents, history of retinal surgery, laser photocoagulation, radiation therapy, or other retinal diseases in the study eye. Furthermore, patients were excluded in whom the area of atrophy exceeded the 30° × 30° cSLO image frame. If both eyes of a patient met the inclusion criteria, both eyes were selected as study eyes.

For inclusion in the current analysis, a foveal-sparing GA had to be present in the study eye. Once the fovea had become fully atrophic during the disease course, all further visits of this eye were excluded from analysis.

Data Acquisition and Image Analysis

Best corrected visual acuity (BCVA) was determined with Early Treatment Diabetic Retinopathy Study charts. Before fundus examination, the pupil of the study eye was dilated with 1% tropicamide eye drops.

FAF and NIR images were acquired using a HRA 2 or Spectralis (Heidelberg Engineering, Heidelberg, Germany). FAF was with an excitation wavelength of 488 nm and an emission spectrum of 500 to 700 nm using the high-speed mode. NIR images were obtained at an 820-nm wavelength. The field of view was set to 30° × 30° with a minimum resolution of 512 × 512 pixels and was centered on the fovea. Single FAF images were automatically aligned and averaged in order to maximize the signal-to-noise ratio using the manufacturer's software.

Measurement of the atrophy and foveal-sparing areas were performed as previously described¹⁸ using commercial software (RegionFinder, version 2.5.5.0; Heidelberg Engineering) including a newly implemented feature that automatically

registers FAF to corresponding NIR images and allows for toggling from one modality to another. Thereby semiautomated quantification of GA and foveal-sparing areas was possible. In case of an incomplete encirclement, the minimal linear dimension of RPE bridges was quantified using the distance tool of commercial software (Eye Explorer, version 1.1.10.0 with viewing module version 6.3.2.0; Heidelberg Engineering) at the most narrow part of intact RPE connecting spared fovea and intact RPE outside the atrophy (Fig. 1). In case multiple bridges were present, the width of the largest bridge was used. All measurements were performed by two independent readers and a third reader in case of discrepancy. Tolerance levels for grading between the first two readers were 0.15 mm² for the size of atrophy and the size of the spared fovea, 50 μ m for the size of the bridge. In case of any disagreement in the grading of complete encirclement versus incomplete encirclement, a senior grader was asked for arbitration.

Statistical Analysis

Data were analyzed using R, version 3.1.2.²¹ Interobserver agreement was assessed using the interclass correlation coefficient (ICC) for continuous and Maxwell's RE test for binary variables. Descriptive analysis of the data was carried out using means \pm standard deviation and medians, 25% quantile (Q1) and 75% quantile (Q3) as appropriate. To quantify centripetal and centrifugal progression rates of GA within the patient collective, linear mixed-effects models with patient- and eye-specific random intercepts and slopes were used. The two-level random effects model used here accounts for the hierarchical nature of the data (visit nested within eye nested within patient). Follow-up time was the only fixed effect in these models. Local regression (LOESS) curves were calculated on an eye-visit basis to analyze the functional forms of the relationships between predictor variables and BCVA.²⁸ Potential threshold values indicating rapid changes in BCVA were visually extracted from the LOESS curves. Sparing size and bridge size were grouped according to these threshold values, and a further linear mixed-effects model with BCVA as outcome variable was fitted to the data. In addition to follow-up time, the grouped versions of sparing size and bridge size were used as predictor variables in this model. Model results are presented as coefficient estimates with estimated SD, and as standardized effect sizes defined by coefficient estimates/SD.

RESULTS

Patients and Baseline Characteristics

A total of 65 eyes from 51 patients (11 men, 40 women; mean age at baseline, 75.68 \pm 8.41 years) with foveal-sparing GA were included in the analysis. At baseline mean BCVA was 0.39 \pm 0.33 logMAR (median 0.30 [Q1: 0.20; Q3: 0.52] logMAR). The size of the atrophic area was 8.3 \pm 4.33 mm². These parameters were acquired with a high interrater agreement (ICC) of 0.989 and 0.879, respectively. There were 13 eyes with complete encirclement of the spared fovea (i.e., the atrophic area entirely surrounded the fovea in a ring configuration) and 52 eyes with incomplete encirclement (i.e., with bridges of intact RPE between the residual foveal island and the peripheral retina; interrater agreement, Maxwell's RE = 0.738). The mean minimal linear dimension of such bridges (measured at the most narrow part of intact RPE-connecting spared fovea and intact RPE outside the atrophy) at baseline was 502.28 \pm 333.18 μ m (only regarding eyes with incomplete encirclement). Interclass correlation coefficient for the size of the bridge between fovea

