BMJ open

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Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001603
Article Type:	Research
Date Submitted by the Author:	02-Jun-2012
Complete List of Authors:	Edwards, Christopher; University Hospital Southampton NHS Foundation Trust, Rheumatology Campbell, Jennifer; General Practice Research Database, Medicines and Healthcare products Regulatory Agency, van Staa, Tjeerd; General Practice Research Database, Medicines and Healthcare products Regulatory Agency, ; Utrecht Institute for Pharmaceutical Sciences, Arden, Nigel; Nuffield Department of Orthopaedics,
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	General practice / Family practice
Keywords:	Rheumatology < INTERNAL MEDICINE, PRIMARY CARE, RHEUMATOLOGY

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

Authors

Christopher J Edwards *consultant rheumatologist*[1,2], Jennifer Campbell *research scientist*[3], Tjeerd Van Staa *head of research*[3,4], Nigel K Arden *professor of rheumatology*[2,5].

[1]Department of Rheumatology, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, SO16 6YD; [2]University of Southampton, Southampton, United Kingdom SO16 6YD; [3]General Practice Research Database, Medicines and Healthcare products Regulatory Agency, London, United Kingdom SW1W 9SZ; [4]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; [5]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, United Kingdom OX3 7HE.

Correspondence to: Christopher J Edwards cedwards@soton.ac.uk

Abstract

Objectives: To describe current DMARD 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 01/01/1995 and 31/03/2010 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 one 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 under-treatment, according to best practice and published national guidelines. Improved implementation of evidence-based best clinical practice to facilitate removal of treatment variation is warranted.

Key words: *Rheumatoid arthritis, DMARDs, General Practice Research Database, regional variation.*

Article summary

Article focus:

- Over recent years there have been fundamental changes in the approach to treatment of rheumatoid arthritis (RA) with a move towards early and more aggressive treatment
- Disease-modifying anti-rheumatic 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 under-treated 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 was 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 health-care costs [2]. A recent report from the National Audit Office (NAO) 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 anti-rheumatic 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, 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].

Much information regarding the use of DMARDs is from published experience within the tertiary care setting however it is unclear 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 [12]. 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 5 million currently active [12, 13]. 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 [13]. 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 computerized 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 level.

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 01/01/1995 and 31/03/2010. 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 01/01/1995 (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 one day of follow-up (n=35,911). We used the same Read codes as in the previous RA validation study [13].

The period of follow-up was from the date of first RA record up (i.e. index date) to the date of censoring (i.e. 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 (i.e., prevalent cases) and also RA patients with a first-ever record of RA at least 1 year after start of GPRD data collection (i.e. 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 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; sulfasalazine; 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 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 9-fold increase in prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) in the 6 months prior to diagnosis.

Prescription practice by region and time period for incident patients

General trends

The data was 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 months 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 was 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) to 73.6% (Scotland). A general trend for increased prescription of DMARDs/methotrexate between 3–12 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–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 2). Regional variation in

DMARD prescribing at 12 months ranged from 19.29–49.06% between 1995–1999; from 36.09–60.17% between 2000–2005; and from 45.32–73.6% between 2006–April 2010. The regional difference in the proportion of patients prescribed DMARD at 12 months ranged from 24–30% 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 five years was analysed to evaluate time from diagnosis to treatment with either DMARD and/or methotrexate. For 5,513 patients prescribed a DMARD, the median time from diagnosis to treatment was 50 days (interquartile range [IQR] 0–1,826); for 3,754 patients prescribed methotrexate, the median time from diagnosis to treatment was 119 days (IQR 0–1,826); while for 1,310 patients prescribed combination DMARD the median time from diagnosis to treatment was 560 days (IQR 0–1,826).

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 ten-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 under-treatment 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.

