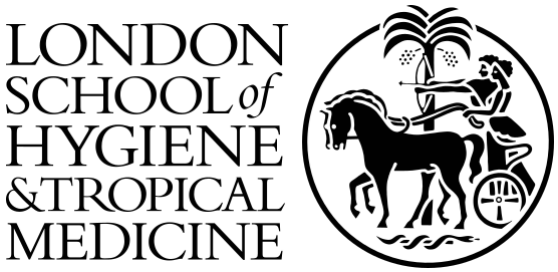

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Regional and temporal variation in the treatment of rheumatoid arthritis across the UK: a descriptive register-based cohort study

Christopher John Edwards,[1,2] Jennifer Campbell,[3] Tjeerd van Staa,[3,4] Nigel K Arden[2,5]

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For numbered affiliations see end of article

Correspondence to
Dr Christopher John Edwards; cedwards@soton.ac.uk

ABSTRACT

Objectives: To describe current disease-modifying antirheumatic drugs (DMARDs) prescription in rheumatoid arthritis (RA) with reference to best practice and to identify temporal and regional trends in the UK.

Design: Descriptive, register-based cohort study.

Participants: Permanently registered patients aged ≥18 years with a recorded diagnosis of RA between 1 January 1995 and 31 March 2010 and matched controls. Participants with RA were identified through screening of all patients in the General Practice Research Database (GPRD) with a clinical or referral record for RA and at least 1 day of follow-up.

Setting: 639 general practices in the UK supplying data to the GPRD.

Main outcome measures: Medication prescribing between 3 and 12 months of RA diagnosis by region and time period (1995–1999, 2000–2005 and 2006–April 2010).

Results: Of the 35 911 patients in the full RA cohort, 15 259 patients (42%) had incident RA. Analysis of prescribing in incident RA patients demonstrated that between 1995 (baseline) and 2010 there was a substantial increase in DMARD, and specifically methotrexate, prescribing across all regions with a less marked increase in combination DMARD prescribing. Taking 12-month prescribing as a snapshot: DMARD prescribing was 19–49% at baseline increasing to 45–74% by 2006–April 2010; methotrexate prescribing was 4–16% at baseline increasing to 32–60%; combination DMARD prescribing was 0–8% at baseline increasing to 3–17%. However, there was marked regional variation in the proportion of RA patients receiving DMARD regardless of time period.

Conclusions: There has been a substantial increase in prescribing of DMARDs for RA since 1995; however, regional variation persists across the UK with relative undertreatment, according to established best practice. Improved implementation of evidence-based best clinical practice to facilitate removal of treatment variation is warranted. This may occur as a result of the implementation of published national guidance.

ARTICLE SUMMARY

Article focus

- Over recent years there have been fundamental changes in the approach to the treatment of rheumatoid arthritis (RA) with a move towards early and more aggressive treatment.
- Disease-modifying antirheumatic drugs (DMARDs) are effective in the treatment of RA and their early use is recommended in national and international clinical guidelines and recommendations.
- We describe both temporal and regional trends in DMARD therapy for RA throughout the UK over a 15-year period and reveal whether the latest knowledge on how RA should be treated has been translated into actual clinical practice.

Key messages

- There has been a substantial increase in DMARD prescription for RA and an increase in the proportion of patients prescribed DMARD earlier in the course of their disease between 1995 and 2010.
- However, RA remains relatively undertreated according to best practice and published national guidelines, and regional variation persists.
- There is a need to optimise dissemination and implementation of high-quality clinical guidelines and to monitor implementation.

Strengths and limitations of this study

- One of the strengths of the study was the size of the study population with 15 259 patients with incident RA and of the long-term follow-up of these patients (mean 5.5 years but up to 15.3 years for some patients). Another is the generalisability of the General Practice Research Database (GPRD) database from which our data were obtained.
- The coding of the diagnosis of RA is a potential limitation; however, GPRD has been validated in previous studies and in this study by the observation of similar demographics for DMARD versus non-DMARD users.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, systemic, autoimmune disease, the most common form of chronic joint inflammation[1] and is associated with substantial long-term morbidity, mortality and healthcare costs.[2] A recent report from the National Audit Office estimates that around 580 000 people have RA in England and that 26 000 patients are diagnosed with RA each year.[3] RA can have a profound effect on patients through the physical manifestations of the disease, associated complications and impact on health-related quality of life (HRQOL).[4] Disease-modifying antirheumatic drugs (DMARDs), used either as monotherapy or in combination, can control disease activity, reduce joint erosions,[5] improve quality of life[6] and also reduce the cardiovascular morbidity associated with RA.[7]

