Special Issue

Maximum Reading Speed in Patients With Geographic Atrophy Secondary to Age-Related Macular Degeneration

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Purpose. Geographic atrophy (GA) is an advanced form of age-related macular degeneration. GA often initially spares the center of the fovea, leading to a functional disconnect between reading speed and distance visual acuity. This study was designed to determine the correlation between baseline GA lesion size, change in lesion size, and maximum reading speed (MRS) over 18 months.

Methods. Post hoc analysis included US patients from the phase 2 Mahalo study of intravitreal lampalizumab with Minnesota low-vision reading (MNREAD) assessments at baseline and 6, 12, and 18 months. Binocular MRS was assessed using MNREAD Acuity Charts and GA lesion size by fundus autofluorescence. Correlations were estimated using Spearman's rank correlation coefficient.

Results. Seventy-seven patients were included in the analysis. Baseline MRS correlated with baseline GA lesion size (correlation coefficient, −0.47; 95% confidence interval, −0.63 to −0.28; $P < 0.0001$). In patients with lesions ≥10 mm^2 (four disc areas), the proportion reading below a nonfluent level (MRS, <40 words/min) at baseline (26.5%) increased to 64.7% by 18 months, versus patients with lesions <10 mm^2 (baseline, 9.3%; 18 months, 7.0%). MRS declined by a median of 40.9% (interquartile range [IQR], −70.2 to −6.9) in patients with ≥2.5 mm^2 lesion growth versus 8.2% (IQR, −34.6 to 11.0) in patients with <2.5 mm^2 lesion growth from baseline to 18 months.

Conclusions. These findings suggest that baseline GA lesion size and magnitude of lesion growth are associated with a decline in MRS over time and support the use of MRS as an evaluation of functional vision in patients with GA.

Keywords: geographic atrophy, maximum reading speed, visual function, quality of life

Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD) characterized by progressive, irreversible loss of retina.[1] The prevalence of GA increases with age[2] and is estimated to occur in approximately 3.5% of those aged >75 years, increasing to approximately 23% to 35% in those aged >90 years.[3–7]

GA causes a severe loss of visual function and typically affects both eyes.[6,8] GA commonly spares the center of the fovea until later in the course of the disease. Patients often show minimal or no changes in central visual acuity when the lesion does not affect the fovea.[6,9] In the later stages of the disease, as the lesion expands into the fovea, a decrease in central visual acuity may occur.[10,11] However, before high-contrast best-corrected visual acuity (BCVA) letter scores deteriorate, visual function and the ability to perform activities of daily living are significantly impacted. BCVA is a single-letter test of foveal function, whereas, in comparison, fluent reading requires a larger area of central macula to perform well. Consequently, reading speed may capture the impact of GA, reflecting the visual impairment on daily life perceived by the patient, even when the fovea is still spared and BCVA letter scores are relatively preserved. Sunness et al.[9,12] demonstrated that, despite BCVA Snellen equivalents of 20/50 or better, eyes with GA may have impaired visual function as measured by reading speed, low luminance visual acuity, and contrast sensitivity. Loss of reading ability is important to patients and is a frequent complaint among patients with low vision, particularly those with central-field vision loss.[10,11,13,14] Reduced reading speed is associated with reduced independence in performing activities of daily living that require reading.[15,16] It also can be associated with distress and depression in patients with AMD and is an important factor in vision-related qualify of life.[17–19]

The Mahalo study was a phase 2, multicenter, randomized, single-masked, sham injection-controlled study conducted at sites in the United States (NCT01229215) and Germany (EudraCT number, 2010-019183-36) that evaluated the safety, tolerability, pharmacokinetics, and evidence of activity of

lampalizumab in patients with GA secondary to AMD.[20] Lampalizumab is an antigen-binding fragment (Fab) of a humanized, monoclonal antibody directed against complement factor D that selectively inhibits the alternative complement pathway.[20] In this article, we describe the reading speed over time in patients with GA and the correlation between progression of the disease, as measured by GA lesion area, and maximum reading speed (MRS) at baseline and through 18 months of follow-up in this phase 2 trial of lampalizumab.