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 [16, 17, 18, 19]. However previous studies indicate that many patients receive insufficient treatment [20] 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–April 2010 for regions in England (i.e. excluding Wales, Scotland and Northern Ireland), the proportion of RA patients receiving DMARDs at 12 months between 2006–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 NHS 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. 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 emphasize the importance of early and appropriate intervention in RA to optimise patient outcomes [10, 21]. A meta-analysis assessing the long-term impact of early treatment on radiographic progression in RA which included 1,133 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 [22]. 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 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, 23] however, the results from our study demonstrate that RA is often suboptimally treated and that regional variation in the management of RA persists after almost two 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 post-NICE recommendations, these appear to reflect a general upward trend rather than rapid implementation and uptake of NICE guidelines. 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 publication of American College of Rheumatology (ACR) treatment recommendations indicates that at best only around 50% of RA patients with active disease receive care consistent with the current recommendations [25].

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 was obtained. The GPRD is representative of patients and practices throughout the UK [14], 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 [13] 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 [14]. 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 (BPI) / IMS Hospital Pharmacy Index (HPA) 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 [15].

Conclusions

In summary, there has been a substantial improvement in the treatment of RA across the UK over the 15-year period from 1995–2010 with increasing use of DMARDs which currently represent best clinical practice. Despite this improvement, RA remains under-treated according to clinical recommendations and guidelines in the UK [10] and elsewhere [24]. In addition regional variation in DMARD and methotrexate prescribing persists across the UK and publication of national clinical guidelines does not appear to have had a marked impact on standardising prescribing behaviour. 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.

Acknowledgements We thank Claire Housden and Kirsty Roberts (Roche Products Ltd) for procuring project funding and Ify Sargeant (ismedica Ltd) for medical writing support, funded by Roche Products Ltd.

Contributors: CJE, NKA, TvS and JC made primary contributions to study design, data collection, data analysis, interpretation of results, and writing the manuscript. All authors contributed to the interpretation of results and critical revision of the manuscript and approved the final manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. CJE is the guarantor.

Funding: This work was supported by Roche-Chugai who funded data generation and analysis by GPRD. Funding sources had no influence on the study design, interpretation of results, or decision to submit the article.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: financial support for the submitted work from Roche-Chugai; CJE has acted as speaker for and received research funding from Roche, UCB, Abbott, GSK and Pfizer; NKA has acted as speaker for and received research funding from Roche, Merck, Q-Med, NICOX, Flexion, Servier, GSK, Amgen and Lilley; GPRD (JC and TvS) has received funding from the MHRA, Wellcome Trust, Medical Research Council, NIHR Health Technology Assessment programme, Innovative Medicine Initiative, UK Department of Health, Technology Strategy Board, Seventh Framework Programme EU, various universities, contract research organisations and pharmaceutical companies. The department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (TvS) has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private-public funded Top Institute Pharma (www.tipharma.nl, includes co-funding from universities, government, and industry), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethical approval was not required

Data sharing: No additional data available.

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Table 1: *Proportion of patients prescribed DMARDs within 12 months vs. number diagnosed according to time period across all regions.*

Time period	No. of patients diagnosed with RA	No. of patients prescribed DMARD (%)	No. of patients prescribed methotrexate (%)	No. 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%

