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Prevalence and Incidence of Wegener's Granulomatosis in the UK General Practice Research Database

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Objective. **Wegener's granulomatosis (WG) is a systemic vasculitis of unknown etiology. The UK General Practice Research Database (GPRD) contains the complete primary care records of ~3.6 million people. There are no data on the incidence and prevalence of WG from primary care. The aim of the study was to estimate the incidence and prevalence of WG in the GPRD population.**

Methods. **We identified all patients who had a first diagnosis of WG during 1990–2005, using Oxford Information System and Read codes. The diagnosis was verified by review of a randomly selected sample of 35 records that had identifying data removed. The annual incidence was calculated as the number of incident cases divided by the total person-years.**

Results. **A total of 295 patients (51.2% male) with a first diagnosis of WG were identified during 1990–2005. The median age was 59 years (interquartile range 47–70 years). The overall annual incidence of WG was 8.4 per million (95% confidence interval [95% CI] 7.5–9.4). The annual rate in women and men was 8.1 per million (95% CI 6.8–9.6), and 8.8 per million (95% CI 7.4–10.3), respectively. The incidence was stable throughout the study period. There was an increase in the annual prevalence from 28.8 per million in 1990 to 64.8 per million in 2005. The diagnosis was verified in 28 of 31 available case records.**

Conclusion. **This is the first study of the incidence and prevalence of WG in a database from a primary care population. The results are similar to previous studies from secondary and tertiary care and suggest that these studies are representative of the general population. The increasing prevalence with a constant incidence suggests that survival is improving with modern treatment protocols.**

INTRODUCTION

Wegener's granulomatosis (WG) is a chronic disease of unknown etiology causing inflammation and necrosis of blood vessels. It is typically associated with the presence of antineutrophil cytoplasmic antibodies (ANCAs) in the serum. WG is a chronic relapsing–remitting disease, which may have long periods of remission.

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The incidence and prevalence of WG is difficult to estimate in primary care populations because of its rarity. In a secondary care population from Norfolk, UK, the annual incidence was estimated to be 9.7 per million (1). To date, incidence and prevalence figures have been estimated from secondary care–based populations with no data being from a primary care population. Studies from secondary/tertiary care centers have the advantage of diagnostic accuracy, but are often limited by incomplete case ascertainment due to referral bias, with only the most severe cases being included, and milder cases or cases in remission being omitted. There has been debate as to whether the incidence of WG is stable or not. Early studies from the UK suggested an increase but this might have been artifactual following the introduction of ANCA testing (2). Our own data together with data from Germany suggest that there has not been an increase (3), but a significant increase has been reported in Scandinavia where the incidence doubled during the 1990s (4–6).

The UK General Practice Research Database (GPRD) provides complete electronic data (with identifying data removed) collected from routine general practice case records. It contains details of primary medical care, pre-

scribing, and prevention. At present ~3.6 million patients from 433 general practices are included. The geographic distribution of the GPRD population is similar to that of the general UK population and comparison of the age and sex distribution has shown that it is similar to that recorded in the UK National Census (7,8). The data are collected routinely and the quality is monitored on a regular basis. The population of practices participating changes with time, as practices join and leave the database. Patient records are included from when either the patient registers with a participating practice or the practice joins the database. Similarly, data collection stops when the patient leaves the practice by transferring to a different practice, the patient dies, or the practice leaves the database. The GPRD has been successfully used to investigate the incidence of other chronic relapsing–remitting conditions, such as systemic lupus erythematosus (SLE) and giant cell arteritis (9–11). The recording of the diagnosis leading to hospital attendance varies from 73% for venous thromboembolic disease to 93% for inflammatory bowel disease, suggesting that recording is better for chronic diseases (12,13). The aim of this study was to investigate the annual incidence and period prevalence of WG in the UK general population using the GPRD between 1990–2005.

PATIENTS AND METHODS

The study population comprised all adults and children who were seen in a general practice that had contributed research quality data for ≥3 years to the GPRD during the study period. These practices are considered by the GPRD to be "up to standard."

