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The changing use of disease-modifying anti-rheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database

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***Objectives*. To describe the use of disease-modifying anti-rheumatic drugs (DMARDs) in the treatment of rheumatoid arthritis (RA) and changing trends in their use.**

***Methods*. We used the General Practice Research Database (GPRD) to describe DMARD use by patients with RA identified using ICD-9 codes. The GPRD is a UK national database containing records of more than 7 million individuals from 683 general practices. Subjects were studied between 1987 and 2002. The prevalence and duration of individual DMARD use and changing trends in DMARD use were investigated.**

***Results*. Thirty-four thousand three hundred and sixty-four patients with RA were identified. Only 17 115 (50%) individuals were prescribed at least one DMARD during the study period. The most commonly prescribed DMARD over the study period was sulphasalazine (46.3%) and then methotrexate (31.4%). Use of methotrexate has increased 17-fold (1.8% of all DMARD prescriptions in 1988 to 30% in 2002) whereas use of gold has fallen (13.2% to 2.3%). Analysis of DMARD persistence using Kaplan–Meier survival curves showed the methotrexate use persisted significantly longer than other DMARDs with an estimated median of 8.1 yr. Prednisolone was used in up to 50% of RA patients in any one year and has remained fairly constant throughout the study period.**

***Conclusions*. Large numbers of individuals with a clinical diagnosis of RA identified from a large primary care database are not receiving DMARDs. This work suggests that many individuals with RA have not been treated appropriately and this may have major long-term consequences on joint damage and general health.**

KEY WORDS: Rheumatoid arthritis, DMARDs, General Practice Research Database.

Rheumatoid arthritis (RA) is associated with substantial long-term morbidity, mortality and healthcare costs [1]. Disease-modifying anti-rheumatic drugs (DMARDs) control disease activity, reduce joint erosions and improve quality of life in individuals with rheumatoid RA. DMARDs may also decrease other morbidity associated with RA such as ischaemic heart disease [2]. In recent years there been a change towards early and more aggressive treatment of RA. DMARDs are now used earlier, in higher doses and often in combination to control disease activity in its early stages [3]. Failure to achieve control with DMARD therapy is then followed by biological agents such as tumour necrosis factor (TNF) inhibitors. Methotrexate has become a commonly used DMARD either as monotherapy or in combination with other DMARDs. This appears to be due to its disease-modifying qualities and tolerability, which result in a long duration of therapy [4–11]. However, despite the proven efficacy of DMARDs, it appears that large numbers of RA patients receive DMARD therapy late and in some cases not at all [12]. Most existing data on DMARD use come from secondary care alone and are susceptible to referral bias.

We have investigated the use of DMARDs in the treatment of RA in the United Kingdom (UK) to assess current practice and, to explore whether recommended changes in RA management are taking place. The UK General Practice Research Database (GPRD) contains the primary care records of 7 million individuals [13–19]. The database provides a powerful resource to examine the history of DMARD prescribing for a large number of RA patients. Although the GPRD is based in primary care, the database contains information on clinical events, hospital referrals, hospital admissions and major outcomes. We sought to identify RA patients from the GPRD and interrogate their DMARD use to determine the proportion receiving DMARD therapy, the most common individual and combination DMARDs, DMARD persistence using survival curves and changing trends in DMARD use.

Patients and methods

Study population

General practitioners (GPs) in the UK play a key role in the delivery of health care by providing primary care and referral to specialist hospital services. Patients are registered with one

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practice that stores medical information from primary care and hospital attendances. The GPRD comprises the entire computerized medical records of a sample of patients attending GPs in the UK, covering a population of more than 7 million men and women from 683 contributing practices. The GPRD records demographic information, prescription data, clinical events, specialist referrals, hospital admissions and their major outcomes [13–19]. Data are stored using OXMIS and Read codes for diseases that are cross-referenced to the International Classification of Diseases (ICD-9). All entries are internally validated by cross-checking within the practice and by comparisons with external statistics [13–19]. Only practices that pass this quality control are used as part of the GPRD database. Independent validation studies have confirmed a high level of completeness and validity of the diagnostic and prescribing data in the GPRD [20]. Deleting or encoding personal and clinic identifiers ensures the confidentiality of information in the GPRD. The GPRD is owned by the UK Department of Health and managed by the UK Medicines Control Agency.

Defining cases

Using the GPRD we identified all patients with a diagnosis of RA (ICD-9 code 714.0) entered onto the database between June 1987 and April 2002 from the 3.5 million individuals on the database at this time. Subjects were included if RA was diagnosed at any stage during this period. Incident cases of RA were defined as individuals whose first recorded GP visit for RA was at least 24 months after their inclusion into the database.