and peripheral retina in eyes with incomplete foveal sparing was 0.835. There was no significant difference in BCVA at baseline between eyes with an incomplete encirclement and eyes with a complete encirclement (0.37 \pm 0.31 [median: 0.30; Q1: 0.20; Q3: 0.50] logMAR versus 0.48 \pm 0.39 [median: 0.30; Q1: 0.20; Q3: 0.60] logMAR, P = 0.318).

Disease Course

Eyes were followed over a median period of 1.50 (Q1: 1.00, Q3: 2.75) years. Over this time, BCVA decreased to a final median value of 0.4 (Q1: 0.3; Q3: 0.7) logMAR. As estimated from linear mixed-model analysis, annual square root transformed centrifugal progression of GA was 0.365 \pm 0.014 mm/year. In contrast, the rate of centripetal progression was lower at 0.114 \pm 0.007 mm/year. In 23 of the eyes (44.23%) exhibiting an incomplete encirclement of the spared fovea at baseline, bridges disappeared and a complete encirclement developed. Overall, 126 visits with incomplete encirclement and 81 visits with complete encirclement of the spared fovea were analyzed.

During the review period, in four eyes (6.15%) the initially spared fovea became entirely atrophic, making them ineligible for further analysis in the context of this study. In these eyes, this loss of foveal sparing was observed after a median of 1.97 (Q1: 1.41, Q3: 3.41) years of follow up and visual acuity dropped by 0.68 \pm 0.33 logMAR (median: 0.7 [Q1: 0.5, Q3: 0.88] logMAR) as foveal sparing subsided.

Explorative Assessment of Factors Influencing BCVA

Local-regression (LOESS) curves were calculated to explore possible relationships between BCVA and retinal imaging predictor variables. The latter included: (1) the size of atrophy; (2) the size of the spared fovea; and (3) the size of the bridge (Fig. 2). Note that correlations between the individual data values were not considered in this exploratory analysis. Graphical analysis did not indicate any strong dependencies of BCVA on any range of GA sizes (Fig. 2A). For the size of the spared fovea, LOESS regression was suggestive for an upward trend of BCVA in the range >1.5 mm² sparing size (Fig. 2B) with better values for BCVA (lower logMAR values) in eyes with larger areas of foveal sparing. Below 1.5 mm² of foveal-sparing size, there was no clear relationship between foveal-sparing size and BCVA. Approaching the effect of the size of the bridge, LOESS regression suggested a positive relationship between BCVA and the width of the broadest bridge within a range of 300 to 550 μ m. Better BCVA (lower logMAR values) were observed for larger bridges. Outside the range of 300 to 500 μ m, no relationship was observed.

Eye-Wise Modeling BCVA Course Over Time

Based on the assessment of the LOESS curves (Fig. 2), we hypothesized that the following retinal imaging parameter defined threshold values indicate most influential changes in visual acuity in individual eyes: (1) the area of the spared fovea exceeds a threshold value of 1.5 mm² and (2) the size of the bridge between spared fovea and the intact RPE surrounding the atrophy underscores a threshold value of 400 μ m or is completely lost. To investigate these hypotheses in an exploratory manner, we constructed a linear mixed-effects model with BCVA as outcome variable.²⁹ Time, categorized values for size of the spared fovea (<1.5 mm², >1.5 mm²), categorized values for the size of the bridge between the foveal

