Changes in Retinal Sensitivity in Geographic Atrophy Progression as Measured by Microperimetry

Annal D. Meleth,^{1,2} Pradeep Mettu,^{1,2,3} Elvira Agrón,¹ Emily Y. Chew,¹ Srinivas R. Sadda,⁴ Frederick L. Ferris,¹ and Wai T. Wong^{1,3}

PURPOSE. To characterize changes in macular sensitivity during geographic atrophy (GA) progression using microperimetry.

METHODS. Retinal sensitivity in the macular area was evaluated by microperimetry in 10 patients with bilateral GA, with adequate data obtained in 9 of 10 patients ($n = 18$ eyes). Patients had been enrolled in an interventional trial in which one eye had been randomized to treatment and the other eye observed. No treatment effect with regard to GA growth and microperimetric measurements was detected, and all eyes were analyzed. Microperimetric assessments of the central 20° of the macula were performed every 6 months over 24 months. Parameters analyzed included number of scotomatous points, mean retinal sensitivity of responding points, and fixation stability. Autofluorescence imaging and fundus photography were also obtained.

RESULTS. Microperimetric parameters demonstrated statistically significant changes as a function of time. Mean number of scotomatous points increased significantly with time ($P = 0.004$) at a rate of 4.4 points/year. Mean retinal sensitivities of all points, all responding points, and all perilesional points all decreased significantly with time ($P < 0.003$), as did fixation quality within the 2° and 4° circles ($P < 0.002$). The growth of GA lesion area was associated with the changes in the number of scotomatous points ($P = 0.01$) but not with changes in the other microperimetric parameters.

CONCLUSIONS. Macular sensitivity and fixation quality undergo progressive change during the GA progression, reflecting alterations in macular function extending beyond the GA lesion proper. Microperimetric measurements may provide useful functional outcome measures for the clinical study of GA. (*Invest Ophthalmol Vis Sci.* 2011;52:1119–1126) DOI: 10.1167/iovs.10-6075

Central geographic atrophy (GA) is the advanced atrophic form of age-related macular degeneration (AMD) that is a cause of progressive moderate and severe vision loss,^{1,2} esti-

mated to affect 3.8 million people in the United States by 2050.³ GA is characterized by central areas of atrophy of the retina, retinal pigment epithelium (RPE), and choroid that enlarge and coalesce with time.^{4,5} Because there is currently no effective treatment for GA to prevent either its onset or progression,^{6,7} clinical trials employing useful and relevant outcome measures in the discovery of a treatment are of important public health significance.⁸

The natural history of the anatomic changes associated with GA progression has been closely examined using a variety of fundus imaging modalities including fundus photography,⁹ autofluorescence imaging,¹⁰ and optical coherence tomography.¹¹ Because the gradual time-dependent increase in the total area of atrophy of the retina-RPE-choriocapillaris complex is a key feature of GA progression, change in area of the atrophic lesion has constituted a key anatomic outcome measure in interventional studies of GA.⁷ At the same time, it is important to demonstrate concurrent development of visual function loss associated with the increase in area of GA. Best corrected visual acuity, as determined using current standard clinical protocols,¹² often does not correlate well with GA progression,¹³ is influenced by the visual function of the contralateral eye,¹⁴ and may not comprehensively reflect visual disability of patients with GA.¹⁵ Previous studies have revealed that patients with GA demonstrate low luminance visual dysfunction and reduced reading speed,^{16,17} but how these measures change with time, or correlate with anatomic outcome measures such as change in the area of GA lesion, have yet to be fully investigated.

Microperimetry is a testing modality that can be used to measure and map central retinal sensitivity in macular diseases such as GA.^{18,19} The MP-1 microperimeter (Nidek, Padua, Italy) is a commercially available device that performs fundus tracking and automated image alignment for eye movements, permitting a precise and repeatable mapping of retinal sensitivities of discrete points in the macula.²⁰ This device has been previously used to map retinal sensitivity in various macular disorders, including central serous choroidopathy, macular telangiectasia, diabetic macular edema, and multiple evanescent white dot syndrome.^{21–27} In the present study, we have used the MP-1 perimeter to follow retinal sensitivities in the central macula in eyes with GA over a follow-up period of 24 months. Our results demonstrate that microperimetric parameters can reveal significant aspects of functional decline in GA, both within and beyond the GA lesion, and may provide potential functional outcome measures for future clinical trials for GA.