Methods

In the Mahalo phase 2 study (NCT01229215), intravitreal lampalizumab injections were administered monthly or every other month for an 18-month treatment period in patients with bilateral GA secondary to AMD.[20] The trial followed the tenets of the Declaration of Helsinki and complied with the Health Insurance Portability and Accountability Act. Patients provided written informed consent prior to enrollment, and the protocols were approved by institutional review boards, ethics committees, or as otherwise applicable at each study site.

The Mahalo study design has been reported in detail previously,[20] and is summarized here. Following completion of a safety run-in phase, eligible patients were randomized to receive sham monthly, lampalizumab 10 mg monthly, sham every other month, or lampalizumab 10 mg every other month.[20] One eye from each patient was designated as the study eye. If both eyes were eligible, the eye with the worst visual acuity and/or least function was selected for study treatment (study eye). The primary efficacy outcome measure was mean change in GA area in the study eye from baseline to month 18, as measured by fundus autofluorescence (FAF). Secondary outcome measures included mean change in GA area from baseline to month 18, as measured by color fundus photography and mean change in BCVA letter score from baseline to month 18 in the study eye by using the Early Treatment Diabetic Retinopathy Study (ETDRS) visual acuity chart.[20] This exploratory, post hoc analysis of the Mahalo study included the change in binocular MRS in the number of read words per minute (wpm) from baseline to month 18.

Study Assessments

All study assessments were carried out prior to the intravitreal injection under a standardized protocol. GA lesion size in the study eye was measured at baseline, and at 6, 12, and 18 months on FAF. The BCVA letter score in the study eye was assessed monthly using ETDRS charts at a starting distance of 4 meters. Reading speed was measured as a binocular assessment by using MNREAD Acuity Charts, as developed by the Minnesota Laboratory for Low-Vision Research, in patients from the United States at baseline and 6, 12, and 18 months.

The MNREAD Acuity Charts are continuous-text reading-acuity charts used for measuring MRS (in wpm). An MNREAD Acuity Chart consists of sentences displayed in a range of letter sizes, which were designed to resemble "normal everyday reading" that demands the visual processing capabilities and eye-movement control required for normal text reading. Reading speed tests can be performed as a monocular or binocular test. Binocular assessments were used in Mahalo and are more relevant than monocular assessments from the patient's perspective because patients read with both eyes in the real world. Although monocular assessments are useful in assessing visual function (i.e., how an eye functions), binocular assessments are useful in assessing functional vision (i.e., how a person functions in vision-related activities).[21] An MNREAD Acuity Chart was used at a distance of 16 inches to measure the patient's reading speed. A stopwatch was used to record time to a 10th of a second. The time taken to read each sentence and the number of errors made were recorded on a score sheet. Reading speed for each sentence was calculated using the entered data and the MNREAD scoring algorithms.[22] MRS was calculated as the arithmetic mean of the three highest reading speeds for the sentences read from the MNREAD Acuity Chart for each patient.

Data Analysis and Statistical Methods

This analysis included all randomized patients with GA lesion size, BCVA, and MRS outcomes at both baseline and 18 months. All treatment groups were combined for analysis because the association between GA lesion size and reading speed was not expected to be subject to treatment effect. Observed data were used in the analysis, with no imputations for missing data. Spearman's rank correlation coefficient was used to estimate correlations due to the existence of outliers in reading speed outcomes. For GA lesion size and BCVA letter score, study-eye outcomes were used. For MNREAD reading speed, only binocular outcomes were available and used.

For baseline comparisons of MRS by GA lesion size, lesions were categorized as <10 mm^2 or ≥ 10 mm^2. The cut point of 10 mm^2 (four disc areas) was a preselected stratification factor in the study, representing a convenient value close to the midpoint of the eligibility criteria.

The change in MRS over time was assessed by percent change relative to baseline rather than absolute difference, to account for the impact of baseline MRS on the change in MRS over time. For an analysis of the percentage change in MRS by GA lesion growth from baseline to month 18, lesion growth was stratified as <2.5 mm^2 or ≥ 2.5 mm^2. The cut point of 2.5 mm^2 (one disc area) was based on the prespecified criteria to use a number close to the median lesion growth over 18 months for all patients in this analysis population (actual median, 2.79 mm^2).