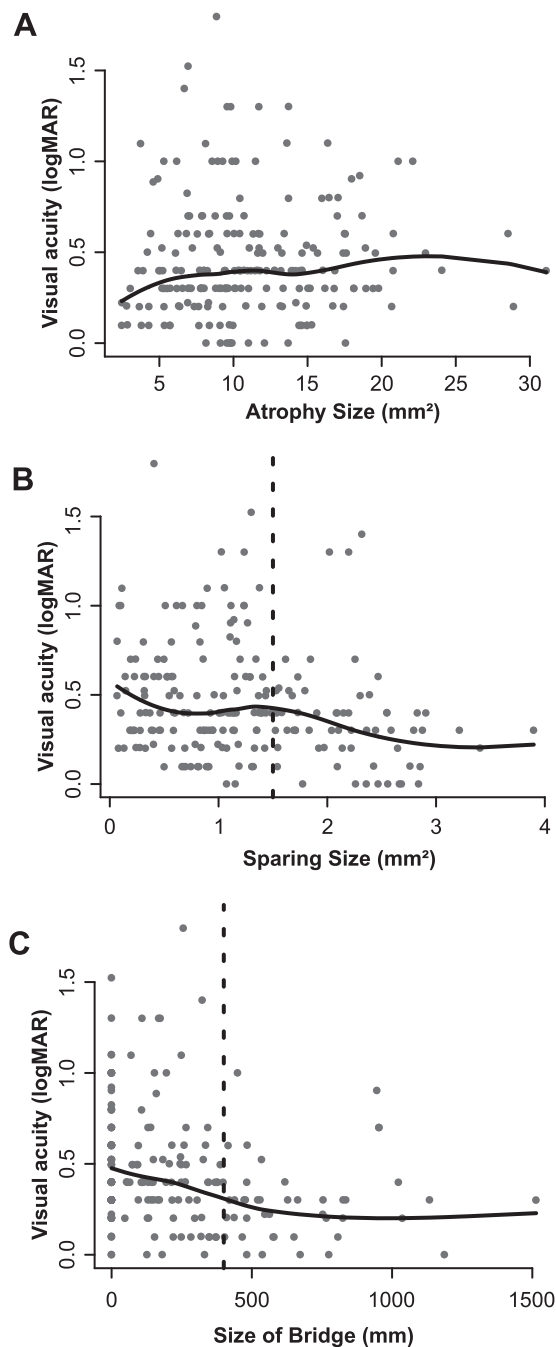


FIGURE 2. LOESS curves used to assess the association between various retinal imaging parameters and visual acuity on an eye-visit basis. (A) Best corrected visual acuity is plotted against the size of the GA, being not suggestive for a strong relationship between both parameters. (B) BCVA decreases with size of the spared fovea, from an apparent threshold value of 1.5 mm² on. (C) BCVA plotted against the size of the bridge of intact RPE between spared fovea and the intact RPE surrounding the GA. LOESS curves show that BCVA drops when the size of the bridge decreases from approximately 300 to 550 μ m.

island and the surrounding intact RPE (<400 μ m, >400 μ m) were included into the model as predictor variables. The results of the model are summarized in the Table. Of note, retinal imaging markers exhibited a pronounced effect on BCVA (standardized effect sizes -2.848 for foveal-sparing size and -2.538 for size of bridge, respectively). In contrast, the effect of time was nominally not significant.

DISCUSSION

This study addresses determinants of visual acuity in patients with foveal sparing and expands the current knowledge on the natural history and a structure-function relationship in eyes with GA secondary to AMD.²⁹ The results indicate that in the median review period of 18 months, morphologic imaging parameters at baseline rather than time impacts the visual acuity course in this patient cohort.

Translating these observations into a practical context implies that a patient with foveal-sparing GA is likely to maintain a certain visual acuity level over a relatively long time period; herein, visual acuity is worse if the spared fovea is <1.5 mm² in size or if the bridge between the spared fovea and the peripheral retina is smaller than 400 μ m. The results are also of particular relevance for the design of interventional clinical trials recruiting patients with foveal sparing: during an observational period (e.g., 18 months), a visual acuity loss is unlikely—at least unless the abovementioned structural alterations occur).

Obviously, it is well established that atrophy progression occurs over time.^{30–32} Both identified imaging parameters (i.e., size of the spared fovea and size of the bridge) are closely linked to GA progression. They must, therefore, be time dependent. Thus, in agreement with clinical findings, visual acuity loss over time must also occur in this cohort. Yet, in the present mixed-effects model time did not reach statistical significance. This highlights the stable visual acuity course in patients with foveal sparing, at least over the 18 months observation period assessed in this analysis.

The observation of a largely stable visual acuity course over 18 months is of particular interest in the context of previous and current multicenter clinical trials, where times until the assessment of the primary outcome measure of comparable length were chosen (e.g., 12 months in the CHROMA/SPECTRI trials or 24 months in the Zimura and the SEATTLE trials [ClinicalTrials.gov numbers, NCT02247479/NCT02247531, NCT02686658, NCT01802866, respectively]). However, 18 months is a rather short time when it comes to providing a prognosis to an individual patient and it is very likely that more severe changes in visual acuity could be detected after longer periods of time.