MATERIALS AND METHODS

Participants

Participants analyzed in the present study were enrolled in a single-center, open-label, phase II study of OT-551 (0.45% eye drop; Othera Pharmaceuticals, Inc., Conshohocken, PA) for the treatment of GA

From the ¹Division of Epidemiology and Clinical Applications and ³Unit on Neuron-Glia Interactions in Retinal Disease, National Institutes of Health, Bethesda, Maryland; and ⁴Doheny Image Reading Center, Doheny Eye Institute, Keck School of Medicine of the University of Southern California, Los Angeles, California.

²Authors contributed equally to this work.

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Corresponding author: Wai Wong, National Institutes of Health, 7 Memorial Drive, Building 7, Room 217, Bethesda, MD 20892; wongw@nih.gov.

conducted at the National Eye Institute, National Institutes of Health. Enrolled participants were at least 60 years old and had a diagnosis of geographic atrophy related to AMD in both eyes. Primary eligibility criteria were an area of unifocal or multifocal geographic atrophy in both eyes between $\frac{1}{2}$ and 12 disc areas that is not contiguous with areas of peripapillary atrophy and with an absence of evidence or history of exudative forms of AMD. An independent data and safety monitoring committee provided study oversight. The study adhered to the tenets of the Declaration of Helsinki and is registered at <http://www.clinicaltrials.gov> (NCT00306488).

The results of this phase II study²⁸ did not reveal any statistically significant differences between treated and fellow eyes in the change of GA area or change in any microperimetric measures for all assessed time points. None of the eyes in the study progressed to exudative AMD within the follow-up period.

Microperimetric assessments and fundus imaging (color fundus photographs and autofluorescence imaging) were performed for all 10 study patients. One participant was consistently unable to complete the microperimetry testing in a reasonable time owing to an inability to maintain sufficiently good fixation during testing; as a result, a total of 18 eyes from the nine other participants were included in the analysis. Demographical information on these nine participants and the mean baseline characteristics of the 18 eyes included in the analysis are summarized in Table 1.

Microperimetric Assessment

Microperimetry testing was performed using the MP-1 microperimeter (NAVIS software version 1.7.1; Nidek) whose software included the automatic tracking of the fundus image, allowing retinal sensitivity at discrete points on the retina to be followed reproducibly during an assessment and between separate assessments.²⁹ Assessments were performed before other fundus examinations or imaging and after pupillary dilation with a one-time administration of one drop each of tropicamide 1% and phenylephrine 2.5%. Retinal sensitivity was calculated with a background luminance of four apostilbs (1.27 cd/m^2) using a 68-loci circular grid centered on the center of the macula covering the central 20° of the macula (10-2 program). The testing stimulus was set at size Goldmann III and the stimulus duration at 200 ms. The starting stimulus light attenuation was set at 10 dB. A 4-to-2 staircase strategy was used, using testing intensities ranging from 127 to 2.54 cd/m^2 , which correspond to retinal sensitivities of 0 to 20 dB. The follow-up testing feature in the testing software was used. Fixation stability was also evaluated by tracking a retinal landmark at 25 Hz while the participant fixated on a target; the software calculated the proportion of tracking assessments in which fixation was maintained within 2° and 4° circles centered on the point of fixation. Microperimetric measurements were conducted at study baseline and every 6 months for up to 24 months. Longitudinal data were available in eight out of nine participants ($n = 16$ eyes) for the 24-month period (five

longitudinal assessments); one participant ($n = 2$ eyes) provided data for 18 months (four longitudinal assessments).