A sensitivity analysis for the correlations of GA lesion size with MRS or BCVA was also undertaken in which the data were stratified based on whether the designated study eye was the worse- or better-seeing eye based on baseline BCVA. The correlation between baseline MRS and BCVA in the better-seeing eye (study eye or fellow eye) was also summarized.

To further explore change in MRS over time, the percentages of patients with nonfluent reading speed and high-fluent reading speed at baseline and 18 months were summarized. Nonfluent reading speed was defined as MRS <40 wpm and high-fluent reading was defined as MRS ≥ 160 wpm. These cutoff values were based on rates from Carver[23] and Whittaker et al.,[24] whereby 40 wpm represents "spot reading," a rate adequate for certain activities of daily living, such as reading an address on an envelope or a price tag, and 160 wpm, a rate considered "high fluent reading" among low-vision patients at approximately a sixth-grade reading level.[24] These MRS outcomes also were stratified according to baseline lesion size (<10 mm^2 and ≥ 10 mm^2).

Qualified researchers may request access to individual patient level data through the clinical study data request platform (www.clinicalstudydatarequest.com). Further details on Roche's criteria for eligible studies are available (https://clinicalstudydatarequest.com/Study-Sponsors/Study-Sponsors-Roche.aspx). Further details on Roche's Global Policy on the Sharing of Clinical Information and how to request access to related clinical study documents are available online (https://www.roche.com/research_and_development/who_we_are_how_we_work/clinical_trials/our_commitment_to_data_sharing.htm).

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Table 1. Baseline Characteristics of Mahalo Study Patients With MNREAD Assessments at Baseline and Month 18 ($n = 77$)

Characteristic	Baseline Value
Age (y), mean (SD)	79.0 (7.4)
Women, *n* (%)	45 (58.4)
White, *n* (%)	77 (100.0)
Maximum binocular reading speed (wpm)	
Mean (SD)	109.5 (61.4)
Median (IQR)	117.2 (56.6–156.7)
BCVA (letter score [approximate Snellen equivalent])	
Mean (SD)	48.9 [20/100] (12.6 [2 lines])
Median (IQR)	49.0 [20/100] (60.0 [20/63]–37.0 [20/200])
Approximate Snellen equivalent	20/100
BCVA Snellen equivalent, *n* (%)	
20/40 to 20/80	33 (42.9)
20/100 to 20/160	23 (29.9)
20/200 or worse	21 (27.3)
Total area of GA (mm^2)	
Mean (SD)	8.9 (4.6)
Median (IQR)	8.2 (4.3–12.1)
Distribution, *n* (%)	
2.5 to 5.0 mm^2	22 (28.6)
5.0 to 7.5 mm^2	11 (14.3)
7.5 to 10.0 mm^2	10 (13.0)
10.0 to 12.5 mm^2	15 (19.5)
12.5 to 15.0 mm^2	8 (10.4)
15.0 to 17.5 mm^2	11 (14.3)
Patients with subfoveal GA, *n* (%)	64 (83.1)
Patients with worse BCVA in study eye, *n* (%)	60 (77.9)

Results

Baseline Patient Characteristics

Mahalo patients were enrolled and randomized between May 2011 and April 2013. Seventy-seven patients from the United States completed MNREAD Acuity Charts at baseline and month 18; baseline characteristics are shown in Table 1. The mean age of these participants was 79 years, the majority (58%) were women, and all were white. The mean baseline BCVA letter score for the study eye was 48.9 (SD, 12.6), approximate Snellen equivalent of 20/100. Of these patients, 83.1% had subfoveal GA and 77.9% had a worse BCVA letter score in the study eye. The mean baseline BCVA letter score in the fellow eye was 58.5 (SD, 20.1).