Over recent years, there have been fundamental changes in the approach to treatment of RA with the availability of newer therapies and a move towards early and more aggressive treatment.[8] A recent meta-analysis including data from 70 trials, demonstrates that aggressive treatment with combination DMARDs is able to reduce structural joint damage.[9] DMARDs have a critical role in the management of RA and are central to both European recommendations[8] and UK guidance.[10] Issued in February 2009, National Institute for Health and Clinical Excellence (NICE) clinical guidelines for the treatment of RA recommend a combination of DMARDs (including methotrexate and at least one other DMARD, plus short-term glucocorticoids) as first-line treatment ideally within 3 months of symptom onset for people with recently diagnosed active RA.[10] The NICE guidance serves as an example of best practice although its publication in 2009 preclude us from determining accurately whether its recommendations have been taken up in this study.

Much information regarding the use of DMARDs is from published experience within the tertiary care setting; however, it is unclear as to how well this reflects routine practice in secondary and primary care settings across the UK. Despite the demonstrated efficacy of DMARDs, data from over 34 000 primary care records collected between 1987 and 2002 indicate that only half of patients diagnosed with RA receive DMARD therapy.[11] The UK General Practice Research Database (GPRD) is an electronic database of primary care medical records. GPRD contains data on over 8% of the population and has data on over 11 million individuals (cumulative) with over five million currently active.[11 12] The GPRD has been used in several studies and the validity of an RA diagnosis in GPRD appears to be high for patients with specific characteristics when using the American College of Rheumatology (ACR) diagnostic criteria as the standard.[12 13] All patients in the UK will be seen by a primary care physician or general practitioner (GP) in addition to any secondary care physician needed for care of a specific illness. Although individuals with RA were recruited to the GPRD by a GP the validation studies described show that a rheumatologist in secondary care will also have seen the vast majority of individuals.[12] The objectives of this study were to provide an updated view of current DMARD prescribing in RA with reference to best practice, to describe both temporal and regional trends in DMARD therapy for RA throughout the UK over a 15-year period, and to assess whether the latest knowledge on how RA should be treated has been translated into actual clinical practice.

METHODS

Data source

We obtained data for this study from the GPRD which collates the computerised medical records of GPs. The data recorded in the GPRD include demographic information, prescription details, clinical events, preventive care provided, specialist referrals, hospital admissions and major outcomes. The GPRD contains the complete anonymised patient medical records from GPs who use the system from In Practice Systems (a software package used for patient medical records) and who agree to adhere to 'Recording Guidelines' that are subject to detailed quality control checks of data at both practice and individual patient levels.

Study design and population

We conducted a descriptive, cohort study in permanently registered patients aged 18 years and over with a recorded diagnosis of RA between 1 January 1995 and 31 March 2010. We identified our study population through screening of all patients in the GPRD (n=11 480 996); who had a clinical or referral record for RA (n=63 238); with a record on or after 1 January 1995 (n=45 057); where this record was on or after the start of follow-up (latest of patient registration or practice up-to-standard (UTS) date; n=36 567); who were aged at least 18 at this date (n=36 035); and who had at least 1 day of follow-up (n=35 911). We used the same Read codes as in the previous RA validation study.[12]

The period of follow-up was from the date of first RA record up (ie, index date) to the date of censoring (ie, latest GPRD data collection, patient's transfer out of the practice or patient's death, whichever date came first). The study population included patients with a record of RA prior to start of GPRD data collection (ie, prevalent cases) and also RA patients with a first-ever record of RA at least 1 year after start of GPRD data collection (ie, incident cases). Each RA patient was matched by age, gender and practice to three patients without a record of inflammatory disease (listed in appendix 1).

Analysis of utilisation characteristics

We conducted an analysis to describe the exposure characteristics of incident RA patients from index date. We measured the prevalence of the use of different medications stratified by age at diagnosis (at date of first-ever record of RA), age at time of measurement, sex,

calendar year and strategic health authority. We determined the prevalence of medication use by evaluating GP prescribing in the 6 months before the index date of the following DMARDS: methotrexate; sulphasalazine; hydroxychloroquine; gold (sodium aurothiomalate); auranofin; penicillamine; leflunomide; azathioprine; ciclosporin and cyclophosomide. Of note, GPRD captures information on all prescriptions issued both acute and repeat, along with dosage instructions.