Scotomatous (or nonresponding) points were defined as testing loci that elicited no participant response even at the highest intensity stimulus. Responding points were defined as all other testing loci for which a response was recorded after stimulus presentation (i.e., points for which a response was elicited within the entire range of stimuli intensities used by the testing algorithm). Responding points were divided into perilesional points and extrasional points by their proximity to scotomatous points; perilesional points were loci on the testing grid immediately adjoining a scotomatous point, and extrasional points included all other responding points which were separated from scotomatous points by more than one testing point. (Figure 4B displays an example of these point categories). The following parameters were calculated from the microperimetric output and analyzed: (1) number of scotomatous points, (2) mean sensitivity (dB) of all tested points ($n = 68$), all responding points, perilesional points, and extrasional points, and (3) fixation quality as measured by percentage of tracked fundus positions lying within the 2° and 4° circle centered at the point of fixation. Fixation is scored as "stable" when 75% of fixations fall within the 2° circle, "relatively unstable" when 75% of fixations fall within the 4° circle, and "unstable" when $<75\%$ of fixations fall within the 4° circle.

Fundus Imaging and Measurements of the Area of GA Lesions

Stereoscopic color fundus photography (CFP) and fundus autofluorescence imaging using a confocal scanning ophthalmoscope (HRA FAF) (HRA2; Heidelberg Engineering, Heidelberg, Germany) were obtained for all study eyes every 6 months up to 24 months. CFP and HRA FAF images were sent to the Doheny Image Reading Center at the University of Southern California for digital manual grading by masked graders. The area of GA in each image was determined by planimetry without direct comparison with corresponding images taken of the same eye at a different time; CFP images were viewed and graded stereoscopically. Scaling factors based on the magnification of the images were used and verified for consistency using invariant landmarks in the image. The area of GA was determined by independently from both CFP and HRA FAF images. The rate of increase of GA was determined by interpolation between time points compared.

Statistical Analysis

A repeated measures regression model with an autoregressive covariance matrix was used to analyze the change in these parameters over time. Commercial statistical software (SAS, v. 9.2; SAS Institute, Cary, NC) was used. Separate analyses for treated eyes (receiving topical investigational agent, OT-551) and fellow control eyes not receiving study treatment were performed. Since these did not reveal significant differences in microperimetric outcomes, treated and fellow eyes were

TABLE 1. Baseline Demographic and Ocular Data for Study Participants ($n = 9$ participants)

Eyes, n	18
Age in years, mean $\pm$ SD (range)	76.8 $\pm$ 8.27 (65–88)
Female, n (%)	6 (66%)
White, n (%)	9 (100%)
Baseline best-corrected visual acuity, mean $\pm$ SD (range)	52 $\pm$ 17.6 letters or $\approx$ 20/100 (9–79)
Baseline area of geographic atrophy, mean $\pm$ SD (range)	
Measured from color fundus photography	6.80 $\pm$ 3.4 mm^2 (1.0–13.8)
Measured from HRA autofluorescence imaging	7.03 $\pm$ 3.4 mm^2 (1.0–14.5)
Baseline microperimetry measurements, mean $\pm$ SD (range)	
Number of scotomatous points (i.e. sensitivity < 0 dB)	29.7 $\pm$ 16.9 points (2.0–62.0)
Mean overall sensitivity of all points	5.28 $\pm$ 3.2 dB (0.3–11.2)
Mean overall sensitivity of responding (nonscotomatous) points	8.59 $\pm$ 3.3 dB (3.0–15.0)

FIGURE 1. Changes in functional scotoma in GA progression on microperimetry testing. Interpolated map demonstrating a progressive expansion in the functional scotoma corresponding to the GA lesion as shown at (A) baseline, (B) 12 months, and (C) 24 months for a representative eye with GA. Areas in red indicate nonresponding points with an absolute scotoma. (D) The mean number of scotomatous points for all study eyes increased steadily as a function of follow-up time, reflecting a progressive increase in the area of functional scotoma with time ($n = 18$ eyes for time points 0, 6, 12, and 18 months; $n = 16$ for time point 24 months).

pooled in the overall analysis. A simple linear regression was performed to determine associations between the changes in GA area and changes in microperimetric parameters analyzed between baseline and month 24 time points. Comparisons with $P < 0.05$ were considered statistically significant. Error bars in graphical displays refer to SE.

