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The Long-term Natural History of Geographic Atrophy from Age-Related Macular Degeneration:

Enlargement of Atrophy and Implications for Interventional Clinical Trials

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Abstract

Purpose—To report the enlargement rate of geographic atrophy (GA) over time, its relationship to size of atrophy at baseline and to prior enlargement rate, and the implications for designing future treatment trials for GA.

Design—Prospective natural history study of GA resulting from age-related macular degeneration.

Participants—Two hundred twelve eyes of 131 patients were included in the analysis.

Methods—Annual follow-up included stereo color fundus photographs. The areas of GA were identified and measured, and the rate of enlargement of the atrophy was assessed. Sample sizes for clinical trials using systemic treatment and uniocular treatment were determined.

Main Outcome Measure—Rate of enlargement of the atrophy.

Results—The median overall enlargement rate was 2.1 mm²/year (mean, 2.6 mm²/year). Eyes with larger areas of atrophy at baseline tended to have larger enlargement rates, but knowledge of prior rates of enlargement was the most significant factor in predicting subsequent enlargement rates. There was high concordance between the enlargement rates in the 2 eyes of patients with bilateral GA (correlation coefficient, 0.76). To detect a 25% reduction in enlargement rate for a systemic treatment (α , 0.05; power, 0.80; losses to follow-up, 15%), 153 patients each in a control and treatment group would be required for a trial with a 2-year follow-up period for each patient. For a uniocular treatment, 38 patients with bilateral GA would be required, with the untreated eye serving as a control for the treated eye.

Conclusions—Treatment trials for GA with an outcome variable of change in enlargement rate are feasible.

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Geographic atrophy (GA), the advanced atrophic form of age-related macular degeneration (AMD), is present in 3.5% of people aged 75 years and older,^{1,2} and its prevalence rises to 22% or more in people older than 90 years in the United States³ (also Quillen et al. Invest Ophthalmol Vis Sci 47[suppl]:S111, 1996). It is a significant cause of both moderate and severe central visual loss and is bilateral in most patients.^{4–8} Areas of GA have dense scotomas that generally correspond in spatial extent exactly to the atrophic areas,⁹ so that measuring the enlargement of the atrophy reflects a loss in visual function.^{10,11}

Because GA is a degenerative rather than a neovascular disorder, the possible methods for treatment of this disorder are likely to be different than those for choroidal neovascularization (CNV). To date, there is no definite treatment for GA. Limited information on GA from the Age-Related Eye Disease Study has been published.¹² The findings presented did not attain statistical significance, and there were some contradictory findings, perhaps because of the small numbers. To design future studies of potential therapies for GA, it is important to know the natural history of GA.

This article reports our long-term prospective findings of the enlargement of the area of atrophy in GA. We also explore issues important for the design of future treatment trials, including sample size calculations and appropriate eligibility criteria for baseline GA area.

Patients and Methods

Patients and Annual Examinations

Patients with GA associated with AMD were enrolled in our National Institutes of Health-funded prospective natural history study, which ran from 1992 through 2000. Patients were evaluated annually. Eligibility criteria included having an area of GA of at least 500 μm in diameter in the absence of CNV (assessed clinically and by fluorescein angiography) in one or both eyes. At each examination, a battery of visual function tests also was performed, as described previously.¹³ Thirty-degree and, when possible, 60° color fundus photographs were obtained at each examination. Fluorescein angiography was performed at baseline to rule out CNV.

Measuring Geographic Atrophy

The fundus photographs were used to make drawings of the areas of GA by the method described in detail previously.¹⁴ Two sources of error had to be considered. First, the extent to which the disc was present within each 30° color fundus photograph could vary, affecting the assessment of the area of peripapillary GA from year to year. To deal with this, the photographs from all years were studied and the amount of disc to be included was set based on the amount that appeared in all the photographs.¹⁴ Second, if the GA extended to, or beyond, the edge of the photographic field at 1 or more examinations (mainly in eyes with large GA areas), the entire GA area could not be measured and a correct enlargement rate (ER) could not be calculated; such examinations were excluded from the analysis.