RESULTS

Baseline characteristics

The full cohort included both incident and prevalent RA cases and comprised a total of 35 911 patients. RA patients and matched controls were well balanced in terms of age, gender and socioeconomic status. However, there was a higher prevalence of smokers and a lower prevalence of drinkers among RA patients. Of the 35 911 patients in the full RA cohort, a subgroup of 15 259 patients (42%) had an incident RA. With regard to treatment, there was a 10-fold increase in prescribing of prednisolone for incident RA patients versus matched controls and a ninefold increase in prescribing of non-steroidal anti-inflammatory drugs in the 6 months prior to diagnosis.

Prescription practice by region and time period for incident patients

General trends

The data were analysed to assess the proportion of incident RA patients prescribed either DMARD, methotrexate or combination DMARD within 3, 6 or 12 months of diagnosis according to geographic region and according to time period (1995–1999, 2000–2005 and 2006–April 2010; appendix 2). In general, the data indicate that across all regions and within each time period, the proportion of patients prescribed DMARDs including methotrexate increased between 3 and 12 months. However, increases in the proportion of patients prescribed combination DMARDs were less marked with either no or little increase between 3–6 and 6–12 months but a modest overall increase between 3 and 12 months.

Temporal change in medication prescribing

In order to provide a snapshot of change in DMARD usage over time, the data were analysed to assess the proportion of patients prescribed either any DMARD, methotrexate or any combination of DMARDs within 12 months according to time period (1995–1999, 2000–2005 and 2006–April 2010; table 1). There was a substantial increase in 12-month prescribing of DMARD (from 36.9% to 60.1%), methotrexate (from 11.6% to 40.7%) and combination DMARD (from 0.9% to 9.1%) over the 15-year time period. Analysis of regional data demonstrated an increase in the proportion of patients prescribed DMARDs at 12 months across all regions during the 15-year time period (figure 1). At baseline (1995–1999) between 19.29% (East Midlands) and 49.06% (Northern Ireland) of patients were prescribed DMARDs at 12 months; by 2006–April 2010 the rate of prescribing had increased from between 45.32% (London) and 73.6% (Scotland). A general trend for increased prescription of DMARDs/methotrexate between 3 and 12 months was also evident across all regions. Of note, combination DMARDs tended to be prescribed after 3 months with increasing prescription between 6 and 12 months and between 1995 and April 2010 across all regions (appendix 2).

Regional variation

Analysis of data focusing on prescribing of DMARDs at 12 months demonstrates substantial regional variation in DMARD prescribing regardless of time period (figure 1). Regional variation in DMARD prescribing at 12 months ranged from 19.29% to 49.06% between 1995 and 1999; from 36.09% to 60.17% between 2000 and 2005 and from 45.32% to 73.6% between 2006 and April 2010. The regional difference in the proportion of patients prescribed DMARD at 12 months ranged from 24% to 30% within each time period. Prescribing patterns of methotrexate and combination DMARDs also varied from region to region regardless of time period (appendix 2).

Time from diagnosis to treatment

The data for incident patients with UTS data of 5 years were analysed to evaluate time from diagnosis to treatment with either DMARD and/or methotrexate. For 5513 patients prescribed a DMARD, the median time from diagnosis to treatment was 50 days (IQR 0–1826); for 3754 patients prescribed methotrexate, the median time from diagnosis to treatment was 119 days (IQR 0–1826); while for 1310 patients prescribed combination DMARD the median time from diagnosis to treatment was 560 days (IQR 0–1826).

DISCUSSION

We have demonstrated that between 1995 and 2010 there was a substantial increase in DMARD, methotrexate and combination DMARD prescribing across all regions. In this 15-year period, 12-month prescribing of DMARD almost doubled rising from 36.9% to 60.1%; 12-month prescribing of methotrexate quadrupled from 11.6% to 40.7% and 12-month prescribing of combination DMARD showed a 10-fold increase from 0.9% to 9.0%. However, some 40% of patients were not receiving DMARD at 12 months despite national clinical guidelines recommending this therapy within 3 months of diagnosis[10] indicating a relative undertreatment of RA. In addition, the marked regional variation in the prescription of DMARDs within the UK persists and has not decreased with time. To our knowledge, this is the first time that data on the use of DMARDs over this time period has been examined in a large RA population in the UK.