The study period was from January 1, 1990 to December 31, 2005. GPRD records for patients with a diagnosis of WG were identified using the Oxford Information System (OXMIS) and Read codes for Wegener's granulomatosis or Wegener syndrome (OXMIS 4462W, 4462WG and Read G754.00) (8). Cases were defined as those with a first diagnosis of WG entered into the general practice record during the period 1990–2005. Entry date was considered as the date at which a first diagnosis of WG was given. To investigate whether we might be identifying quiescent cases newly presenting with a flare, we identified cases for which there was a 6- or 12-month interval between the date the patient was first registered with a practice and the date at which the diagnosis of WG was first made.

The diagnosis of WG was verified by reviewing case records that had the identifying data removed. A random sample of records comprising 10% of the identified cases was requested from the GPRD. We could only obtain from the GPRD copies of letters between primary and secondary care providers and we were prohibited by data protection laws from accessing the original secondary care records. The records did not contain the patient name, age, sex, or the location of the hospital.

Data were extracted from the records, and the patients were classified using the recently-described European consensus classification algorithm for the classification of vasculitis (14). This method uses an algorithm to classify vasculitis and uses the American College of Rheumatology (ACR) criteria (15) and the Chapel Hill Consensus Conference (CHCC) definitions (16). Where this was not possible because of inadequate data, a diagnosis of WG was considered if there was evidence of consistent clinical features, positivity for ANCA, or therapy with cyclophosphamide. We used the same surrogate markers for WG as described for use with the consensus algorithm (14). Surrogate markers for WG (granulomatous disease) refer to symptoms suggestive of granulomatous disease affecting the upper and lower respiratory tract (in all cases other causes must be excluded). Symptoms in the lower airways are radiologic evidence of fixed pulmonary infiltrates, nodules, or cavitations present for more than 1 month, or bronchial stenosis; and symptoms in the upper airways are bloody nasal discharge and crusting for more than 1 month, nasal ulceration, chronic sinusitis, otitis media, mastoiditis, retro-orbital mass or inflammation (pseudotumour), subglottic stenosis, or saddlenose deformity/destructive sinonasal disease. Only 1 surrogate marker is needed to support a diagnosis of WG. In each case there was no other obvious diagnosis such as infection or malignancy. We did not accept evidence of ANCA positivity and cyclophosphamide therapy alone as sufficient evidence for a diagnosis of WG because both occur in other types of vasculitis. The records were reviewed by an expert in the classification of patients with vasculitis (RAW).

Details of the denominator population were provided by the GPRD by age and sex for each year of the study (8). The population included in the GPRD increased from 1,213,000 in 1990 to 3,300,700 in 2005.

The annual incidence of WG was calculated as the number of incident cases divided by the total person-time. The prevalence was calculated as the number of prevalent cases divided by the number of people registered with the database in each calendar year. The 95% confidence intervals (95% CIs) were calculated using the Poisson distribution.

The study received ethical approval from the Independent Scientific Advisory Committee of the GPRD under the terms of general approval for observational studies from the UK Multicentre Research Ethics Committee.

RESULTS

A total of 319 patients (164 [51.4%] men) with a first diagnosis of WG were identified during 1990 and 2005. Twenty-four patients were identified at practices that were not "up to standard," therefore 295 cases (151 [51.2%] men) were included in the study.

The median age of the 295 patients was 59 years (interquartile range [IQR] 47–70 years). The median age for women was 61 years (IQR 47–71 years) and for men 58 years (IQR 48–68 years) ($P = 0.4$). The overall annual incidence of WG was 8.4 per million (95% CI 7.5–9.4). The annual incidence among women was 8.1 per million (95% CI 6.8–9.6) and in men 8.8 per million (95% CI 7.4–10.3). The incidence of WG was stable throughout the study period (Figure 1). The age-specific incidence peaked in patients ages 65–74 years (Figure 2). Twenty-four cases in

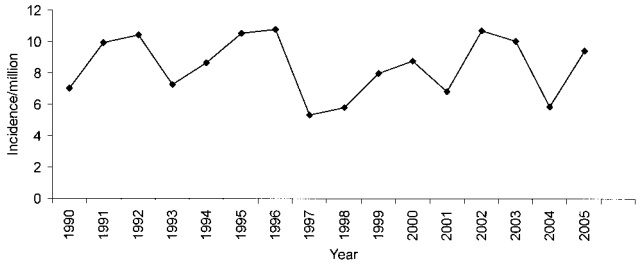

Figure 1. Incidence of Wegener's granulomatosis in the UK General Practice Research Database.

the practices were not up to standard; if these cases were included, the overall incidence became 9.1 per million (95% CI 8.2–10.2), which is not significantly different from the figure obtained using only the up to standard practices.