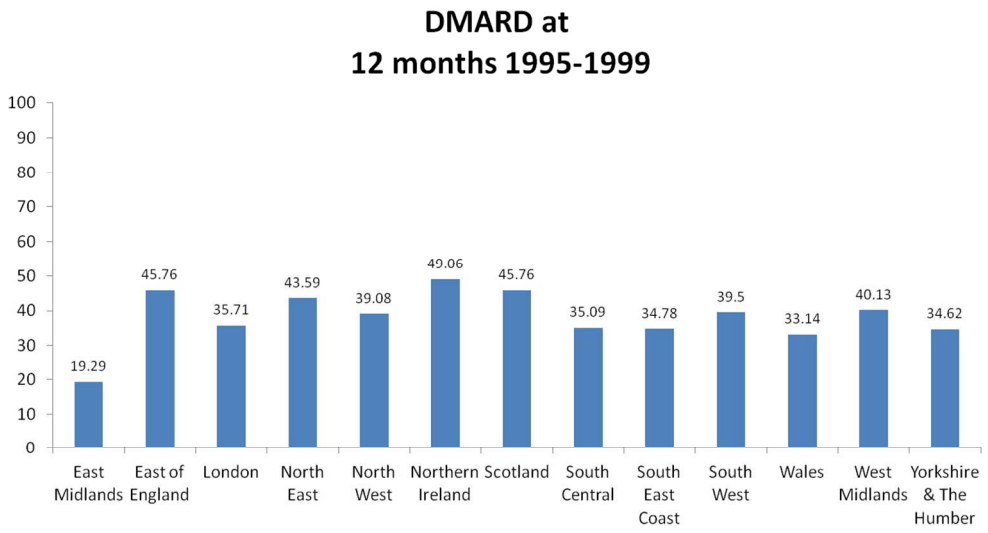

Figure 1a: Percentage of patients prescribed DMARDs at 12 months by region for the time period 1995–1999.
228x125mm (150 x 150 DPI)

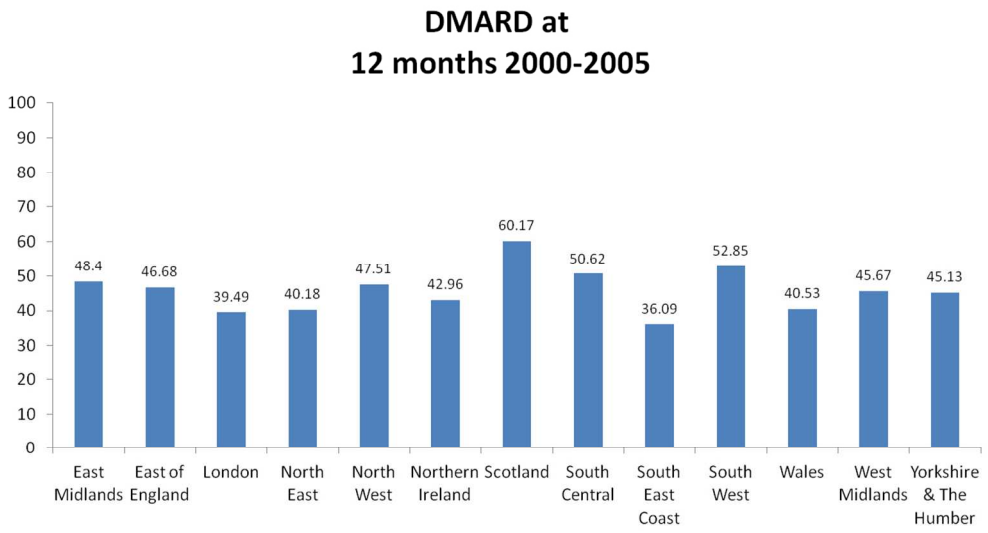

Figure 1b: Percentage of patients prescribed DMARDs at 12 months by region for the time period 2000–2005.
228x125mm (150 x 150 DPI)