Table 1 Proportion of patients prescribed DMARDs within 12 months versus number diagnosed according to time period across all regions

Time period	Number of patients diagnosed with RA	Number of patients prescribed DMARD (%)	Number of patients prescribed methotrexate (%)	Number of patients prescribed DMARD combination (%)
1995–1999	1620	36.9	11.6	0.9
2000–2005	3411	46.1	23.6	3.5
2006–April 2010	3218	60.1	40.7	9.0

DMARD, disease-modifying antirheumatic drugs; RA, rheumatoid arthritis.

Clinical implications

Several studies indicate that appropriate and timely use of DMARDS and biologics for management of RA can improve outcomes such as mortality risk and HRQOL.[14–17] However, previous studies indicate that many patients receive insufficient treatment[18] and that there is variation in practice in the management of RA.[3] Our current data confirm the significant regional variation both in the timing of DMARD or methotrexate therapy and in the proportion of patients diagnosed with RA receiving these therapies at specific time points. Based on the latest data from 2006 to April 2010 for regions in England (ie, excluding Wales, Scotland and Northern Ireland), the proportion of RA patients receiving DMARDs at 12 months between 2006 and April 2010 ranges from 45.32% (London) to 66.83% (South Central). In addition, the proportion of RA patients in England receiving methotrexate at 12 months in this latest time period ranges from 32.11% (North East) to 51.62% (South Central); at best two-thirds of RA patients in England are being prescribed DMARDs and approximately one-half of RA patients in England are being prescribed methotrexate by 12 months (appendix 2).

The underlying reasons for this variation are not clear but could be due to several factors such as differences in RA health spend or differences in implementation and sharing of best practice. With the devolution of the National Health Service in 1999, differences in health services management and delivery exist between England, Scotland, Wales and Northern Ireland. Interestingly, our data indicate that Scotland and Northern Ireland have the highest proportion of RA patients prescribed DMARDs at 12 months (73.6% and 70.14%, respectively) and Northern Ireland the highest proportion of patients prescribed methotrexate at 12 months (60.42%; 34.78% in Scotland). This may suggest that there are lessons to be learned from regions which demonstrate good practice, possibly through understanding the impact of different networks, interaction and communication and the impact of different health spend priorities. In addition, it would be interesting to examine if regions with more aggressive use of DMARDs may use more or less biological therapies. Of note, there is as yet no benchmark defining the proportion of RA patients who should be prescribed DMARDs. These drugs are not suitable for *all* RA patients for example those with contraindications and women trying to conceive. Therefore the 'ideal' would be less than 100% of patients and possibly around 80% seems a realistic estimate of the proportion of RA patients eligible for DMARD therapy.

Several reports emphasise the importance of early and appropriate intervention in RA to optimise patient outcomes.[10 19] A meta-analysis assessing the long-term impact of early treatment on radiographic progression in RA which included 1133 patients identified a critical period for the initiation of RA therapy, a 'therapeutic window of opportunity' early in the course of RA which was associated with durable benefit in radiographic progression for a period of up to 5 years. In this analysis, there was a 33% reduction in long-term progression rates in patients receiving early therapy for their disease compared with those treated later.[20] Importantly, suboptimal treatment can lead to joint damage necessitating surgery (with the associated resource implications), and to a higher mortality risk from cardiovascular disease, a risk which can be mitigated with appropriate and timely methotrexate treatment.[7]

In our study, median time from diagnosis to treatment with DMARD, methotrexate or combination DMARD was 50, 119 and 560 days, respectively. This compares with NICE clinical guideline recommendations for combination DMARD treatment (including methotrexate) to be used as first-line therapy within 3 months of the onset of persistent symptoms.[10] Our findings indicate that RA patients who do receive methotrexate have it prescribed a median 4 months after diagnosis. Prior to diagnosis many patients in our study were already receiving treatment or therapies that may ameliorate the symptoms of RA (appendix 3): this may further delay treatment as RA symptoms are masked though damage continues and can impact on outcomes. Given the likely delay between symptom onset and diagnosis, the time from symptom onset to methotrexate is probably greater than 4 months. Furthermore, it should be noted that during the most recent time period (2006–April 2010) by 12 months at best only half of diagnosed RA patients were prescribed methotrexate (51.62%; South Central region).