Defining DMARD use

DMARD use was defined as at least one DMARD prescription for an individual with RA during the study period. DMARD therapy was taken to be continuous if the gap between prescriptions was less than 14 weeks. The length of individual DMARD use was defined as the time between the first and last prescription of that drug within the previously defined continuous period plus 15 days based on the average prescription lasting 30 days and allowing for patients not to complete the course. These data were used to plot Kaplan–Meier survival curves for DMARD use. A prescription of more than one DMARD simultaneously was defined as combination therapy.

Statistical methods

The prevalence of RA was estimated mid-year in 1998 by dividing the total number of patients with a diagnosis of RA by the total number of subjects in the GPRD at that time. The incidence of RA was calculated by dividing the number of new diagnoses of RA in 1998 by the total person years follow-up in 1998. The characteristics of DMARD users *vs* non-users were compared using the unpaired *t*-test. The duration of DMARD usage was compared using the log rank test. All analyses were performed using Stata version 8.2 (Stat Corporation, College Station, TX, USA).

Results

Numbers of RA patients

A total of 34 364 patients with an ICD-9 code for RA were identified. The median follow-up period was 7 yr 153 days. The prevalence of RA was 0.50% (500/100,000) with an incidence of 0.22% (220/100,000). The mean age of individuals with RA was 58.4 yr and 71.4% were female.

DMARD use

Seventeen thousand one hundred and fifteen (50%) individuals were prescribed at least one DMARD during the study period. A further 17 249 (50%) individuals were not prescribed a DMARD during the study period, although 4942 (28.7% of 17,249) did receive one or more courses of oral prednisolone. Those not receiving DMARDs were older [59.2 (17.2) *vs* 57.6 (14.0) yr; $P = 0.05$] but there were no gender differences. The most commonly prescribed DMARD over the whole study period was sulphasalazine (used by 46.3% of individuals prescribed a DMARD) and then methotrexate (31.4%). In 1996, 51.6% of patients were prescribed oral prednisolone at least once, which is more than any one individual DMARD.

Changing trends in DMARD use

The number of individuals on any DMARD remained at about 50% between 1987 and 2002. However, the relative use of different DMARDs has changed over the 15 yr studied (Fig. 1a). Methotrexate prescriptions increased more than 17-fold from 1.8% of all DMARDs used in 1988 to 30% in 2002. The reverse trend was seen for gold (13.2 to 2.3%) and penicillamine (14.2 to 2.5%). The use of prednisolone and sulphasalazine has remained fairly stable over the study period, with around one-third of all RA patients having received each. For individuals with a new diagnosis of RA, the first DMARD prescribed showed similar trends (Fig. 1b). The use of new therapies including leflunomide and TNF antagonists are represented in the database in the last years of follow-up but are present in small numbers. Four thousand five hundred and sixty-seven (66%) of the individuals taking methotrexate were also prescribed folic acid during the period of methotrexate use. The use of combination therapies increased over the study period, with 6.2% of individuals prescribed more than one DMARD simultaneously in 1990 and 9.3% in 2000.

DMARD persistence

The use of Kaplan–Meier survival curves allowed an estimation of the persistence of individual DMARD monotherapy (Fig. 2). This showed methotrexate to be the longest-lasting DMARD, with an estimated median treatment time of 8.1 yr. However, newly introduced DMARDs did not have as long for follow-up since the study finished in 2002. Therefore estimates of drug survival at 1 yr and, where longer-term data were available, 5 yr were made (Table 1). This showed leflunomide use remaining at 84.6% and methotrexate at 78% after 1 yr, both well above other DMARDs. At 5 yr there were no data available for leflunomide but methotrexate use was highest at 57.1%.

Discussion

Our study provides information on DMARD use in a large number of RA patients identified from a primary care-based database in the UK. The diagnosis of RA was recorded in a pragmatic way by GPs in the patient notes. Expert coders then determined the ICD-9 coded diagnosis. Defined clinical classification criteria were not used. The data held by the GPRD have been extensively cross-checked and validated for accuracy [18, 19]. The reliability of the diagnosis of RA and other connective tissue diseases in the GPRD is currently being investigated. However, studies of osteoporosis have demonstrated that specificity for the diagnosis of chronic diseases is very high but sensitivity is low [18]. Thus, the diagnosis of RA in this dataset would be expected to include definite cases of RA but may miss mild or uncertain cases. In addition to diseases such as osteoporosis, the

