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Natural History of Geographic Atrophy in Untreated Eyes with Nonexudative Age-Related Macular Degeneration

A Systematic Review and Meta-analysis

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Topic: Systematic review and meta-analysis of the natural history of geographic atrophy (GA).

Clinical Relevance: Several different models have been used to describe the natural history of GA in untreated eyes, and the reported progression rates vary widely across clinical trials.

Methods: We searched in MEDLINE, EMBASE, Cochrane Library, Clinicaltrials.gov, and PubMed for studies that measured GA size in untreated eyes over a follow-up period ranging from the start dates of the databases through June 6, 2017. Data were analyzed using 3 models: (1) the area linear model, in which the lesion area enlarges linearly with time; (2) the radius linear model (RLM), in which the lesion radius expands linearly with time; and (3) the area exponential model, in which the lesion area changes exponentially with time. A horizontal translation factor was added to shift each data set to correct for the differences in participant entry time into the studies. The model that best fit data was determined by performing residual analyses, determining the dependence of growth rate on time, and the predicted age of GA onset. The risk of bias was assessed using the Newcastle-Ottawa scale.

Results: We included 25 studies with data from 2942 eyes. The RLM yielded the best goodness of fit and predictive performance of GA progression. Cumulative data for untreated eyes fit a straight line in the RLM ($r^2 = 0.986$) with a randomly dispersed residual plot. The GA radius enlarged at a constant rate of 0.163 mm/year (95% confidence interval, 0.158−0.167 mm/year), which was independent of time ($r = -0.108$). The RLM predicted the mean age of onset of GA as 67.4±5.2 years. Our analysis also suggested that the GA progression rate may be associated with the age of onset.

Conclusions: In this meta-analysis, the progression pattern of GA was uniform across a wide range of studies, and best fit the RLM. Our analysis may shed light on the natural history of GA and may influence the design of future clinical trials. *Ophthalmology Retina 2018;■:1−8 © 2018 by the American Academy of Ophthalmology*

Supplemental material available at www.ophthalmologyretina.org.

Age-related macular degeneration (AMD) is the primary cause of blindness in developed countries and the third leading cause worldwide.[1] Geographic atrophy (GA), the end stage of nonexudative AMD, is characterized by loss of the retinal pigment epithelium (RPE), overlying retina, and underlying choriocapillaris.[2] It is reported that GA affects roughly 6 million people worldwide, and approximately 42% of the patients with GA are legally blind.[3,4] The underlying mechanism of GA progression remains unknown,[5] and treatment options are limited.

In clinical trials, the change in GA area is the primary outcome measure used to evaluate the efficacy of treatments.[6] However, estimates of the GA progression rates in untreated eyes vary widely across clinical trials, ranging from 0.53 to 2.8 mm^2 (0.21−1.10 disc areas) per year, corresponding to 0.053 to 0.264 mm/year in radius assuming circular lesions with baseline sizes of 3 disc areas.[6−8] In addition, there are disagreements over the GA growth pattern as a function of elapsed time, and 3 models have been proposed previously (Table 1, available at www.ophthalmologyretina.org). The first model assumes a linear relationship between GA area and time. In this model, the expansion rate of GA area is always constant as GA enlarges, and thus is independent of baseline lesion size. This hypothesis is supported by Batıoğlu et al[7] and Holz et al,[9] who reported that GA area progression rates are not significantly different among groups with baseline GA of 1 to 3 disc areas, 3 to 5 disc areas, and 5 to 10 disc areas. The second model states that the radius of the GA lesion grows linearly with time. This idea is supported by Yehoshua et al,[10] who reported that the enlargement rate of the effective GA radius is independent of the

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baseline lesion size. The third model is an exponential mixed-effects model proposed by Dreyhaupt et al[11] in which GA area grows exponentially as a function of elapsed time. In this study, compared with a linear mixed-effects model, the exponential model was found to be more in agreement with the model assumption of normality of residuals, but resulted in worse prediction of GA sizes.[11] Finally, it is unclear how patient age affects GA progression rate. Caire et al[12] and others have reported statistically significant associations between the age and the progression rate of GA area,[13] whereas Jeong et al[14] and others have reported no significant associations.[15,16] Meanwhile, there has been limited information regarding the impact of the age of onset on the GA progression rate.

To address the inconsistency in clinical data, we performed a meta-analysis of the GA progression rates and patterns using previously published studies. The main intent of this study was to determine the GA progression pattern in untreated eyes with nonexudative AMD. By using the determined progression model for GA, we then inferred the age of onset of GA and assessed the impacts of the age and age of onset on the GA progression rate.