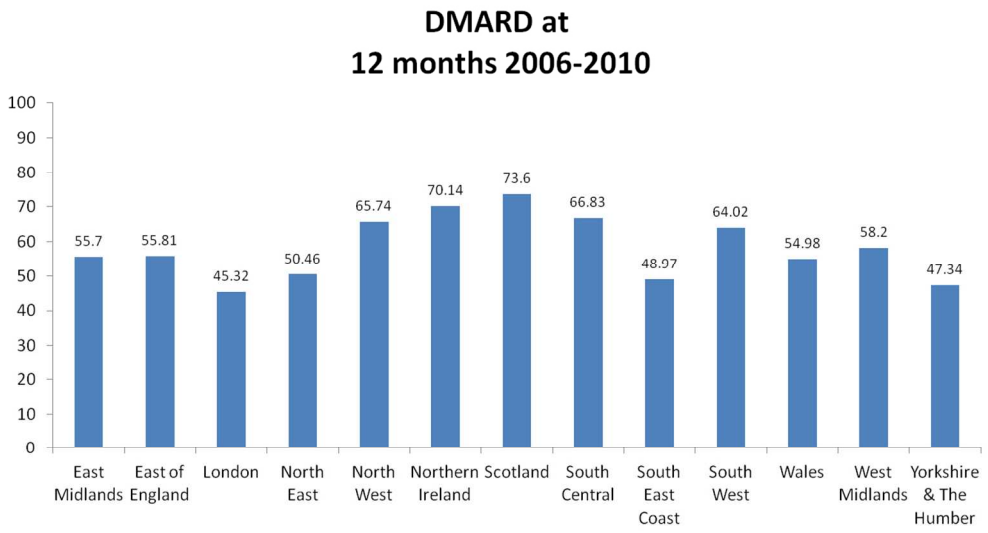

Figure 1c: Percentage of patients prescribed DMARDs at 12 months by region for the time period 2006–2010.
228x125mm (150 x 150 DPI)

Appendix 1

Each RA patient was matched by age, gender and practice to three patients without a record of inflammatory disease such as RA, juvenile arthritis, ankylosing spondylitis, enteropathic arthritis, reactive arthritis, inflammatory arthritis [seronegative], systemic lupus erythematosus [SLE], Sjogren's syndrome, mixed connective tissue disease [MCTD], polymyositis/dermatomyositis, scleroderma, polymyalgia rheumatica, giant cell arteritis, vasculitis [Wegeners], microscopic polyangiitis [MPA], Churg-strauss syndrome, polyarteritis nodosa [PAN], Takayasu arteritis, inflammatory bowel disease, sarcoidosis and psoriasis.

Appendix 2: Medications usage by region and by time period

Region	Time period	No. of patients diagnosed	No. of patients prescribed DMARD at 3 months (%)	No. of patients prescribed DMARD at 6 months (%)	No. of patients prescribed DMARD at 12 months (%)	No. of patients prescribed methotrexate at 3 months (%)	No. of patients prescribed methotrexate at 6 months (%)	No. of patients prescribed methotrexate at 12 months (%)	No. of patients prescribed combination DMARDs at 3 months (%)	No. of patients prescribed combination DMARDs at 6 months (%)	No. of patients prescribed combination DMARDs at 12 months (%)
East Midlands	1995_1999	197	22 (11.17%)	31 (15.74%)	38 (19.29%)	1 (0.51%)	2 (1.02%)	7 (3.55%)	. (.%)	. (.%)	. (.%)
	2000_2005	219	57 (26.03%)	84 (38.36%)	106 (48.40%)	20 (9.13%)	44 (20.09%)	58 (26.48%)	. (.%)	. (.%)	4 (1.83%)
	2006_April 2010	149	63 (42.28%)	75 (50.34%)	83 (55.70%)	27 (18.12%)	38 (25.50%)	49 (32.89%)	. (.%)	4 (2.68%)	7 (4.70%)
East of England	1995_1999	236	68 (28.81%)	92 (38.98%)	108 (45.76%)	18 (7.63%)	22 (9.32%)	31 (13.14%)	. (.%)	. (.%)	2 (0.85%)
	2000_2005	512	157 (30.66%)	204 (39.84%)	239 (46.68%)	64 (12.50%)	85 (16.60%)	113 (22.07%)	2 (0.39%)	2 (0.39%)	16 (3.13%)
	2006_April 2010	353	143 (40.51%)	178 (50.42%)	197 (55.81%)	86 (24.36%)	111 (31.44%)	129 (36.54%)	13 (3.68%)	16 (4.53%)	23 (6.52%)
London	1995_1999	154	33 (21.43%)	44 (28.57%)	55 (35.71%)	11 (7.14%)	14 (9.09%)	18 (11.69%)	1 (0.65%)	1 (0.65%)	1 (0.65%)
	2000_2005	314	80 (25.48%)	102 (32.48%)	124 (39.49%)	43 (13.69%)	60 (19.11%)	76 (24.20%)	1 (0.32%)	3 (0.96%)	7 (2.23%)
	2006_April 2010	331	91 (27.49%)	123 (37.16%)	150 (45.32%)	65 (19.64%)	91 (27.49%)	116 (35.05%)	9 (2.72%)	15 (4.53%)	26 (7.85%)
North East	1995_1999	39	9 (23.08%)	12 (30.77%)	17 (43.59%)	1 (2.56%)	2 (5.13%)	5 (12.82%)	. (.%)	. (.%)	. (.%)
	2000_2005	112	28 (25.00%)	41 (36.61%)	45 (40.18%)	6 (5.36%)	13 (11.61%)	18 (16.07%)	. (.%)	. (.%)	1 (0.89%)
	2006_April 2010	109	30 (27.52%)	43 (39.45%)	55 (50.46%)	17 (15.60%)	25 (22.94%)	35 (32.11%)	1 (0.92%)	1 (0.92%)	7 (6.42%)