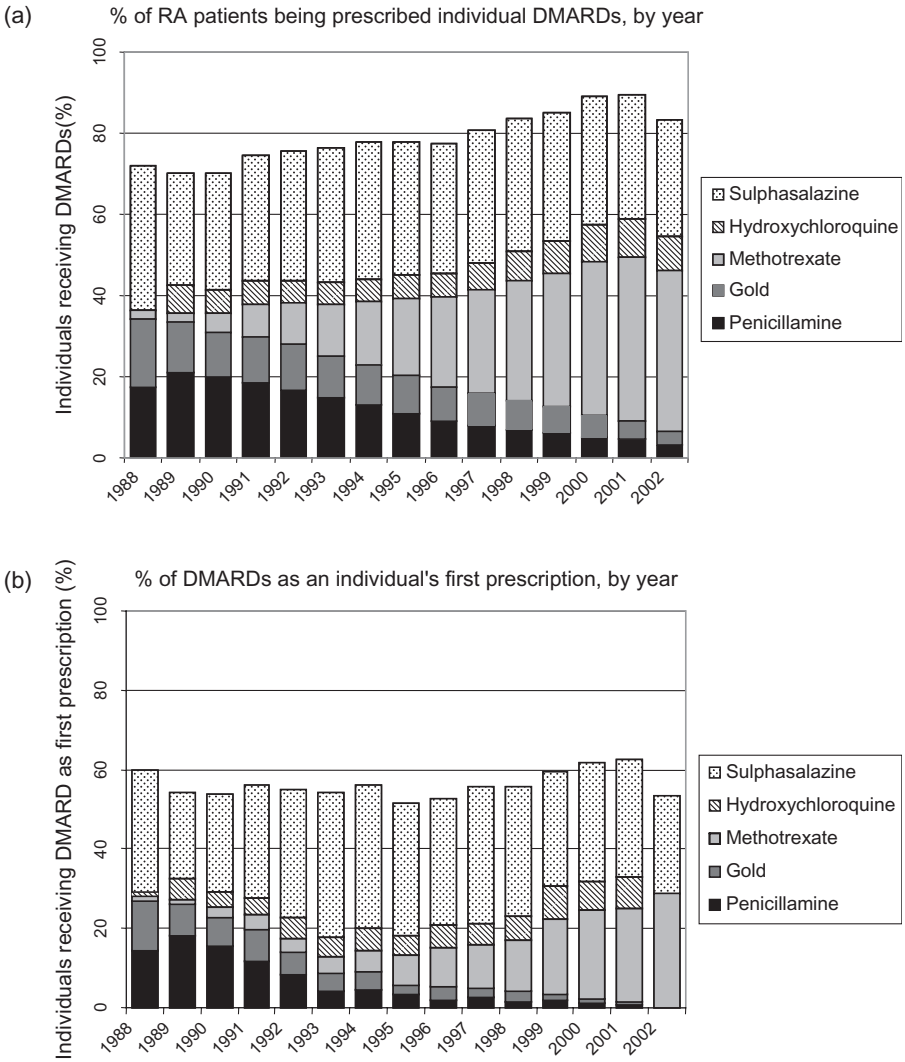

FIG. 1. (a) Changing trends in the use of DMARDS over the 15-yr study period from 1987 to 2002. (b) Changing trends in the first ever DMARD prescriptions in RA over the 15-yr study period from 1987 to 2002.

database has also been validated for diagnoses of other inflammatory diseases that are similar to RA such as inflammatory bowel disease [21]. Those individuals receiving a DMARD and attending secondary specialist rheumatological care are very likely to have a correct diagnosis. In addition, the RA population in this study has a sex distribution and mean age consistent with other published populations of RA patients. The incidence and prevalence are also similar to that seen in most populations [22], although lower than recently published figures for a UK population [23, 24]. There is often a considerable lag time between the onset of clinical RA and a diagnosis being made [25]. As our study uses data collected over 15 yr, this bias is likely to be reduced.

RA patients were identified from primary care records of attendance. In the UK all individuals have a designated GP. The GP is the first port of call for all health care including referral to secondary and tertiary care. For this reason the population studied will include most individuals with RA, including individuals being cared for solely by the GP and those attending specialist rheumatological care. The prescribing of all medication is generally performed by GPs making it unlikely that DMARD prescribing has been missed. As the data for this study come from primary care, the assumption might be that these individuals have mild RA. However, previous UK studies have shown that individuals with RA seen in primary care have disease just as severe as those in specialist secondary rheumatological care [26, 27].

It is surprising that only half of individuals with a clinical diagnosis of RA were prescribed DMARDs at any time. Our data do not include dosing schedules, and those individuals receiving DMARDs may have been on low or inadequate doses. This is not just a problem in the UK, as data from the USA lead to similar conclusions about the low number of RA patients receiving DMARDs [12]. The last 10 yr has seen enormous changes in the management of RA. We realize that early aggressive therapy with DMARDs produces better outcomes. However, it is clear that this suggested change in practice has not reached all patients. The numbers of individuals being prescribed DMARDs have remained fairly constant at 50% over the whole of the 15-yr study period. Previous studies have also shown that individuals with RA are significantly less likely to be prescribed DMARDs such as methotrexate if treated by non-rheumatologists [28]. Studies have also shown that primary care practitioners' knowledge of the importance of DMARD use is often high [29]. However, the prescription of DMARDs depended on experience with similar patients.