MRS at Baseline

The baseline median MRS was 117.2 wpm (interquartile range [IQR], 56.6–156.7), and the median total area of the GA lesion at baseline was 8.2 mm^2 (IQR, 4.3–12.1) (Table 1). On average, patients with larger GA lesion sizes at baseline had a slower MRS at baseline. For patients with larger GA lesion sizes ($\geq$10 mm^2), the median baseline MRS was 71.1 wpm (IQR, 37.9–121.8) compared with 150.0 wpm (IQR, 77.3–166.7) for patients with smaller GA lesion sizes ($<$10 mm^2) (Fig. 1).

The baseline MRS was correlated with the baseline size of the GA lesion (correlation coefficient, –0.47; 95% confidence interval [CI], –0.63 to –0.28; $P < 0.0001$), as was BCVA letter score to a lesser degree (correlation coefficient, –0.21; 95% CI, –0.41 to 0.02; $P = 0.069$) (Table 2). The correlation between GA lesion size and MRS persisted when stratified by baseline BCVA ($<$48 letter score [approximate Snellen equivalent 20/125 or worse]: correlation coefficient, –0.40; 95% CI, –0.65 to –0.06; $P = 0.02$; and $\geq$48 letter score [approximate Snellen equivalent 20/100 or better]: correlation coefficient, –0.34; 95% CI, –0.58 to –0.05; $P = 0.02$). The correlation between GA lesion and MRS also persisted when the data were stratified according to whether the study eye was the worse-seeing eye (based on baseline BCVA; $n = 60$; correlation coefficient, –0.51; 95% CI, –0.67 to –0.29; $P < 0.0001$) or better-seeing eye ($n = 17$; correlation coefficient, –0.41; 95% CI, –0.74 to 0.09; $P = 0.1059$), as did the correlation between GA lesion size and BCVA (Table 2). The baseline MRS was significantly correlated with baseline BCVA in the better-seeing eye (study or fellow eye; correlation coefficient, 0.62; 95% CI, 0.46 to 0.74; $P < 0.0001$).

Change in MRS Over 18 Months

The median MRS declined from 117.2 wpm (IQR, 56.6–156.7) at baseline to 75.6 wpm (IQR, 30.3–124.0) at 18 months. The median percent decline from baseline in MRS was 12.7% (IQR, –38.3 to 13.0) at 6 months, 14.5% (IQR, –43.2 to 16.4) at 12 months, and 22.8% (IQR, –56.5 to 0.0) at 18 months (Fig. 2). Two of the 77 patients (2.6%) had an improvement in MRS of greater than 1 SD (44.6 wpm) at 18 months.

Over the 18-month period, patients with a larger GA lesion growth had a greater decline in MRS compared with patients with smaller lesion growth. Median MRS declined by 40.9% (IQR, –70.2 to –6.9) in patients with GA growth of $\geq$2.5 mm^2 from baseline to 18 months, compared with only an 8.2% (IQR, –34.6 to 11.0) decline in patients with growth of $<$2.5 mm^2 (Fig. 3). The observed correlation of percent change in MRS and change in GA lesion size in the study eye over time was –0.33 (95% CI, –0.52 to –0.12; $P = 0.0029$) (Table 2). Similar results were observed using alternative cut-point values (data not shown). This correlation was also maintained when the data were stratified by better- versus worse-seeing eye, with a stronger correlation being observed when the study eye was the better-seeing eye (–0.60; 95% CI, –0.84 to –0.17; $P = 0.009$ for better-seeing study eyes and –0.26; 95% CI, –0.48 to –0.004; $P = 0.0467$ for worse-seeing study eyes).

Nonfluent Versus High-Fluent Reading: Baseline and Change Over 18 Months

Reading speed was also summarized according to the proportions of patients reading at a nonfluent versus a high-fluent level. At baseline, 16.9% of patients were reading below a nonfluent level (MRS, $<$40 wpm) compared with 32.5% at 18 months, a difference of 15.6% (95% CI, 5.4 to 25.8). In contrast, the percentage of patients reading at a high-fluency level (MRS, $\geq$160 wpm) decreased from 24.7% at baseline to 11.7% at 18 months, a difference of 13.0% (95% CI, 3.2 to 22.8).