Previous publications have addressed visual acuity in patients with GA secondary to AMD. We have shown that foveal atrophy is the main determinant of BCVA in patients with GA,²⁹ an observation which is in agreement with the overall stable visual acuity course observed herein. However, it is noteworthy that the pure passing of time was significantly associated with BCVA loss in GA patients in general,²⁹ while in the foveal-sparing cohort presented here, this association was lost. The Age-Related Eye Disease Study research group has reported on visual acuity (VA) data in the subgroup of 181 participants with GA.³¹ In that study cohort, VA dropped from 20/50 (0.4 logMAR) at baseline to 20/160 (0.9 logMAR) by year 5. This equals a loss of 0.1 logMAR per year. Though visual loss over time was not significant in the present analysis, the net value was 0.021 logMAR/year, indicating that visual acuity loss in foveal-sparing eyes is at least five times slower than that observed in GA in general.

Sunness and coworkers^{11,24} have previously investigated functional aspects of foveal sparing in patients with GA in detail. They found that eyes with a foveal-sparing atrophy may have similar levels of visual acuity as compared to eyes with multifocal GA, for example, despite considerably smaller areas of atrophy in the latter group.²⁴ In a small cohort ($n=10$ eyes with foveal sparing) they additionally observed that eyes with areas of spared fovea of <0.2 disc areas (<0.508 mm²) may still achieve a BCVA of at least 0.4 logMAR.¹¹ In addition, in nine

TABLE. Factors Influencing BCVA in Patients With Foveal-Sparing GA as Assessed by the Linear Mixed-Effects Model

| Model Parameter | Clinical Description | Coefficient Estimates (logMAR) | Standard Error (logMAR) | Standardized Effect Size | P Value |
|----------------------|---|--------------------------------|-------------------------|--------------------------|--------------|
| Intercept | Visual acuity at baseline | 0.515 | 0.045 | 11.358 | |
| Sparing size | Effect of the size of the spared fovea at baseline on visual acuity | | | | |
| <1.5 mm ² | | 0.000 (reference category) | | | 0.004 |
| ≥1.5 mm ² | | −0.140 | 0.049 | −2.848 | |
| Bridge size | Effect of the size of the bridge at baseline on visual acuity | | | | |
| <400 μm | | 0.000 (reference category) | | | 0.01 |
| >400 μm | | −0.120 | 0.047 | −2.538 | |
| Time | Effect of time (in years) passing by on visual acuity | | | | |
| Per year | | 0.021 | 0.025 | 0.852 | n.s. (0.399) |

n.s., not significant.

eyes with a complete encirclement of a spared fovea at baseline, only in one eye the fovea became entirely atrophic during the observation interval.²⁴ These data are consistent with the good level of visual acuity we observed in several eyes with small residual foveal islands (Fig. 2B), and the fact that only 6.15% of the eyes in this cohort lost foveal sparing during the review period.

Comparing studies addressing the phenomenon of foveal sparing, it has to be considered that a uniform definition of this term is still lacking as distinct study settings may require differential definitions. In the present study, we used the term to describe RPE atrophy surrounding a nonatrophic foveal island by at least 270°. In the context of GA due to AMD, other authors have used a broader definition including eyes with atrophy surrounding the fovea by at least 180°,²⁴ and/or including a BCVA cutoff level (20/50²⁴ or 20/40³³). These discrepancies in definition may contribute to the lower average levels of BCVA at baseline (0.54 logMAR) observed in the current analysis as compared to the results by Sunness and coworkers²⁴ (0.24 logMAR).

Progression of GA has been previously recognized by the US Food and Drug Administration as an anatomic endpoint.³⁴ However, BCVA is considered by some as the key functional outcome measure. In trials with GA, patients with foveal sparing may be considered a preferred study cohort as they have stable fixation allowing for high quality retinal imaging and high baseline BCVA with the highest risk to lose vision in the future. However, the results of the current analysis suggest that during an observational period of 12 to 24 months, eyes with foveal-sparing GA are not likely to lose visual acuity. Therefore, in such a study design, comparison of BCVA between the treatment and the sham arm does not appear to be reasonable. The data presented herein indicate that it takes a relatively long period until a patient with foveal sparing loses visual acuity. Thus, longer follow-up times would be needed to detect a biological effect of an interventional drug, if visual acuity was the primary outcome measure. Furthermore, the results are suggestive for a relevant dissociation between GA progression and change in visual acuity (Figs. 2A, 2B), which must be considered when interpreting trial results. Therefore, BCVA may remain stable for some time despite disease progresses. These results should not be misinterpreted as questioning GA progression as an anatomic endpoint. Rather, it must be considered that the functional parameter BCVA is far off from being acceptable as the only measure to track disease progression.

