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Characterizing Disease Burden and Progression of Geographic Atrophy Secondary to Age-Related Macular Degeneration

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Purpose: To understand levels of disease burden and progression in a real-world setting among patients from the United Kingdom with bilateral geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

Design: Retrospective cohort analysis of a multicenter electronic medical record (EMR) database.

Participants: Patients who were aged ≥50 years with bilateral GA and no history of choroidal neovascularization (CNV) and who attended 1 of 10 clinical sites using the EMR.

Methods: A deidentified data set was constructed from the records held at the 10 sites. An algorithm was used to extract cases with a GA diagnosis, of which 1901 had bilateral GA and form the basis of this report. A sample of records randomly selected from each center was used to validate disease definitions.

Main Outcome Measures: Progression to blindness (visual acuity [VA] <20 letters or Snellen 3/60 in the better-seeing eye), driving ineligibility (VA ≤70 letters or Snellen 6/12 in the better-seeing eye), progression to CNV, loss of 10 or more letters, and mean change in VA over time.

Results: At first record of GA, 7.1% had a VA in the better-seeing eye equal to or lower than the cutoff for blindness registration and 71.1% had a VA that would have rendered them ineligible to drive. Over time, 16% became legally blind (median time to outcome, 6.2 years) and 66.7% became ineligible to drive (median time to outcome, 1.6 years). In the worse-seeing eye, 40.1% lost ≥10 letters in 2.4 years. Among patients with baseline and 24-month VA measurements, mean VA decline was 6.1 letters in the worse-seeing eye (n = 413) and 12.4 letters in the better-seeing eye (n = 414). The rate of progression to CNV in either eye was 7.4% per patient-year.

Conclusions: At initial diagnosis, based on VA in the better-seeing eye, a high proportion of patients with bilateral GA were ineligible to drive and approximately 7% were eligible for UK blindness registration. The subsequent reduction in VA that occurred in the better-seeing eye would render a further two-thirds ineligible to drive. These findings emphasize the severity of the visual disability associated with GA secondary to AMD. *Ophthalmology 2017;■:1–8 © 2017 by the American Academy of Ophthalmology. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).*

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Geographic atrophy (GA) is an advanced form of age-related macular degeneration (AMD), characterized by progressive and irreversible loss of the retinal pigment epithelium, photoreceptors, and underlying choriocapillaris.[1,2] Geographic atrophy has been estimated to afflict some 5 million people worldwide and has similar prevalence rates to neovascular AMD, both in the United States and globally.[3–5] It was previously estimated that GA accounted for one-tenth of the blindness due to AMD and neovascular AMD for the remainder.[6] However, the global incidence of blindness due to neovascular AMD has been significantly reduced over the last decade with the introduction of anti–vascular endothelial growth factor therapy.[7–10] Recent studies have reported that GA accounts for approximately one-quarter of legal blindness in the United Kingdom and the United States.[1,2]

It has also been reported that even when distance visual acuity (VA) is marginally reduced or indeed unaffected, patients with GA experience difficulty with reading and seeing in low-light conditions, problems that may not be reflected in VA measurements.[11] Currently, there are no approved treatments to prevent GA or limit its progression

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when already present, nor are there treatments that can reverse pathology. Geographic atrophy is usually bilateral, and with its major impact on vision-related quality of life, this lack of a treatment for GA represents an important unmet need.[2,11,12]

Both GA and neovascularization are manifestations of the advanced stages of AMD. Epidemiologic studies, while estimating prevalence and incidence of these 2 phenotypes, have mainly classified eyes with both manifestations under the category of neovascular. Also, for the purposes of analyzing risk factors at a person level, most studies classify persons with neovascular AMD in 1 eye under this label. Thus, the historical classification regimens are likely to have underestimated the prevalence and incidence of GA. Additionally, relationships between GA and choroidal neovascularization (CNV) remain largely unexplored.

Data on the development and progression of GA have been well characterized in prospective, longitudinal studies.[13–18] However, natural history data on visual function decline and the temporal changes of clinically relevant functional end points remain limited,[19] and existing evidence has been mainly derived from small clinic-based GA cohorts or from the few GA cases that were found within large epidemiologic studies.[20,21] Particularly important are the outstanding questions on the interrelationship between GA and neovascular AMD,[22] and the functional impact of GA when it is the sole manifestation, as well as when occurring concomitantly with neovascular AMD.