Trends by baseline lesion size were consistent when summarized by reading fluency level. Patients with a larger baseline lesion size ($\geq$10 mm^2) had, on average, a lower reading level at baseline and at 18 months compared with patients with a smaller baseline lesion size ($<$10 mm^2). At baseline, 26.5% of patients with larger lesion sizes read below a nonfluent level compared with 9.3% of patients with smaller lesion sizes. At 18 months, 64.7% of patients with larger lesion sizes read below a nonfluent level compared with 7.0% of patients with smaller lesion sizes. Conversely, fewer patients with larger lesion sizes at baseline had high-fluent reading compared with those with smaller lesion sizes. At baseline, 11.8% of patients with larger lesion sizes read at 160 wpm or

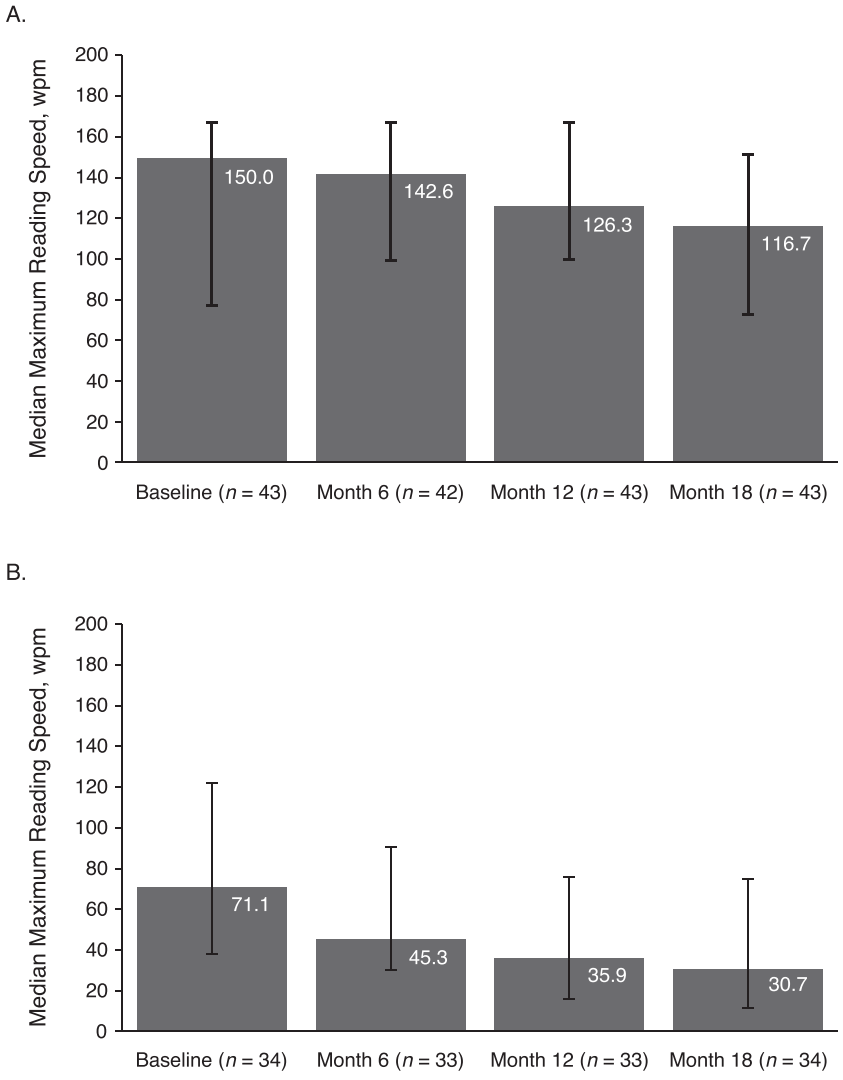

Figure 1. Maximum binocular reading speed over time by baseline GA lesion size. **(A)** GA lesion size <10 mm^2 at baseline; **(B)** GA lesion size ≥10 mm^2 at baseline. Data shown are median ± IQR.