RESULTS

Change in the Number of Scotomatous Points with Time

The total number of scotomatous points was followed over time for all eyes analyzed ($n = 18$). All eyes demonstrated an overall increase in the number of scotomatous points during the follow-up period, reflecting an increase in the size of an absolute scotoma (Figs. 1A–C). The mean number of scotomatous points (Fig. 1D) increased monotonically as a function of time. The change in the number of scotomatous points was

also significantly associated with follow-up time ($P < 0.01$; Table 2), increasing at a mean rate of +4.4 points per year.

Change in Macula Sensitivity with Time

Changes in macular sensitivity in the tested area were monitored in all study eyes. In study participants, a general trend of decreasing sensitivity was observed in the overall tested area, including at retinal loci outside the GA lesion itself (Figs. 2A–C). The mean sensitivity of responding points identified at baseline declined continuously as a function of follow-up time (Fig. 2D). This overall decrease in sensitivity was contributed to by both the expansion of central scotoma, which resulted in an increase in the number of scotomatous points, as well as decreases in sensitivity in responding points just outside the functional scotoma (perilesional points). Mean macular sensitivity considering only responding (i.e., nonscotomatous) points also demonstrated a decreasing trend with

TABLE 2. Change in Microperimetric Parameters as a Function of Time for All Study Participants

	Mean Rate of Change per Year	95% Confidence Intervals	P
Change in best-corrected visual acuity, letters	−2.34	(−5.21 to 0.52)	0.107
Change in area of geographic atrophy			
As measured from color fundus photography, mm ²	+1.26	(1.05 to 1.47)	<0.0001
As measured from HRA autofluorescence imaging, mm ²	+1.15	(0.97 to 1.33)	<0.0001
Microperimetry measurements			
Number of scotomatous points	+4.44	(1.50 to 7.37)	0.004
Macular sensitivity of all points, dB	−1.05	(−1.59 to −0.50)	0.0003
Macular sensitivity of responding points, dB	−1.26	(−2.05 to −0.46)	0.0023
Macular sensitivity of perilesional points, dB	−1.20	(−1.93 to −0.47)	0.0015
Macular sensitivity of extrasional points, dB	−0.57	(−1.76 to 0.62)	0.340
Quality of fixation at 2 degrees, %	−11.89	(−20.09 to −3.68)	0.005
Quality of fixation at 4 degrees, %	−11.75	(−18.82 to −4.67)	0.0014

Numbers in bold indicate parameters that are statistically associated with follow-up time ($P < 0.05$).

FIGURE 2. Changes in overall macular sensitivity in GA progression on microperimetry testing. Interpolated map demonstrating progressive changes in macular sensitivity at (A) baseline, (B) 12 months and (C) 24 months in a representative eye with GA. Color coding in maps and their temporal progression illustrate overall decreases in areas of higher sensitivity (green and yellow) and increases in areas of lower sensitivity (orange and red). (D) Graph of the mean change in macular sensitivity of all tested points as a function of time. Error bars, SE.

follow-up time. Statistical analyses demonstrate that mean macular sensitivity of responding points was significantly associated with follow-up time ($P < 0.01$; Table 2), with the mean sensitivity of responding points decreasing at a rate of -1.26 dB/year.

Changes in macular sensitivity was also followed by identifying responding points at the baseline visit and tracking how these points decrease in sensitivity with time. Figure 3 shows the percentage of responding points at baseline that have decreased in sensitivity by at least 10, 6, or 4 dB or have become a nonresponding, scotomatous point at the 1- and 2-year time points. This analysis demonstrates that decreases in sensitivity are reflected in multiple tested points and become progressively more prominent with time.