This study aimed to address and bridge current knowledge gaps on the progression of GA to CNV and the impact of the former on VA change using a large patient cohort assimilated within a common electronic medical record (EMR) platform used by multiple centers in the United Kingdom. The primary objective was to better understand the natural history of patients with bilateral GA using large, longitudinal, real-world data. Specifically, we evaluated baseline characteristics and progression to precise or unambiguous clinical outcomes. The secondary objective was to explore risk factors associated with disease progression. A validation exercise was also conducted across all sites to ensure that the algorithm to identify disease and assess progression was valid.

Methods

Study Design

This was a retrospective cohort study using anonymized data collected using the Medisoft EMR software system.[23] All patient data were fully compliant with UK National Health Service (NHS) rules governing the use of patient-level health care data (as defined in the Data Protection Act of 1998) and had approval of the individual NHS center's Caldicott Guardian. Ten NHS clinical sites (Table S1, available at www.aaojournal.org) contributed data that had been accumulated between October 2000 (date of first EMR record at earliest site) and February 16, 2016 (date of data extraction from all sites), although the exact time frame was variable for each center and patient, depending on when the EMR system was introduced. The centers were selected as they fulfilled the following criteria: EMR system adoption and utilization by center physicians and staff for routine clinical management; willingness to provide EMR data and undertake the necessary governance procedures to allow extraction of the data; sufficient duration of use of the EMR and adequate size of early/intermediate AMD and GA populations under clinical management; geographic spread of centers; year from which there was continuous data recording; and consistency of VA data entry by the center.

A project oversight committee comprising key members with clinical expertise (4 retina specialists from the contributing sites), statistical and data expertise (QuintilesIMS), and the funder (Roche, Basel, Switzerland), whose representatives had epidemiology, study design, and interpretation expertise, ensured the scientific integrity of this study.

Study Population

After confirmation from each of the selected sites that permission from the local NHS data guardian was granted to provide data for the construction of the amalgamated data set, the software provider (Medisoft Limited, Leeds, United Kingdom) created data files for transfer to the biostatistics support unit (QuintilesIMS). These files consisted of patient data in which the diagnoses or clinical findings suggested early/intermediate AMD or GA. The data were stripped of all patient identifiers and pseudoanonymized before transfer to the biostatistics support unit. Research ethics committee review and approval were not required. An algorithm was used to identify the study population and consisted of patients meeting prespecified inclusion criteria.

Inclusion and Exclusion Criteria

For inclusion, patients had to have at least 1 eye meeting the GA case definition (Table S2, available at www.aaojournal.org) and no evidence of CNV in that eye before the first GA record during the study period. The earliest record indicating the diagnosis of GA was taken as the index date for the patient.

Main exclusion criteria were age <50 years at index date; study eye with <30 days' follow-up (defined as the absence of any record of visits, measures, or procedures); missing age or sex information; no information for the fellow eye in the EMR system, or fellow eye not classifiable (i.e., not meeting the early/intermediate AMD, GA or CNV case definition, and VA missing within ±90 days of index date).

For all patients, a study eye and a fellow eye were designated. If both eyes met the inclusion criterion on the same day, then the eye with the worse VA was designated as the study eye. If both eyes had the same VA, then the right eye was designated as the study eye. For outcomes of functional measures (blindness eligibility and driving ineligibility), the eye with better VA was used. For all other outcomes, the study eye was used. The study time period for all patients was from the index date to the end of follow-up, defined as the date of the last available record for that eye in the EMR.

The patients were divided into 3 subgroups depending on the conditions of both eyes at the index date: GA:GA (both study and fellow eye with GA); GA:CNV (study eye with GA, fellow eye with CNV); and GA:early/intermediate AMD (study eye with GA and fellow eye with early/intermediate AMD). The aim of this analysis was to characterize the subgroup of patients with GA in both eyes (i.e., GA:GA).

Outcome Measures

Primary and secondary outcome measures are shown in Table 1. Most outcomes were derived from measures of routinely collected VA, which was primarily captured in the clinical sites as Early Treatment Diabetic Retinopathy Study (ETDRS) letters in the majority of patients. In a minority of patients, Snellen VA may have been recorded and converted to logarithm of the