Table 2. Correlation of BCVA and MRS With GA Lesion Size at Baseline and Change Over an 18-Month Period

Variables	Correlation Coefficient	95% CI	*P* Value
Baseline BCVA (letter score) vs. baseline GA lesion size (mm^2)			
All patients (n = 77)	−0.21	−0.41 to 0.02	0.069
Worse-seeing study eye (n = 60)	−0.25	−0.47 to 0.008	0.0578
Better-seeing study eye (n = 17)	−0.18	−0.61 to 0.33	0.4978
Baseline maximum binocular reading speed (wpm) vs. baseline GA lesion size (mm^2)			
All patients (n = 77)	−0.47	−0.63 to −0.28	<0.0001
Worse-seeing study eye (n = 60)	−0.51	−0.67 to −0.29	<0.0001
Better-seeing study eye (n = 17)	−0.41	−0.74 to 0.09	0.1059
Change in BCVA from baseline at month 18 (letter score) vs. change in GA lesion size (mm^2) from baseline to month 18			
All patients (n = 77)	−0.32	−0.51 to −0.10	0.004
Worse-seeing study eye (n = 60)	−0.26	−0.48 to −0.005	0.0458
Better-seeing study eye (n = 17)	−0.42	−0.75 to 0.08	0.0962
Change in maximum binocular reading speed from baseline at month 18 (%) vs. change in GA lesion size (mm^2) from baseline to month 18			
All patients (n = 77)	−0.33	−0.52 to −0.12	0.0029
Worse-seeing study eye (n = 60)	−0.26	−0.48 to −0.004	0.0467
Better-seeing study eye (n = 17)	−0.60	−0.84 to −0.17	0.009

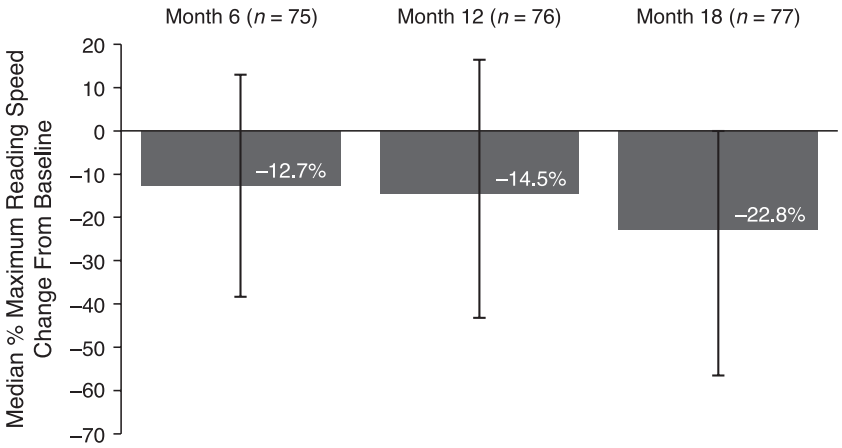

Figure 2. Percent change in MRS over time. Data shown are median ± IQR.