Statistical Methods

The overall long-term enlargement rate for each eye, that is, the rate including all visits with measurable areas of atrophy for that eye, was calculated by linear regression analysis using the least squares method using Microsoft Excel (Microsoft, Redmond, WA). However, for the purpose of characterizing enlargement rates to design future treatment trials, it was more relevant to look at the 2-year ER, defined as the ER over the first follow-up interval of between 1.5 and 2.5 years. The ER was calculated as the ratio of the difference in area measurements to the time difference from the baseline to the 2-year follow-up visit. To determine whether knowledge of the prior ER of a given eye was predictive of the subsequent ER, the subsequent

2-year ER (subsequent ER) was calculated. The subsequent ER was the rate of enlargement over the 2-year nonoverlapping interval immediately after the first 2-year interval. The subsequent ER, compared with the first 2-year ER, also was used to determine the extent of dependence of ER on area. If ER and area were highly correlated, the subsequent 2-year ER should have been larger than the first 2-year ER.

A critical consideration in the design and cost of a clinical trial is the length of follow-up. To determine whether 1 year of follow-up is adequate, as compared with 2 years of follow-up, the ER and variability were assessed for the first 9- to 15-month follow-up interval and compared with the 2-year ER measure.

JMP expert data analysis software (SAS Institute, Cary, NC) was used to perform the calculations provided below. Probabilities of 0.05 or less were deemed to indicate statistical significance. Sample size calculations were performed using 1 eye per patient with bilateral GA. (Other possible methods of assessing sample size are provided by Gauderman and Barlow.¹⁵) A power of 80% was used for the Age-Related Eye Disease Study trial¹⁶ and is a common choice that was used in our calculations. Based on our data, we estimate a 15% loss to follow-up for a 2-year trial, and a 10% loss to follow-up for a 1-year trial.

For the area data, the Macular Photocoagulation Study disc area (MPS disc area) is provided because of the familiarity that many retinal specialists have with this measure. One MPS disc area is equivalent to 2.54 mm² on the retina. However, with a transition to digitized photographs, square millimeters has become the more useful measurement. The data therefore are presented as square millimeters and square millimeters per year, with MPS disc area given only for baseline area measurements.

Results

One hundred thirty-five patients with GA completed 2 or more annual examinations. Two hundred twelve eyes of 131 patients met the eligibility criteria for GA in this study and had adequate photographs to assess for progression. There were a total of 908 eye examinations usable for measuring GA area. The median length of follow-up for the 212 eyes was 4.3 years (range, 1–8 years), with 86% having 2 or more years of follow-up.

Sixty-three percent of patients had bilateral GA without clinical or angiographic evidence of CNV (bilateral GA group), 27% had GA without CNV in 1 eye and CNV or disciform scar in the fellow eye (fellow eye CNV group), 8% had GA in 1 eye and drusen or pigmentary changes without advanced AMD in the fellow eye (fellow eye drusen group), and 2% had fellow eyes that could not be evaluated (other). The median age of the patients at the baseline examination was 78 years, with a range of 64 to 92 years. Eighty-five percent of the patients were between 70 and 89 years of age, inclusive. Fifty-nine percent of the patients were women.

Table 1 to Table 3 provide baseline visual acuity and total area of GA for all eyes. There was no significant difference between the bilateral GA group and the fellow eye CNV group in visual acuity or in the total area of GA at baseline in the study eyes, but the fellow eye drusen group had a smaller total area of GA at baseline in the study eye, compared with these 2 other groups.

Rate of Enlargement of Atrophy

For the total follow-up of GA enlargement for each eye, the mean overall ER was 2.6 mm²/year and the median ER was 2.1 mm²/year. Figure 1 illustrates the progression over time for 3 patients differing in the rate of enlargement. The 2-year ER was similar, with mean and

median ERs of 2.5 mm²/year and 2.2 mm²/year, respectively. Table 4 shows the distribution of 2-year ERs.