We investigated whether we might be identifying quiescent cases that were newly presenting with a flare, by looking for cases for which there was a 6- or 12-month interval between the date the patient was first registered with a practice and the date at which the diagnosis of WG was first made. If there was a 6-month interval, the number of cases declined to 248 giving an annual incidence of 7.1 per million (95% CI 6.2–8.0); if a 12-month interval was used the number of cases was 232 giving an annual incidence of 6.6 per million (95% CI 5.8–7.5).

The annual prevalence of WG for the years 1990–2005 is shown in Figure 3. There was an increase in the 1-year period prevalence from 28.8 per million (95% CI 20.1–40.1) in 1990 to 64.8 per million (95% CI 56.4–74.1) in 2005.

Photocopies of the case records from 31 (88.6%) of the 35 sets requested were available for review. We were able to confirm a diagnosis of WG in 28 (90%) of 31 cases. The provided clinical information was of insufficient detail in 20 cases to formally apply the classification algorithm, or the ACR criteria and CHCC definitions. Eleven cases fulfilled the ACR criteria for WG (15). In an additional 17 cases, there was sufficient evidence provided that the patient had WG (consistent clinical features, ANCA positivity, or therapy with cyclophosphamide). After review, it was discovered that 1 patient had microscopic polyangiitis and not WG. There was insufficient detail provided in the remaining 2 sets of notes to confirm a diagnosis of WG, although it was likely that the patients had some form of vasculitis.

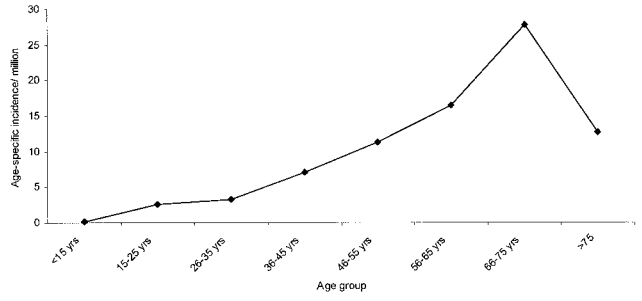

Figure 2. Age-specific incidence of Wegener's granulomatosis in the UK General Practice Research Database.

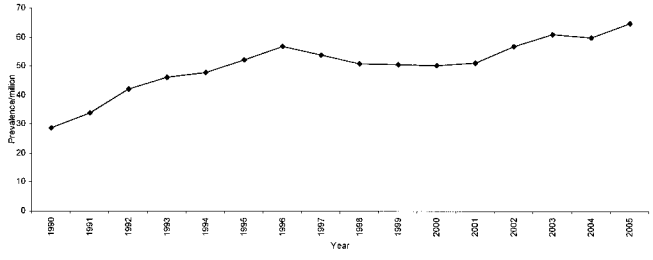

Figure 3. Prevalence of Wegener's granulomatosis in the UK General Practice Research Database.

DISCUSSION

This is the first study of the incidence and prevalence of WG in a primary care population. Other population based studies have been hospital based and did not use primary care records. The incidence figures in this study are consistent with previous studies from the UK. In particular, the data are consistent with data from our local population in Norfolk where the annual incidence of WG is 9.7 per million (1), suggesting that this population is representative of the rest of the UK. The estimated incidence and prevalence figures are also within the range reported from European centers, and do not show an increased incidence, which is similar to our local UK data and the German data (3). In contrast, however, the Scandinavian studies reported an increase during the 1990s. In Finland, the annual incidence between 1996 and 2000 was 9.3 per million, compared with 1.9 per million during 1981 and 1985 (6). Knight et al in Sweden also observed an increase in incidence between 1975–2001 from 3.3 per million in 1975–1985 to 11.9 per million in 1991–2000 (5). Whether this was due to better case ascertainment following the introduction of ANCA testing is uncertain.