Region	Time period	No. of patients diagnosed	No. of patients prescribed DMARD at 3 months (%)	No. of patients prescribed DMARD at 6 months (%)	No. of patients prescribed DMARD at 12 months (%)	No. of patients prescribed methotrexate at 3 months (%)	No. of patients prescribed methotrexate at 6 months (%)	No. of patients prescribed methotrexate at 12 months (%)	No. of patients prescribed combination DMARDs at 3 months (%)	No. of patients prescribed combination DMARDs at 6 months (%)	No. of patients prescribed combination DMARDs at 12 months (%)
North West	1995_1999	284	70 (24.65%)	96 (33.80%)	111 (39.08%)	21 (7.39%)	28 (9.86%)	34 (11.97%)	. (.%)	. (.%)	1 (0.35%)
	2000_2005	583	215 (36.88%)	253 (43.40%)	277 (47.51%)	85 (14.58%)	111 (19.04%)	135 (23.16%)	8 (1.37%)	11 (1.89%)	23 (3.95%)
	2006_April 2010	470	247 (52.55%)	286 (60.85%)	309 (65.74%)	151 (32.13%)	178 (37.87%)	201 (42.77%)	28 (5.96%)	44 (9.36%)	60 (12.77%)
Northern Ireland	1995_1999	53	22 (41.51%)	24 (45.28%)	26 (49.06%)	4 (7.55%)	5 (9.43%)	6 (11.32%)	1 (1.89%)	2 (3.77%)	4 (7.55%)
	2000_2005	135	42 (31.11%)	53 (39.26%)	58 (42.96%)	21 (15.56%)	28 (20.74%)	38 (28.15%)	1 (0.74%)	2 (1.48%)	5 (3.70%)
	2006_April 2010	144	84 (58.33%)	97 (67.36%)	101 (70.14%)	69 (47.92%)	80 (55.56%)	87 (60.42%)	6 (4.17%)	6 (4.17%)	9 (6.25%)
Scotland	1995_1999	59	22 (37.29%)	25 (42.37%)	27 (45.76%)	2 (3.39%)	4 (6.78%)	5 (8.47%)	. (.%)	. (.%)	. (.%)
	2000_2005	231	101 (43.72%)	126 (54.55%)	139 (60.17%)	16 (6.93%)	18 (7.79%)	30 (12.99%)	2 (0.87%)	3 (1.30%)	7 (3.03%)
	2006_April 2010	322	206 (63.98%)	228 (70.81%)	237 (73.60%)	75 (23.29%)	94 (29.19%)	112 (34.78%)	14 (4.35%)	22 (6.83%)	33 (10.25%)
South Central	1995_1999	114	32 (28.07%)	37 (32.46%)	40 (35.09%)	12 (10.53%)	13 (11.40%)	18 (15.79%)	. (.%)	1 (0.88%)	1 (0.88%)
	2000_2005	324	123 (37.96%)	145 (44.75%)	164 (50.62%)	69 (21.30%)	90 (27.78%)	111 (34.26%)	11 (3.40%)	18 (5.56%)	35 (10.80%)
	2006_April 2010	401	215 (53.62%)	253 (63.09%)	268 (66.83%)	163 (40.65%)	192 (47.88%)	207 (51.62%)	33 (8.23%)	52 (12.97%)	67 (16.71%)