Methods

This meta-analysis is reported in accordance with the Meta-analysis of Observational Studies in Epidemiology checklist (Table 2, available at www.ophthalmologyretina.org).[17]

Sources and Search Methods

On June 6, 2017, a senior medical librarian (H.G.H.) performed a comprehensive search of multiple databases—MEDLINE, EMBASE, Cochrane Library (Wiley), Clinicaltrials.gov, and the National Library of Medicine's PubMed—from the start dates of the databases. The search strategy is outlined in Appendix 1 (available at www.ophthalmologyretina.org). A flowchart according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses is presented in Figure 1 (available at www.ophthalmologyretina.org).

Selection Criteria

The inclusion criteria were the following: (1) a group of patients diagnosed with GA secondary to nonexudative AMD in at least 1 eye without any treatment; (2) use of at least 1 imaging method to assess GA area photographically; and (3) reported GA area on at least 2 occasions a minimum of 6 months apart. The articles with the largest and most recent data set were selected in the case of multiple publications derived from an overlapping study population.

Data Collection

For each study, 2 reviewers (L.S. and F.L.) independently collected and calculated the data regarding study quality; demographic characteristics of the study population; the mean, standard deviation, and 95% confidence interval of GA area and radius at all follow-up times; and GA area and radius growth rate in eyes with untreated GA. Extrapolation of GA sizes was necessary for some studies, as detailed in Table 3 (available at www.ophthalmologyretina.org). Disparities between the reviewers were resolved through discussion and subsequent consensus.

Study Quality and Risk for Bias Assessment

The risk of bias and quality of each study were assessed by 2 independent reviewers (L.S. and F.L.) using the Newcastle-Ottawa scale.[18] Inconsistencies were discussed until agreement was reached. Publication bias analyses were performed in Comprehensive Meta-Analysis Software (Biostat, Inc, Englewood, NJ)[19] using funnel plots, the Egger test, and the Begg test.

Data Synthesis and Statistical Analysis

The statistical analysis was performed in MATLAB software (The MathWorks, Inc, Natick, MA). To determine the GA growth pattern, we compared 3 GA progression models proposed in the literature: (1) the area linear model (ALM), in which the lesion area changes linearly with time; (2) the radius linear model (RLM), in which the lesion radius (which is equivalent to the square root transformation of the lesion area) grows linearly with time; and (3) the area exponential model (AEM), in which the lesion area expands exponentially with time, meaning the natural logarithm−transformed area, that is, *ln*(area), grows linearly with time. For the ALM and RLM, the GA area was defined as 0 mm^2 at the onset. Because an exponential model would not reach 0, we defined the GA area as 0.05 mm^2 (which was the predefined minimum GA size in several previous studies[5,20]) at the onset for the AEM. For each model, we first plotted the reported average GA sizes (area, radius, or *ln*[area]) from all included studies as a function of time after enrollment. To correct for the differences in participants' entry time into the clinical studies, we added a horizontal translation factor (in years) to each individual data set, which essentially converted the horizontal axis from "time after enrollment" to "duration of GA," where duration of GA = time after enrollment + translation factor. Time 0 on the duration of GA axis represented the time of GA onset. To find the optimal translation factors, we first estimated a wide range for the translation factor for each study. Then we adjusted one translation factor by 1 month at a time and repeated this process iteratively until the r^2 value was maximized for the cumulative trend line of all data sets from the included studies.[21–23] The translation factor for each study was calculated separately for the ALM, RLM, and AEM.

To assess the goodness of fit, we analyzed residual plots of the translated data and determined the appropriateness of linear regression in the ALM, RLM, and AEM. Data in each residual plot were generated by subtracting the estimated values in the cumulative trend lines of the translated data from the observed values. We then averaged the residuals in 1-year intervals and assessed the randomness by performing the Ljung−Box test,[24] where the null hypothesis was the residuals were dispersed randomly and were not dependent on time. Next, we assessed the curvature of the translated data sets in each model by analyzing the derivatives in each model. To calculate the derivatives, we averaged GA sizes in 1-year intervals and then derived the slopes between 2 adjacent averaged values. Additionally, to assess the predictive performance, we calculated each model's predicted age of onset by subtracting the optimized translation factor from the reported average age in each study.

Heterogeneity among the studies was assessed through the I^2 statistic using the mean and standard deviation of GA radius growth rate in each study.[25] To evaluate the robustness of the pooled analysis, we performed a sensitivity analysis by removing 1 study at a time and repeated the cumulative trend line for the ALM, RLM, and AEM. We analyzed the impacts of the differences in the sample size and imaging method among the included studies on the GA radius growth rate. To evaluate the impact of the sample size, we compared the GA radius growth rate and predicted age of GA onset between studies with less than 100 eyes and studies with more than 100 eyes using an