The 2-year ER was used to look at dependence of ER on baseline area. Figure 2 and Table 5 show the relationship of ER to the area at the beginning of the 2-year follow-up interval. Those eyes with a baseline area of less than 1.3 mm² (0.5 MPS disc areas) grew most slowly. There also was a significant difference in mean ER between the groups with baseline areas between 1.3 and 8.3 mm² (0.5–3.24 MPS disc areas, i.e., below the median baseline area) and those with baseline areas of 8.3 mm² or more (3.25 MPS disc areas, i.e., above the median baseline area). However, as Figure 2 shows, there is wide variation of ER for a given baseline area of atrophy.

The mean ERs were 2.6 mm²/year for the bilateral GA group, 2.2 mm²/year for the fellow eye CNV group, and 1.3 mm²/year for the fellow eye drusen group. The difference between the bilateral GA group and the fellow eye drusen group was significant at the $P = 0.05$ level, but the difference is accounted for by the lower baseline area in the fellow eye drusen group. There also was no statistically significant difference in ER between the 10 eyes with GA in which CNV developed after 2 or more years of follow-up and the 152 eyes in which CNV did not develop (mean, 2.1 mm²/year for those in whom CNV developed and 2.5 mm²/year for those in whom CNV did not develop; Student's t test, -0.72 ; $P = 0.47$). There was no statistically significant difference in ER based on age, gender, or baseline visual acuity.

For 90 eyes, there was adequate follow-up so that the first 2-year ER and a subsequent (nonoverlapping) 2-year ER could be compared. Figure 3 shows the results. There is high correlation of the subsequent ER with the first 2-year ER ($r = 0.58$), with a mean difference of -0.3 mm²/year, and a median difference of -0.02 mm²/year between the subsequent and first 2-year ERs. Fifty eyes (56%) had the subsequent ER within 0.8 mm²/year of the first 2-year ER. When the first 2-year ER is taken into account, there is no longer a statistically or clinically significant dependence of the subsequent ER on the area at the beginning of the later interval. If the area dependence were predominant, one would expect the subsequent ERs to be greater than the corresponding earlier ERs, and this is not the case. Our findings are more consistent with a fairly constant ER over time characterizing each individual's eye.

Concordance between Eyes

Figure 4 shows the relationship of ER between the 2 eyes for patients with bilateral GA. The correlation coefficient is 0.76. Thirty-six of the 62 bilateral GA patients (58%) with 2-year follow-up had a difference in ER between eyes of 0.6 mm²/year less. The baseline areas also were highly correlated (correlation coefficient, 0.81) between the 2 eyes.

Sample Size Calculation

To design future treatment trials for potential therapies to slow progression of GA, one must define the sample size needed. Table 6 gives the sample sizes required for 3 types of trial design: systemic treatment with no prior knowledge of ERs (2 groups of patients, half treated and half control), systemic treatment taking into account prior ER (2 groups of patients, half treated and half control), and uniocular treatment using the fellow eye as a control. The strong concordance between eyes in ER leads to a small sample size for uniocular trials.

Length of Observation Period

One-year ERs were compared with the 2-year ER measure. In general, the 1-year ER mirrored the findings of the 2-year ER. Fifty-one of the 60 eyes with 1-year and 2-year follow-up visits (85%) had ERs for both the 1-year and 2-year interval that were concordant for being more or less than the median ER. Table 6 provides sample size estimates using the 1-year ERs. There

is more variability in the 1-year ER, leading to a larger sample size requirement for both systemic and unioocular treatments. Also, a 2-year study provides an additional set of annual fundus photographs (i.e., at baseline, 1 year, and 2 years), which is useful for quantifying the area of GA in difficult cases.

Discussion

In this study, the median rate of enlargement of the atrophy was 2.1 mm²/year. When prior follow-up was available, the ER was strongly correlated with the prior ER. There is a dependence of ER on the baseline size of the atrophy as well, but this was found to be less strong in 2 respects. First, looking at patients cross-sectionally, when the prior ER is included, the effect of baseline atrophy size is not statistically significant, and there is wide variation in ERs among patients with similar baseline atrophic areas (Fig 2). In addition, looking at patients longitudinally, the subsequent ER was not larger than the first 2-year ER, contrary to what one would expect because the subsequent interval began with a larger atrophic area. Thus, the rate seems to be more closely determined by individual patient characteristics than by the size of the atrophy alone.