Responding points on microperimetric testing were separated into perilesional and extralesional points to further analyze the location of macular sensitivity decrease (Figs. 4A, 4B). Considering all microperimetric evaluations for all eyes, we found that responding points closer to the area of absolute scotoma (i.e., perilesional points) had a lower sensitivity com-

pared with the surrounding points farther away from the scotoma (i.e., extralesional points; $P < 0.0001$; Fig. 4C). Also, although there was a statistically significant relationship between the decrease in the mean sensitivity of perilesional points and follow-up time ($P < 0.01$), the relationship between the mean sensitivity of extralesional points and time was not statistically significant (Table 2). Extralesional points also showed a slight nonsignificant increase in mean sensitivity at 6 and 12 months and declined slightly at 18 and 24 months. Mean sensitivity of perilesional points also demonstrated a greater and more general decrease with time (Fig. 4D), with that for perilesional points was calculated as -1.20 dB/year, compared with -0.57 dB/year for extralesional points (Figs. 4C, 4D).

Changes in Fixation Stability with Time

Fixation quality, defined as the percentage of tracked eye positions falling within the central 2° and 4° circles during fixation assessment, was followed in study eyes over time (Figs. 5A, 5B). Decreases in mean fixation quality over time were found for both measures using the 2° and 4° circles (Figs. 5C, 5D). Both measures of fixation quality were also found to decrease significantly with time ($P < 0.01$), with the mean percentage of fixation positions located within the 2° circle decreasing by -11.9% per year, and that located within the 4° circle decreasing by -11.7% per year.

Fixation assessments were also categorized into one of three quality categories: stable fixation, relatively unstable fixation, and unstable fixation. At baseline, out of a total of 18 eyes assessed, six (33%) eyes had "stable" fixation; one out of these six eyes progressed to "relatively unstable" fixation at the end of the follow-up period. Ten (56%) eyes at baseline had "relatively unstable" fixation; of these, six of 10 progressed to "unstable" fixation. The two (11%) remaining eyes had "unstable" fixation at baseline and remained "unstable" throughout the study. None of the eyes evaluated demonstrated an improvement in fixation category over the follow-up period.

FIGURE 3. Changes in sensitivity of responding points at baseline after 1 and 2 years on microperimetry testing. Responding points at baseline were identified and scored at 1 and 2 years of follow-up as to whether they had decreased in sensitivity by at least 10, 6, or 4 dB or transitioned to a nonresponding/scotomatous point. Error bars, SE.

FIGURE 4. Location of macular sensitivity change with time outside the GA lesion on microperimetry testing. (A) Symbolic microperimetric map in a representative eye with GA. (B) Corresponding map showing the segmentation of tested eyes into scotomatous or nonresponding points (pink), perilesional points (i.e., points immediately adjacent to scotomatous points, blue), and extralesional points (i.e., all remaining points, gray). (C) Comparison of the mean sensitivity of perilesional and extralesional points in all study eyes ($n = 18$) demonstrate a significantly greater sensitivity in extralesional points. (D) Graph of mean change in sensitivity from baseline for perilesional and extralesional points as a function of time demonstrates a more marked decline in perilesional compared with extralesional points. Error bars, SE.

Relationship between Changes in GA Lesion Area and Microperimetric Parameters

The total area of the GA lesion for all study eyes at all time points was measured from both CFP and HRA FAF images. Statistical analyses were performed to correlate changes in GA lesion area between baseline and month 24 with changes in microperimetric parameters analyzed. Statistically significant associations were found between the change in GA area and the increase in the number of scotomatous points and the decrease in the number of responding points (Table 3). The remaining microperimetric parameters were not found to be significantly associated with change in GA area. Similar results were obtained using GA areas assessed from CFP and HRA FAF images.

DISCUSSION

In the present study, we have characterized functional changes in GA progression using the MP-1 microperimeter and have analyzed parameters that reflect retinal sensitivity in the macula, both within and around GA lesions and fixation quality. By testing eyes with GA at regular time intervals using a standard microperimetric protocol over 24 months, we have detected patterns of progressive change that reveal the nature, rate, and location of functional decline inherent during GA progression.