Effective treatments for RA are available;[8 21] however, the results from our study demonstrate that RA is often suboptimally treated and that regional variation in the

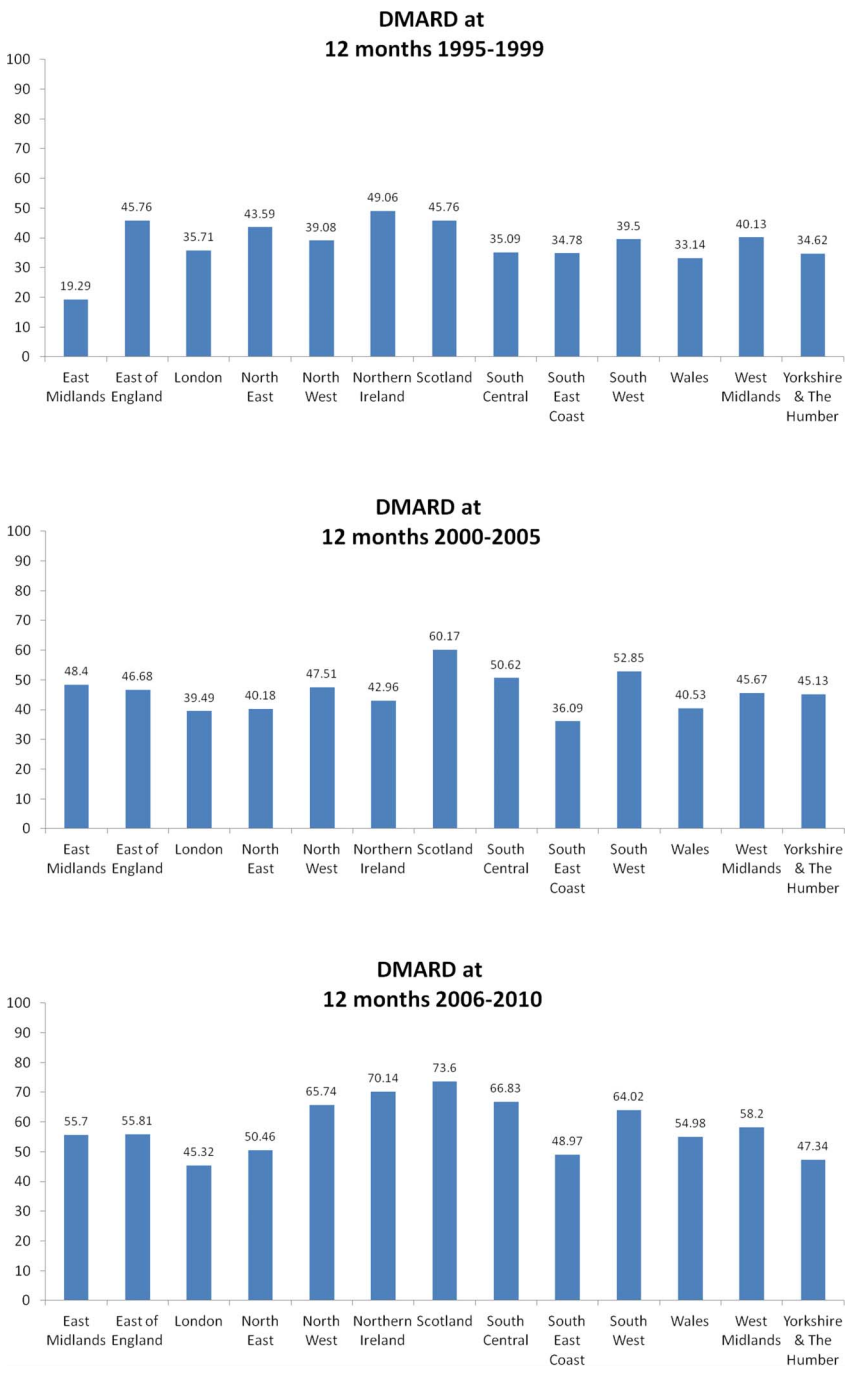

Figure 1 (A) Percentage of patients prescribed disease-modifying antirheumatic drugs (DMARDs) at 12 months by region for the time period 1995–1999. (B) Percentage of patients prescribed DMARDs at 12 months by region for the time period 2000–2005. (C) Percentage of patients prescribed DMARDs at 12 months by region for the time period 2006–2010.