Reading acuity and speed as well as microperimetry may be a more meaningful measure for functional impairment and changes over time in patients with foveal-sparing GA. Similar

considerations may be also relevant when assessing the individual patient's functional impairment in the context of social legislation. Accordingly, a stable visual acuity observed in a patient with foveal sparing in clinical practice over a long time should not be misinterpreted as disease inactivity. Thus, further studies are necessary to better characterize the functional impairment of this patient collective.

Several FAF imaging markers predicting overall atrophy progression have been discovered in the past years (e.g., Refs. 35 through 37). While the patterns of increased FAF³⁵ are considered as an eye-specific feature, other approaches as the quantification of the rim area focal hyperautofluorescence (RAFH) may also allow correlation with local atrophy progression. In the context of foveal sparing, it will be interesting to analyze if RAFH might be lower in fovea-close atrophy borders compared to fovea-distant borders. This may correlate with the observed slower progression of atrophy toward the fovea¹⁸ and deliver hints on the pathogenetic mechanism(s) underlying the development of foveal sparing.

These pathogenetic mechanisms to date remain incompletely understood and are discussed in detail elsewhere.^{18,38} In brief, a preferential vulnerability of the rod system³⁹ or S-cones,^{40,41} the unique choroidal blood supply to the fovea⁴² (but see also Ref. 43) and the rod/RPE-cell ratio^{44,45} have been proposed to underlie the phenomenon of foveal sparing. Also, a role of single nucleotide polymorphisms in genes other than the disease causing,³⁸ the rod-derived cone viability factor⁴⁶ or the macular pigment⁴⁷ are under debate. Although it is unclear which of these mechanisms is underlying the development of foveal sparing, it is worth mentioning that they are exclusive to a subset of eyes (approximately 20%^{18,48,49}), providing the fovea with a particular resilience against atrophy development. As foveal preservation may greatly add to the independence of an individual patient in daily routine a better understanding of the underlying mechanisms and development of pharmacological strategies to support the development and maintenance of foveal sparing seems attractive.

There are possible explanations for the observed anatomic cutoff levels for visual acuity loss. We hypothesize that larger foveal-sparing areas or bridges with a certain size serve the patient to guide eye movement to localize an object of interest and project it onto the fovea. This may explain these observations rather than the assumption that an optotype would not fit into the residual foveal island if it is smaller than 1.5 mm². Even a large logMAR 1 optotype⁵⁰ would easily fit—obviously, smaller letters would fit even better.

This study is limited by the fact that spectral-domain optical coherence tomography data were not assessed. Therefore, it was not possible to further dissect cross-sectional, particularly

foveolar morphology. It is likely that a multimodal approach, including the assessment of cross-sectional foveal morphology, will reveal parameters that could explain a notable degree of the variability observed in this study and allow better stratification of trial cohorts in the future. Furthermore, to avoid a splitting of the dataset, LOESS curves on eye-visit basis and the mixed-effects model accounting for eye- and patient-specific factors were obtained from the same dataset. Thus, the results of the mixed-model do not provide an external validation for the determinants of visual acuity as identified by the LOESS-based threshold values. Recruitment of an independent, larger cohort seems necessary to validate the results obtained here. Finally, it is important that patients in this cohort were observed over a median of 18 months. It must be considered that conversion of 'foveal sparing' atrophy into fovea-involving atrophy may occur after a longer interval of time. Thus, this midterm observation should not be extrapolated to longer periods. Long-term comparative analyses between eyes with and without foveal sparing in GA will be necessary to evaluate its importance for the prognosis of an individual patient.

Overall, the present work describes the determinants of visual acuity in patients with foveal-sparing GA in AMD over a period of 18 months. This provides important information for the design of future clinical trials and may be considered when patients are managed in clinical routine whereby stable visual acuity must not be misinterpreted as disease inactivity.

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