In our study, we discovered that a number of microperimetric measures undergo significant change as a function of time. One of these is the total number of scotomatous (or nonresponding) points, which increased progressively with follow-up time. This finding indicated the ability of the MP-1 microperimeter to detect and measure the expansion of the functional scotomata expected from the anatomic enlargement

of the GA lesion. We had calculated a mean annual rate of increase of scotomatous points of +4.4 points/year, which we estimated to correspond to an increase in the area of nonresponsive retina by $1.85 \text{ mm}^2/\text{year}$ (estimating the tested 20° field to be $6000 \mu\text{m}$ in diameter and 28.3 mm^2 in area, and the approximate area covered by each tested point to be $28.3/68 = 0.42 \text{ mm}^2$), a value that is comparable to previous estimates for the annual growth of GA area.^{6,13,30–32} We also found that the change in the number of scotomatous points could be statistically associated with the increase of GA lesion area as measured by CFP and HRA FAF. This relationship confirmed the ability of MP-1 microperimetry to commensurately quantify changes in scotoma size occurring as a result of GA lesion expansion.

We also examined microperimetric parameters relating to the sensitivity of macula areas outside the GA lesion. In study eyes, the retinal sensitivity measured in areas outside the GA lesion were in general lower than those found in equivalent areas in healthy aged subjects,²⁰ and that the mean sensitivity, considering all responding points, declined significantly as a function of time. This result indicated that functional decline in GA involved not only an increase in the size of an absolute scotoma but also a general decrease in macular sensitivity in the tested area.

Segmentation of these responding points into perilesional points and extralesional points demonstrated that this time-related decrease in sensitivity occurred to a greater extent in areas closer to, rather than farther away from, the GA lesion borders. We found that perilesional points were consistently less sensitive than extralesional points in multiple microperimetric assessments and declined in sensitivity more rapidly with follow-up time. Previous cross-sectional studies have doc-

FIGURE 5. Changes in fixation quality with time on microperimetry testing. Representative study eye at baseline (A) with recordings of eye position (blue points) around a fixation cross. Fixation was quantified by calculating the percentage of eye positions during fixation assessment that fall within circle of either 2° or 4° diameter centered on fixation (inset). (B) Fixation measurement of the same eye at 24 months. Changes in fixation quality with time were followed by calculating the percentage of fixation points falling within the (C) 2° circle or (D) 4° circle. Reduction in fixation quality as a function of time was evident in both measures. Error bars, SE.

umented sensitivity loss by perimetry in the so-called junctional zone of GA lesions,^{18,19} relating this to the excessive accumulation of lipofuscin in RPE cells in areas bordering the GA lesion. Autofluorescence imaging data in GA had indicated that perilesional autofluorescence features may influence the GA progression rate, although this may still be controversial.^{32,33} Although many of the eyes analyzed in the present study contained areas of increased fundus autofluorescence (FAF) signal in the perilesional zones, the relatively low density of testing loci used here precluded an analysis of the correlation between macular sensitivity and abnormal FAF signal. Finally, we did not detect a correlation between the magnitude

of change in retinal sensitivity and the size of increase in GA lesion area. The absence of a detectable relationship may have resulted from imprecision in the quantification of retinal sensitivity using a relatively sparse array of tested points; alternatively, it may be that the more general loss of macular sensitivity in areas around GA lesion occurs as a separate process from the local expansion of the GA lesion itself. Future studies may investigate further the loss of retinal sensitivity in GA as a separate functional outcome variable and its potential correlation with other causative influences.^{34,35}

We found that fixation stability, as quantified by the MP-1 microperimeter, decreased significantly as a function of time.