The age-specific incidence peaked at 65–74 years, which is similar to other studies (1,6). We feel that the variations seen in the annual incidence from year to year (Figure 1) are due to random fluctuations because the number of cases recorded in each year was small (<20 per year). One possible explanation is the failure of case recognition in the elderly, because elderly patients may not be as intensively investigated as younger patients.

The prevalence figures (28.8–64.8 per million) are consistent with most other European studies. In Germany during 1994, the prevalence of WG in the north and south of the country was reported to be 58 per million and 42 per million, respectively (3). A retrospective study from Norway in 1996 reported a WG prevalence of 53 per million (17). The highest reported prevalence figures to date come from Sweden where the prevalence of WG at the end of 2002 was 160 per million (18). This Swedish study attributed the high prevalence to careful case ascertainment, extensive ANCA testing, and good survival. In our study the prevalence increased during 1990–2005, which may be due to better care with reduced mortality and earlier diagnosis following the introduction of ANCA testing during the 1990s. A similar increase has been observed in studies of the prevalence SLE in the GPRD population (11). This increase is most likely due to the increased likeli-

hood of detecting or confirming cases of chronic relapsing–remitting diseases with increasing time contributed to the GPRD (12).

There are several potential weaknesses of our study. One of which is that we were dependent on the diagnosis given in the case records. We verified the recorded diagnosis by obtaining case records with the identifying characteristics removed for 35 randomly selected patients from general practices via the GPRD. These cases recorded the correspondence between primary and secondary care. We were not permitted to access the original secondary care records. The records confirmed the diagnosis in 28 (90%) of the 31 cases suggesting that overall the recorded diagnosis was accurate, which is in keeping with other studies of chronic diseases in the GPRD. We had hoped to be able to apply the classification algorithm, but the data quality in the copied records was inadequate for this to occur. Typically, the poor data quality was due to a lack of ANCA test data. We accepted evidence of treatment with cyclophosphamide as a surrogate for the diagnosis of WG, but only in the presence of consistent clinical features and surrogate markers of WG. We accepted that some cases of limited WG may not be treated with cyclophosphamide.

A further weakness was that cases may not be recorded, however, WG is a rare disease and unlikely to diagnosed or managed solely in primary care. Therefore, in most cases the recorded diagnosis reflected a secondary care diagnosis. Patients presenting with very severe disease and those who died in the first few days might be missed. In the UK, there would in this event still be written correspondence recording the fact that we would have identified. In the event of rapid progression to end-stage renal disease, the cause of the renal failure is documented. We might however miss cases in which the diagnosis of WG was never made. Studies in other chronic conditions such as inflammatory bowel disease have shown that hospital contact is recorded in the GPRD at a high frequency for major medical events (12).

We investigated whether we might have inadvertently identified previously diagnosed but quiescent cases as new cases, by identifying cases for which there was a 6- or 12-month interval between the date the patient first registered with a practice and the date a diagnosis of WG was first made. Failure to exclude prevalent cases from the calculation of incidence rates will have the effect of overestimating disease incidence (12). This misclassification is most likely to occur in data immediately following patient registration with a general practitioner. Participating practices are instructed by the GPRD to enter past diagnoses retrospectively; the data may be entered at the first visit to the practice. Also recrudescence of quiescent disease may precipitate a patient into visiting a new practice or doctor. The observed incidence was lower with both a 6- and 12-month interval. The mortality of WG despite modern immunosuppressive therapy is still high, up to 22.5% at 6 months in France (19), and 14.5% in the UK, between 1998 and 2000 (20). A patient who presents with new onset WG to a new general practitioner will be excluded from the incidence figures if we insist on a 6- or 12-month interval between registration with a practice and diagnosis. For a condition such as WG where there is a high mortality in the first year, we believe that the most accurate figures are those obtained at registration. Therefore, we believe that our estimated incidence and prevalence figures accurately reflect the occurrence of WG in the UK general population.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Watts had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Watts, Al-Taiar, Scott, MacGregor.

Acquisition of data. Watts, Al-Taiar, Scott, MacGregor.

Analysis and interpretation of data. Watts, Al-Taiar, Scott, MacGregor.

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