Eyes with small areas of GA, less than 1.3 mm² (0.5 MPS disc area), had a significantly lower rate of enlargement than eyes with larger areas of GA. It would be logical to use this amount of atrophy as the minimum eligibility criterion for a clinical trial. Although the area of GA continues to enlarge for large baseline areas (22.9 mm² [9 MPS disc areas] or more), at these larger areas, the boundaries of the GA may extend past the edge of the fundus photograph at subsequent examinations, thus not allowing for a calculation of ER using fundus photographs as the basis of measurement. Thus, the upper limit for atrophy at baseline should be determined based on the size of the photographic field used for measuring the GA.

A recent paper by Dreyhaupt et al¹⁷ modeling the findings of the Fundus Autofluorescence in Age-Related Macular Degeneration study, a prospective multicenter study of GA in Germany, quantified enlargement of GA area by measuring the dark (atrophic) areas in the autofluorescent image. Median follow-up time for the 114 patients in the study was 1.9 years. They found a mean growth rate of the atrophy to be 1.8 mm²/year. Our findings were a mean ER of 2.6 mm²/year. Their graph suggests that our study may have had more patients with larger atrophic areas, which may explain the difference in ER. They report that an exponential model (ER is directly correlated with size of atrophy) best fits the curve up to an area of atrophy of 5 mm², and again for an atrophic area greater than 15 mm², whereas a linear model (ER is constant) best fits atrophic areas between 5 and 15 mm². Our findings suggest (Table 5) that the growth rate is lowest for baseline areas less than 1.3 mm², is at a middle level for baseline areas between 1.3 and 8.3 mm², and levels off at the highest level for baseline areas of more than 8.3 mm². The similarity of the first 2-year ER and the subsequent ER also suggests a constant ER, characteristic of the individual.

There is a high concordance of the ER between eyes in patients with bilateral GA. For future clinical trials that may involve treatment of 1 eye only, such as intraocular reservoirs of growth factors or other interventions, the sample size required to detect or rule out a statistically significant difference in ER is quite small.

Most clinical trials have relied on visual acuity as the primary outcome measure of treatment efficacy. In GA, visual acuity change often is an underestimate of disease progression, because in early GA, the fovea may be spared while scotomas surrounding the fovea enlarge and interfere with reading and other tasks.^{5-8,13} When the fovea is already atrophic, visual acuity may change little over time, but the area of GA may continue to increase. In previous papers, we showed that for patients with visual acuity between 20/80 and 20/200 from GA, their

maximum reading rate was highly correlated with the size of the atrophy when analyzed cross-sectionally,¹⁰ and that longitudinally, the reading rate continued to decline with further enlargement of atrophy.¹¹ Thus, the enlargement of the atrophy is a measure that also captures further visual function impairment. It is straightforward to measure area from fundus photographs, and this can be done reliably and reproducibly. The methods used for measuring atrophy on film-based photographs in the 1990s are easily transferred to the use of digital color fundus images.

Fundus autofluorescence imaging is informative for the understanding of GA. Areas lacking RPE, and therefore lacking lipofuscin, have reduced autofluorescence and are clearly defined in autofluorescence images as dark areas surrounded by the background autofluorescence of the retina.^{18–20} Autofluorescence imaging allows for more automated measurement of GA, but comparison with color fundus photographs or infrared images must be made to eliminate the false-positive reduced autofluorescence seen in some patients in areas of drusen.¹⁸ In addition, the patterns of increased autofluorescence that are seen surrounding the area of GA, reflecting increased accumulation of lipofuscin, may provide insight into the rate and retinal site into which enlargement will occur.²¹ At present, there is not enough prospective data to set eligibility criteria based on autofluorescence characteristics, but autofluorescence imaging is recommended as an adjunct in any new study, so that its role can be assessed.