Region	Time period	No. of patients diagnosed	No. of patients prescribed DMARD at 3 months (%)	No. of patients prescribed DMARD at 6 months (%)	No. of patients prescribed DMARD at 12 months (%)	No. of patients prescribed methotrexate at 3 months (%)	No. of patients prescribed methotrexate at 6 months (%)	No. of patients prescribed methotrexate at 12 months (%)	No. of patients prescribed combination DMARDs at 3 months (%)	No. of patients prescribed combination DMARDs at 6 months (%)	No. of patients prescribed combination DMARDs at 12 months (%)
South East Coast	1995_1999	115	20 (17.39%)	29 (25.22%)	40 (34.78%)	6 (5.22%)	10 (8.70%)	17 (14.78%)	. (.%)	. (.%)	. (.%)
	2000_2005	327	73 (22.32%)	96 (29.36%)	118 (36.09%)	48 (14.68%)	63 (19.27%)	83 (25.38%)	2 (0.61%)	2 (0.61%)	6 (1.83%)
	2006_April 2010	290	101 (34.83%)	130 (44.83%)	142 (48.97%)	72 (24.83%)	95 (32.76%)	104 (35.86%)	7 (2.41%)	9 (3.10%)	16 (5.52%)
South West	1995_1999	200	51 (25.50%)	66 (33.00%)	79 (39.50%)	13 (6.50%)	20 (10.00%)	26 (13.00%)	1 (0.50%)	1 (0.50%)	5 (2.50%)
	2000_2005	316	133 (42.09%)	149 (47.15%)	167 (52.85%)	55 (17.41%)	63 (19.94%)	90 (28.48%)	2 (0.63%)	2 (0.63%)	14 (4.43%)
	2006_April 2010	378	180 (47.62%)	212 (56.08%)	242 (64.02%)	110 (29.10%)	139 (36.77%)	164 (43.39%)	11 (2.91%)	21 (5.56%)	30 (7.94%)
Wales	1995_1999	169	46 (27.22%)	55 (32.54%)	56 (33.14%)	5 (2.96%)	12 (7.10%)	17 (10.06%)	. (.%)	. (.%)	1 (0.59%)
	2000_2005	338	92 (27.22%)	112 (33.14%)	137 (40.53%)	28 (8.28%)	42 (12.43%)	53 (15.68%)	. (.%)	1 (0.30%)	2 (0.59%)
	2006_April 2010	271	112 (41.33%)	136 (50.18%)	149 (54.98%)	69 (25.46%)	88 (32.47%)	105 (38.75%)	2 (0.74%)	4 (1.48%)	13 (4.80%)
West Midlands	1995_1999	152	40 (26.32%)	50 (32.89%)	61 (40.13%)	2 (1.32%)	5 (3.29%)	12 (7.89%)	. (.%)	2 (1.32%)	3 (1.97%)
	2000_2005	497	140 (28.17%)	201 (40.44%)	227 (45.67%)	43 (8.65%)	82 (16.50%)	102 (20.52%)	. (.%)	. (.%)	6 (1.21%)
	2006_April 2010	366	147 (40.16%)	185 (50.55%)	213 (58.20%)	89 (24.32%)	123 (33.61%)	146 (39.89%)	8 (2.19%)	15 (4.10%)	29 (7.92%)
Yorkshire & The Humber	1995_1999	156	33 (21.15%)	47 (30.13%)	54 (34.62%)	7 (4.49%)	12 (7.69%)	16 (10.26%)	. (.%)	. (.%)	. (.%)
	2000_2005	277	90 (32.49%)	107 (38.63%)	125 (45.13%)	37 (13.36%)	49 (17.69%)	67 (24.19%)	2 (0.72%)	7 (2.53%)	13 (4.69%)
	2006_April 2010	169	50 (29.59%)	65 (38.46%)	80 (47.34%)	33 (19.53%)	42 (24.85%)	58 (34.32%)	1 (0.59%)	2 (1.18%)	5 (2.96%)