TABLE 3. Association between the Change in the Area of Geographic Atrophy (GA) and Microperimetric Parameters from Baseline to Month 24

Microperimetry Parameters	Change in GA Lesion Area as Measured from Color Fundus Photography (CFP)		Change in GA Lesion Area by Fundus Autofluorescence (HRA FAF)	
	Estimate (95% CI)	P	Estimate (95% CI)	P
Number of scotomatous points	0.07 (0.01 to 0.13)	0.04	0.06 (0.01 to 0.10)	0.015
Number of responding points	-0.07 (-0.13 to -0.01)	0.04	-0.06 (-0.10 to -0.01)	0.015
Macular sensitivity of all points (dB)	-0.22 (-0.73 to 0.29)	0.37	-0.15 (-0.53 to 0.23)	0.409
Macular sensitivity of responding points (dB)	0.06 (-0.57 to 0.70)	0.83	0.01 (-0.46 to 0.48)	0.97
Macular sensitivity of perilesional points (dB)	0.20 (-0.32 to 0.73)	0.41	0.11 (-0.28 to 0.50)	0.56
Fixation quality at 2° (%)	0.00 (-0.03 to 0.04)	0.88	0.00 (-0.02 to 0.02)	0.90
Fixation quality at 4° (%)	0.00 (-0.03 to 0.02)	0.92	0.00 (-0.02 to 0.02)	0.77

Numbers in bold indicate parameters that are statistically associated with change in area of GA ($P < 0.05$). CI, confidence interval.

Previous studies have reported on the changes in the nature and location of fixation patterns in GA patients over time,^{17,36} but quantification of fixation quality over time in GA has not been previously reported. Previous investigators have shown that although MP-1 parameters for fixation may grossly correlate with reading speed, measurements of fixation with the bivariate contour ellipse formula may correlate better.^{37,38} Despite this limitation, the fixation quantification method used by the MP-1 microperimeter provides a rapid recording of fixation ability that agrees with previous measurement methods³⁹ and an accessible method for detecting progressive change in fixation ability. Our results indicate that fixation quality may indeed decline progressively during GA progression, although refinements in methodology and further validation may be necessary to establish this as an outcome measure in GA.

The present study contains a number of limitations, including a relatively small number of participants, an exposure to a novel topical agent in an interventional study,²⁸ and a reliance on the accuracy of both the device and the study participant. The study relies on the accuracy of the eye-tracking software used by the MP-1 device to return consistently to the tracked retinal loci between examinations. We have also not quantified the test-retest variability in our patient population; however, previous studies examining this issue in healthy volunteers⁴⁰ and patients with macular disease⁴¹ have reported that mean measures, such as those used in this study, have the lowest variability and may be recommended for monitoring macular function. These mean or "global" measures have the shortcoming of not providing spatial information regarding the location of interval changes. On the other hand, the present study had the advantage of employing MP-1 assessments that were collected using a standard testing pattern at regular 6-month intervals over a period of 2 years, increasing the likelihood that actual changes in retinal sensitivity are being detected and measured. Also, corresponding stereoscopic fundus photographs and autofluorescence images were obtained on the same visit as the MP-1 assessments, with the GA lesion areas being quantified by masked graders at a reading center, promoting the accurate correlation of MP-1 parameters to GA lesion area change. We had considered a priori that there may be a confounding "learning" effect in the subjective performance of microperimetry, in which participants gain more familiarity and thus "improve" with repeated testing.⁴² However, all microperimetric parameters (except for macular sensitivity of extralesional points) demonstrated statistically significant longitudinal trends that were in the opposite direction of any potential learning effect and cannot be explained as arising from repeated testing effects.

Taken together, our results indicate that the progression of functional decline in GA involves not only an expansion of an absolute scotoma, as can be expected from the growth of a central atrophic lesion, but also a more widespread decrease in retinal sensitivity, particularly in perilesional areas, as well as a loss of fixation stability. These changes are apparent in individual cases over a relatively short period of 24 months and are statistically associated with follow-up time when considered as a group. These trends may be relevant to the development of outcome measures in clinical trials of GA. As visual acuity in GA is not an outcome measure that correlates well with follow-up time or GA lesion expansion, there is a need for relevant and feasible functional outcome measures that relate to GA progression. As the microperimetric findings described here are relevant to the visual function of patients and correlate highly with the course of progression of GA, we propose that microperimetry may deserve further consideration for development as a useful functional outcome measure for future clinical trials of GA.

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