Over the whole period of follow-up, sulphasalazine was the most commonly prescribed DMARD, with methotrexate in second place. However, there has been a large change in the relative

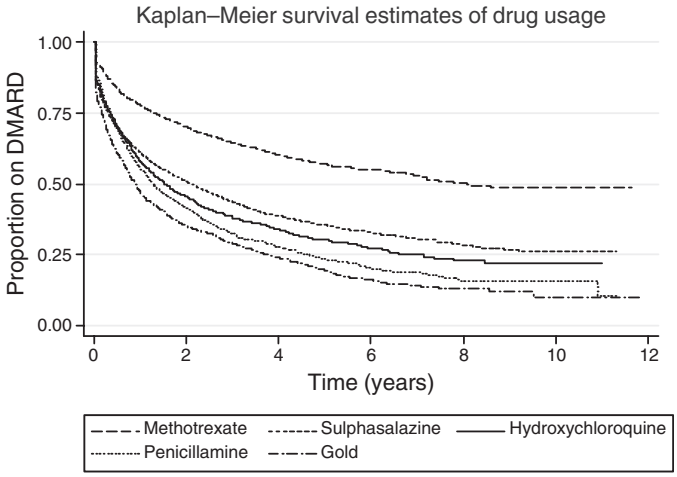

FIG. 2. Kaplan–Meier survival estimates of DMARD use over the 15-yr study period.

TABLE 1. Percentage and 95% confidence interval (CI) of DMARD users remaining on treatment at 1 and 5 yr

	Percentage of DMARD users remaining on treatment (95% CI)	
	After 1 yr	After 5 yr
Oral gold	45.9 (38.8, 52.7)	17.6 (11.5, 24.7)
Hydroxychloroquine	58.3 (55.9, 60.6)	30.5 (27.5, 33.5)
Methotrexate	78.0 (76.8, 79.1)	57.1 (55.3, 58.8)
Penicillamine	55.9 (53.2, 58.4)	23.5 (20.8, 26.3)
Intramuscular gold	47.2 (44.9, 49.4)	19.5 (17.3, 21.9)
Sulphasalazine	61.1 (59.9, 62.3)	35.6 (34.2, 37.1)
Prednisolone	54.8 (53.8, 55.7)	38.7 (37.5, 39.9)
Azathioprine	56.9 (54.0, 59.7)	34.8 (31.2, 38.4)
Cyclophosphamide	49.2 (38.6, 58.9)	16.0 (7.2, 27.9)
Cyclosporin	62.0 (57.0, 66.6)	34.2 (27.0, 41.5)
Leflunomide	84.6 (78.3, 89.2)	–

proportions of different DMARDs being prescribed. Methotrexate use has increased more than 17-fold, with sulphasalazine use remaining stable, and gold and penicillamine use falling considerably. The use of combinations of DMARDs has increased a little but is still used in a minority of individuals (9.3% of individuals in 2000). Increased use of methotrexate is partly due to greater use of methotrexate as the first-line DMARD for RA patients, but is also due to its use continuing longer than any other DMARD. The long-term survival of methotrexate compared with other DMARDs has been described in previous studies [4–11]. These have generally concentrated on the use of DMARDs in secondary and tertiary care. They confirm that methotrexate use continues in about 50% of individuals at 5 yr and the major reason for stopping are adverse events, not lack of efficacy. The popularity of methotrexate use in practice probably results from the long period of time for which individuals stay on methotrexate once it is first prescribed. Drug survival depends on a number of factors including speed of action, efficacy, side-effects and convenience/acceptability to patients. Our study was not able to distinguish whether DMARDs were stopped due to lack of efficacy or adverse drug reactions. However, this study provides long-term data in a large population of individuals with RA. RA is a chronic disease with limited spontaneous remission. For this reason effective DMARDs must be used for many years. Previous information on drug survival has come from randomized controlled trials that are always relatively short-term (6–12 months) or from single secondary and tertiary centres.

This is the largest series of data on DMARD use published to date and has the strength that it has come from a national database without the inherent bias seen in data from a single centre. It has shown that in the UK large numbers of individuals with a clinical diagnosis of RA were not prescribed DMARDs in the 15 yr between 1987 and 2002. This work suggests that many individuals with RA have not been treated appropriately and this may have major long-term consequences for joint damage and general health. We believe this highlights the importance of early referral of individuals with RA to a consultant with expertise in treating inflammatory arthritis. Further studies are required to assess the consequences of failing to use DMARDs in such large numbers of RA patients.

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