Appendix 3: Baseline characteristics for the incident RA patients (N=15,259)

Characteristic	Incident RA Patients (N=15,259)	Matched Controls (N=45,777)	Crude Odds Ratio (95% CI)
Age 18–29 years	418 (2.7%)	1,254 (2.7%)	*
Age 30–39 years	1,139 (7.5%)	3,417 (7.5%)	*
Age 40–49 years	2,035 (13.3%)	6,105 (13.3%)	*
Age 50–59 years	3,387 (22.2%)	10,161 (22.2%)	*
Age 60–69 years	3,513 (23.0%)	10,539 (23.0%)	*
Age 70–79 years	3,136 (20.6%)	9,408 (20.6%)	*
Age 80+ years	1,631 (10.7%)	4,893 (10.7%)	*
Female gender (%)	10,565 (69.2%)	31,695 (69.2%)	*
Year of diagnosis: 1995	589 (3.9%)	1,767 (3.9%)	*
1996	563 (3.7%)	1,689 (3.7%)	*
1997	659 (4.3%)	1,977 (4.3%)	*
1998	709 (4.6%)	2,127 (4.6%)	*
1999	780 (5.1%)	2,340 (5.1%)	*
2000	981 (6.4%)	2,943 (6.4%)	*
2001	1,171 (7.7%)	3,513 (7.7%)	*
2002	1,321 (8.7%)	3,963 (8.7%)	*
2003	1,308 (8.6%)	3,924 (8.6%)	*
2004	1,306 (8.6%)	3,918 (8.6%)	*
2005	1,204 (7.9%)	3,612 (7.9%)	*
2006	1,195 (7.8%)	3,585 (7.8%)	*
2007	1,113 (7.3%)	3,339 (7.3%)	*
2008	1,068 (7.0%)	3,204 (7.0%)	*
2009	1,098 (7.2%)	3,294 (7.2%)	*
2010	194 (1.3%)	582 (1.3%)	*
Length of follow-up (mean, years)	5.2	4.9	*
Smoking status[1] Non smoker (%)	6,453 (42.3%)	22,052 (48.2%)	Reference
Ex smoker (%)	3,747 (24.6%)	9,230 (20.2%)	1.45 (1.38 - 1.53)
Smoker (%)	3,798 (24.9%)	8,862 (19.4%)	1.51 (1.43 - 1.58)
History of a presenting symptom (any)[2]	10,091 (66.1%)	15,015 (32.8%)	4.99 (4.77 - 5.22)
Joint pain (%)	9,275 (60.8%)	13,118 (28.7%)	4.73 (4.53 - 4.95)
Swollen tender joints (%)	1,587 (10.4%)	1,543 (3.4%)	3.53 (3.27 - 3.81)
Morning stiffness (%)	701 (4.6%)	465 (1.0%)	4.77 (4.22 - 5.38)
Previous prescribing of[3]:			
Steroid injections	704 (4.6%)	316 (0.7%)	7.30 (6.36 - 8.39)
Prednisolone	2,732 (17.9%)	990 (2.2%)	10.03 (9.26 - 10.86)
NSAIDs	10,698 (70.1%)	10,305 (22.5%)	8.95 (8.54 - 9.38)
Analgesics/ opioids	1,801 (11.8%)	1,275 (2.8%)	4.84 (4.48 - 5.23)
H2 antagonists and PPIs	3,971 (26.0%)	5,302 (11.6%)	2.89 (2.75 - 3.03)
Statins	1,847 (12.1%)	5,348 (11.7%)	1.05 (0.99 - 1.12)
Aspirin	1,975 (12.9%)	5,726 (12.5%)	1.05 (0.99 - 1.11)
Antihypertensives	4,581 (30.0%)	12,573 (27.5%)	1.16 (1.11 - 1.22)
Diabetic medications	745 (4.9%)	2,013 (4.4%)	1.12 (1.03 - 1.22)

*Patients were matched on this variable.