The rate of enlargement was not statistically significantly different between the bilateral GA group and the fellow eyes CNV group. This suggests that the mechanism of enlargement may be similar in both types of patients. However, patients with CNV in the fellow eye had a significantly higher rate of CNV developing in the GA study eye than did patients with bilateral GA.²² This higher rate of CNV development is a reason to consider not enrolling patients who have CNV in the fellow eye in early clinical trials.

Patients with drusen only and no GA in the fellow eye had smaller areas of atrophy and lower rates of enlargement in general. These patients are likely to experience GA in the eye with drusen and are important to study if the question is whether GA can be prevented in the first place, but they are not the optimal patients for inclusion in a clinical trial designed to evaluate whether progression can be slowed by a given therapy. Again, this would lead to limiting initial clinical trials to patients with bilateral GA.

It is reasonable to assume that an effective treatment for GA also may be effective in earlier stages of AMD. A treatment trial for GA requires a relatively small sample size, compared with trials looking for progression to advanced AMD in eyes with only drusen and pigmentary change. A trial for GA thus can be regarded not only as a test of efficacy for this condition, but as a less expensive and shorter way of discovering treatments for AMD as a whole.

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Figure 1.

Fundus photographs of 3 eyes showing the variation between patients in enlargement rate and the consistency of enlargement rate over time. The areas of atrophy are outlined. **Top**, Low enlargement rate. Left, Baseline atrophic area was 11.2 mm² (4.4 Macular Photocoagulation Study [MPS] disc areas). Center, Appearance at 2.0 years. The enlargement rate was 0.3 mm²/year for the first 2 years. Right, Appearance at 4.0 years. The enlargement rate was 0.5 mm²/year for the second 2 years. **Middle**, Enlargement rate near the mean. Left, Baseline atrophic area was 10.9 mm² (4.3 MPS disc areas). Center, Appearance at 2.3 years. The enlargement rate was 2.8 mm²/year for the first 2 years. Right, Appearance at 4.0 years. The enlargement rate was 3.3 mm²/year for the second 2 years. **Bottom**, High enlargement rate. Left, Baseline atrophic area was 8.9 mm² (3.5 MPS disc areas). Center, Appearance at 2.2 years. The enlargement rate was 6.1 mm²/year for the first 2 years. Right, Appearance at 4.3 years. The enlargement rate was 4.6 mm²/year for the second 2 years.

Figure 2. Scatterplot showing the 2-year enlargement rate as a function of baseline area of atrophy.

Figure 3. Scatterplot showing the subsequent 2-year enlargement rate versus the first 2-year enlargement rate. There is strong correlation between these measures (correlation coefficient, 0.58).

Figure 4.

Scatterplot showing the concordance in enlargement rate between eyes in patients with bilateral geographic atrophy (GA). The correlation coefficient was 0.76. The strong concordance between eyes will allow for a small sample size when conducting future uniocular studies that treat 1 eye and use the fellow eye as a control.

Table 1
Baseline Visual Acuity of Eyes with Geographic Atrophy

Snellen Visual Acuity	No. of Eyes (% of 212 Eyes)
20/25 or better	11 (5)
<20/25 and >20/50	71 (34)
≤20/50 and >20/80	48 (23)
<20/100 and >20/200	37 (17)
≤20/200	45 (21)

Median visual acuity, 20/71 (0.55 logarithm of the minimum angle of resolution [logMAR]); mean, 20/80 (0.60 logMAR).

Table 2

Baseline Total Atrophic Area

Area [mm ² (Macular Photocoagulation Study Disc Areas)]	No. of Eyes (%)
≤1.3 (<0.5)	13 (6)
1.4–7.6 (0.5–3)	89 (42)
7.7–12.7 (3.1–5)	42 (19)
12.8–17.8 (5.1–7)	24 (11)
17.9–22.9 (7.1–9)	16 (8)
23.0–38.1 (9.1–15)	26 (12)
38.2–50.8 (15.1–20)	2 (1)

Median area, 7.9 mm² (3.1 Macular Photocoagulation Study [MPS] disc areas); mean area, 10.9 mm² (4.3 MPS disc areas).