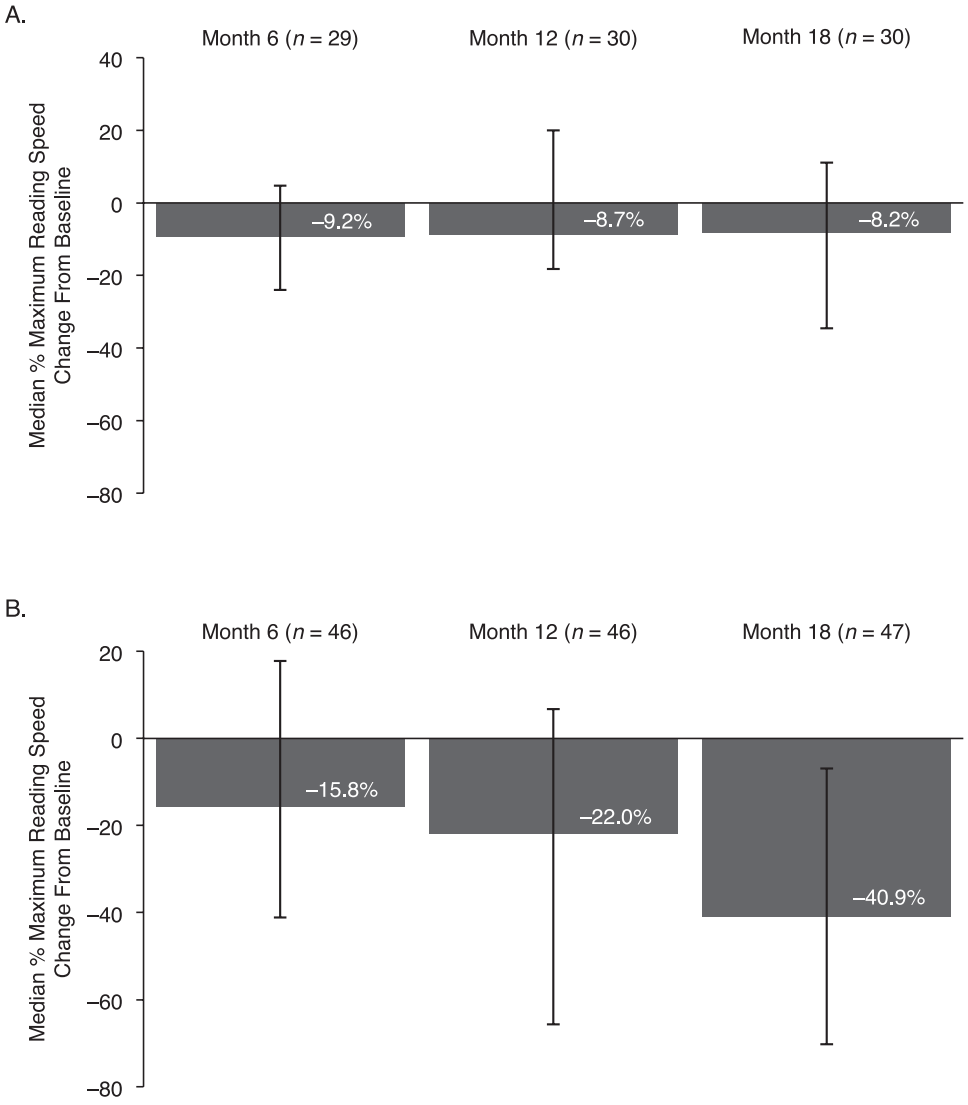

Figure 3. Percent change in maximum binocular reading speed over time stratified by magnitude of GA lesion growth. (**A**) Patients with GA lesion growth <2.5 mm^2 from baseline to month 18; (**B**) Patients with GA lesion growth ≥ 2.5 mm^2 from baseline to month 18. Data shown are median ± IQR.

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more, whereas 34.9% of patients with smaller lesion sizes could read at this high-fluency level. At 18 months, 5.9% of patients with larger lesion sizes read at or above a high-fluency level compared with 16.3% of patients with smaller lesion sizes.

Discussion

These data from Mahalo demonstrate the impact of GA lesion size in the study eye (worse-seeing eye in 60/77 patients) on the binocular functional vision of patients measured by MRS. Many patients with GA experience compromise in reading function and the ability to perform activities of daily living that require reading (e.g., reading labels or signs and writing checks), presumably due to the location and size of scotomas resulting from their disease, in one or both eyes.

At baseline, greater GA lesion size in the study eye as measured by FAF was associated with worse binocular MRS. The relationship between binocular MRS and GA lesion size described here seems important because it indicates that reading speed is a valuable assessment in GA. The relatively modest correlation between GA lesion size and BCVA letter score (correlation coefficient, –0.21; 95% CI, –0.41 to 0.02; $P = 0.069$) at baseline compared with that between GA lesion size and MRS (correlation coefficient, –0.47; 95% CI, –0.63 to –0.28; $P < 0.0001$) further shows that reading speed measured by the MNREAD captures the impact of GA on functional vision that cannot be reflected by BCVA, as has been reported in patients with focal sparing GA lesions.[25] It is also interesting to note that GA lesion size was more highly correlated with reading speed than with BCVA at baseline despite the fact that reading speed was measured binocularly, while both BCVA and GA lesion size were measured in the study eye only. The significant correlation between change in MRS or BCVA and GA lesion size at 18 months indicated that visual acuity and functional vision worsen over time as GA progresses, even in those with a clinical appearance of foveal sparing.[25] The correlations between MRS or BCVA and GA lesion size were also maintained when the data were stratified based on whether the designated study eye was the worse- ($n = 60$) or better-seeing ($n = 17$) eye based on baseline BCVA.