management of RA persists after almost 2 years of guidance being available. Despite a recommendation for first-line treatment with combination DMARDs, fewer than 1 in 10 RA patients in the UK receive this therapy. Although there has been an encouraging increase in DMARD and methotrexate prescribing it is too early for us to conclude with any accuracy whether the more recently published NICE and EULAR guidelines have influenced DMARD prescribing in the UK. Recently published data indicate that the challenge of RA guideline implementation is not restricted to the UK. Assessment of prescribing practices in a US cohort of RA patients before and after the publication of ACR treatment recommendations indicates that at best only around 50% of RA patients with active disease receive care consistent with the current recommendations.[22]

The longer-term impact of our findings should be considered including the cost of surgical intervention when RA is suboptimally controlled resulting in joint damage. Policymakers should be aware of the persistence of variation and assess how best to minimise inequalities in RA care. A future challenge is how best to disseminate and embed new standards of care into routine clinical practice especially for chronic diseases

such as RA where treatment is undertaken by a range of healthcare professionals in different settings. This is likely to be ever more relevant as the care of patients with chronic disease increasingly is being transferred into the community setting.

We conclude that there is a need to optimise dissemination and implementation of high-quality clinical guidelines, that systems and processes for monitoring implementation should be developed, and that relevant indicators should be incorporated to ensure that guidelines are followed. Furthermore, accurate information on current prescribing in RA is vital to inform the development of the planned NICE Quality Standard for RA.

Strengths and weaknesses

One of the strengths of our study was the size of the study population with 15 259 patients with incident RA and of the long-term follow-up of these patients (mean 5.5 years but up to 15.3 years for some patients). Another is the generalisability of the GPRD database from which our data were obtained. The GPRD is representative of patients and practices throughout the UK,[23] and encompasses patients treated in primary, secondary and tertiary care. The regional variation observed in prescribing of DMARDs could be due to regional differences in the incidence of RA. However, data on age of diagnosis over the duration of the study (appendix 3) together with data (for 2009) on point prevalence and incidence rates for RA in the GPRD (appendix 4) were as expected, indicating robustness of the data.

The coding of the diagnosis of RA is a potential limitation. However, GPRD has been validated in previous studies[12] and again in this study by the observation of similar demographics for DMARD versus non-DMARD users. Furthermore, practices are monitored for the accuracy and completeness of data they submit to the GPRD data by running set queries on the data and as they are reimbursed by GPRD, penalties can be levied against practices that routinely fail to meet recording standards.[23] It is also unlikely that our results are compromised by healthcare seeking behaviour given the similar rates of prescribing of non-antirheumatic medication (statins, aspirin, antihypertensives and diabetic medications) in the full RA cohort versus matched controls (appendix 3). There may be temporal and regional variation in when GPs start to prescribe DMARDs. In some areas the GP initiates the first DMARD prescription on the advice of the rheumatologist; in other areas the hospital rheumatologist may initiate prescribing for a period of time. However, by 12 months it seems likely that most prescribing will be via the GP. This is supported by data from the IMS British Pharmaceutical Index/IMS Hospital Pharmacy Index which demonstrates that across all indications, over 90% of all DMARDs prescribing is carried out within primary care; for methotrexate, around 75–80% of all prescribing is carried out in the primary care setting.[24] We have recently performed a survey of primary care trust in England that suggests more than 90% of methotrexate prescribing is ultimately performed in primary care with 77% by 6 months (personal communication submitted for publication). Prescribing data for the use of DMARDs appears to be strong in the GPRD. However, as biological therapies are not usually prescribed by primary care we are unable to comment on their use as the GPRD only contains very limited information on their prescribing.

CONCLUSIONS

In summary, there has been a substantial improvement in the treatment of RA across the UK over the 15-year period from 1995 to 2010 with increasing use of DMARDs which currently represent best clinical practice. Despite this improvement, RA remains undertreated according to clinical recommendations and guidelines in the UK[10] and elsewhere.[25] In addition, regional variation in DMARD and methotrexate prescribing persists across the UK.

Improvement in RA treatment is needed UK-wide: identification and assessment of models of RA treatment that demonstrate implementation of evidence-based best clinical practice would minimise variation, facilitate nationally a uniform approach to RA treatment, to both improve patient outcomes and optimise resource use.

Author affiliations
[1]Department of Rheumatology, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[2]University of Southampton, Southampton, UK
[3]General Practice Research Database, Medicines and Healthcare Products Regulatory Agency, London, UK
[4]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, The Netherlands
[5]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, UK

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Notes