Table 3
Comparison of Mean Visual Acuity and Mean Total Atrophic Area

	Mean Snellen Visual Acuity (Logarithm of the Minimum Angle of Resolution)*	Mean Total Atrophic Area, mm ² (Macular Photocoagulation Study Disc Areas)
All study eyes	20/60 (0.48)	10.4 (4.1)
Bilateral GA, all eyes	20/85 (0.63)	11.8 (4.6)
Bilateral GA, better-seeing eye	20/60 (0.47)	11.7 (4.6)
GA eyes with fellow CNV eye	20/63 (0.50)	10.1 (4.0)
GA eyes with fellow drusen eye	20/65 (0.51)	4.2 (1.6) [†]

CNV = choroidal neovascularization; GA = geographic atrophy; MPS = Macular Photocoagulation Study.

Study eye means 1 eye with GA per patient as described in "Patients and Methods." One MPS disc area = 2.54 mm² on the retina.

* No significant difference among the groups in mean acuity.

[†] The mean area is smaller for the fellow drusen eye group than for either of the other groups.

Table 4

Two-Year Enlargement Rate

Enlargement Rate (mm ² /yr)	No. of Eyes (% of 162 Eyes)
≤0.8	25 (15)
0.9–1.5	32 (20)
1.6–2.3	30 (19)
2.4–3.1	28 (17)
3.2–4.6	27 (17)
4.7–7.6	16 (10)
7.6–10.2	4 (2)

Median, 2.2 mm²/yr; mean, 2.5 mm²/yr.

Table 5

Enlargement Rate as a Function of Atrophic Area

Baseline Area Quartile	Baseline Area (mm ² , MPS Disc Areas)	No. of Eyes	Mean 2-yr Enlargement Rate (mm ² /yr [95% Confidence Interval]) [*]	% Eyes with Enlargement Rate More than Median
1a	<1.3 (<0.5)	9	0.8 [-0.4 to 1.9]	11
1b	1.3–4.0 (0.5–1.58)	31	2.1 [1.5 to 2.7]	45
2	4.0–8.3 (1.59–3.24)	40	2.1 [1.5 to 2.6]	30
3	8.3–14.1 (3.25–5.59)	41	3.0 [2.4 to 3.5]	56
4	>14.1 (>5.6)	40	3.0 [2.4 to 3.5]	75

One Macular Photocoagulation Study (MPS) disc area equals 2.54 mm² on the retina.

The lowest area quartile is divided into (1a) eyes with atrophy less than 0.5 MPS disc areas and (1b) eyes with atrophy of 0.5 MPS disc areas or more, because the lowest group has a significantly lower enlargement rate.

^{*} The mean for the baseline area in quartile 1a is significantly different from the other groups. The means for baseline area in quartiles 1b and 2 are significantly different from those of quartiles 3 and quartile 4. Student's *t* test each pair, *P* = 0.05.

Table 6

Sample Size Calculations

Type of Treatment	Outcome Variable	2-yr Follow-up	1-yr Follow-up
		<i>Total Patients Required</i>	<i>Total Patients Required</i>
Systemic treatment, without prior data	Difference in ER between groups	306 (153 per group) *	378 (189 per group) †
Systemic treatment, knowing prior enlargement rate	Difference in ER (ER minus prior ER) between groups	220 (110 per group) *	Not applicable
Unilateral treatment, using fellow eye as control	Difference in ER between eyes	38	103

ER = enlargement rate.

$\alpha = 0.05$, power = 0.80 for all calculations.

Difference to detect is a 25% reduction ($0.64 \text{ mm}^2/\text{yr}$) in enlargement rate.

Assuming 15% loss to follow-up for 2-year estimates, and 10% loss to follow-up for 1-year estimates.

Sample size is based on distribution for 1 eye per patient.

* For systemic treatment, half the patients would be in treatment group and half in control group.

† The 1-year enlargement rate data included only those patients for whom the first follow-up visit was between 9 and 15 months after baseline.