At baseline, the median binocular MRS (117.2 wpm) of patients in Mahalo was considered "fluent" in low-vision populations, approximately at or above the reading speed of a second grader.[26] By the end of 18 months, the median binocular MRS had dropped below 80 wpm (to 75.6 wpm), the cut-point for fluent reading in low-vision populations, and below the reading speed of a second grader.[23,24]

Over an 18-month period, an increased growth of the study eye lesion size was associated with a greater decline in binocular reading speed. Among patients with ≥ 2.5 mm^2 lesion growth over 18 months, the decline in reading speed was five times greater than the decline in those with <2.5 mm^2 lesion growth over 18 months.

At 18 months, the percentage of nonfluent readers more than doubled among those with larger lesion sizes at baseline. In contrast, among those with smaller lesion sizes at baseline, the percentage of nonfluent readers was relatively stable over the 18 months. Although there were more high-fluent readers at baseline among the smaller lesion sizes group, the percentages of high-fluent readers over time dropped by more than half for both groups of patients. Thus, although the patients with smaller lesions may be more likely to be high-fluent readers than those with larger lesions, both groups may be at risk of losing their high-fluency reading over time.

A small proportion of patients in the study experienced an improvement in reading speed above 1 SD. Although our data alone cannot explain this observation, spontaneous improvements in visual acuity in the worse-seeing eye have been reported in patients with advanced bilateral GA in whom the visual acuity of the better-seeing eye had started to deteriorate.[27] These improvements have been related to improved use of the remaining retina, including improvements in fixation.[27] Although this phenomenon could have contributed to our findings, the locus of fixation was not measured in this study, and, thus, additional research will be required to investigate this further.

There are some potential limitations to this study. First, the data are from a relatively small number of patients studied over a relatively short duration. It is not known whether the patients and findings from these clinical trial populations are representative of what would be seen in a clinical practice setting. This is not a natural history study because treatment groups were combined with sham patients to create a larger dataset for analysis; however, this combination of treatment and sham groups would not impact baseline results, nor the association between MRS and GA lesion size over time. Also, although we have demonstrated an association between MRS and GA lesion size, which persisted when stratified by baseline BCVA letter scores, the potential association with GA lesion location could not be assessed because of the lack of variability in this analysis sample (83.1% [64/77] of lesions were subfoveal at baseline).

An additional limitation is that this study compared changes in GA lesion size and visual acuity measured in the study eye only with binocular reading speed (with the patient using both eyes simultaneously). The impact of the fellow eye was not considered and is an area for future study. With visual acuity, binocular BCVA is often similar to BCVA in the better-seeing eye, although summation or inhibition may occur.[28] Similarly for MRS, a study of patients with neovascular AMD found that binocular MRS measured using the MNREAD Acuity Chart was similar to MRS in the better-functioning eye for the majority of patients. However, binocular MRS was better than monocular MRS in the better-functioning eye for 13% of patients and worse in 19% of patients.[29] In our analysis, we found a strong correlation between baseline BCVA in the better-seeing eye and binocular MRS. Finally, further research may seek to assess the correlation between monocular reading speed and GA lesion size.

In summary, these data demonstrate the correlation between binocular MRS, an objective patient performance measure of functional vision, and GA lesion size, an anatomic, clinical measurement of disease severity. The decline in functional vision over time as measured by MRS was associated with anatomic evidence of disease progression measured by GA lesion growth. The data from this analysis are, therefore, supportive of the use of binocular reading speed as a patient-relevant measure of functional vision in patients with GA and as an end point in clinical trials. These findings are especially important given that GA lesions generally initially spare the center of the fovea, and, hence, BCVA letter score alone may not initially fully capture the impact of retinal atrophy on functional vision. Reading speed, thus, represents a viable and practical measure of functional vision for assessing GA progression and consequent deterioration of functional vision.

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