[1]Smoking status not known in 1,261 (8.3%) and 5,633 (12.3%) of RA patients and matched controls, respectively.

[2] Medical records were analysed in the 5 years before index date.

[3] Prescriptions were analysed in the six months before index date.

Appendix 4: Incidence rates and point prevalence of RA in the GPRD 2009

Region	Person years at risk (years)	Incident RA cases 2009	Incidence rate per 100,000 persons (30/06/09)	GPRD Population 2009	RA Cases 2009	Point Prevalence per 100,000 persons (30/06/09)
North East	85016.28	34	0.400	84831	491	5.788
North West	534355.5	146	0.273	544693	2,930	5.379
Yorkshire & The Humber	123289.3	34	0.276	123910	770	6.214
East Midlands	123771.1	31	0.250	130367	781	5.991
West Midlands	363201.7	111	0.306	374308	2,074	5.541
East of England	377678	96	0.254	389617	2,041	5.238
South West	349426.3	125	0.358	354863	1,918	5.405
South Central	474538	106	0.223	483299	2,250	4.656
London	514153.7	113	0.220	519717	1,877	3.612
South East Coast	381501.3	89	0.233	387344	1,718	4.435
Northern Ireland	121126.8	35	0.289	124176	725	5.838
Scotland	339703.9	97	0.286	343287	1,676	4.882
Wales	331040.5	81	0.245	338133	1,787	5.285

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Done – page 1 and 2 of PDF proof**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Done – page 2 of PDF proof**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Done – page 3 of PDF proof**
Objectives	3	State specific objectives, including any prespecified hypotheses **Done – page 3 of PDF proof**
Methods		
Study design	4	Present key elements of study design early in the paper **Done – page 4 of PDF proof**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Done – page 4 of PDF proof**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Done – page 4 of PDF proof**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **Done – page 4 of PDF proof**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Done – page 4 of PDF proof**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Done – page 4 of PDF proof**
Bias	9	Describe any efforts to address potential sources of bias **Done – page 8, 23 and 24 of PDF**
Study size	10	Explain how the study size was arrived at **(Not applicable – this is a descriptive study without definition of any a-priori hypothesis)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(Not applicable)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **(Not applicable)**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed

		Done – page 5 and 23 of PDF proof
		(b) Give reasons for non-participation at each stage **(Not applicable)**
		(c) Consider use of a flow diagram **(Not applicable)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Done – page 5 and 23 of PDF proof**
		(b) Indicate number of participants with missing data for each variable of interest **(Not applicable)**
		(c) Summarise follow-up time (eg, average and total amount) **Done – page 4 of PDF proof**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Done – page 5 and 6 of PDF proof**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **(Not applicable)**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **(Not applicable)**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Done – pages 6, 7 and 8 of PDF proof**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Done – pages 8 and 9 of PDF proof**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Done – pages 6–10 of PDF proof**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Done – pages 6–10 of PDF proof**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Done – page 11 of PDF proof**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001603.R1
Article Type:	Research
Date Submitted by the Author:	31-Aug-2012
Complete List of Authors:	Edwards, Christopher; University Hospital Southampton NHS Foundation Trust, Rheumatology Campbell, Jennifer; General Practice Research Database, Medicines and Healthcare products Regulatory Agency, van Staa, Tjeerd; General Practice Research Database, Medicines and Healthcare products Regulatory Agency, ; Utrecht Institute for Pharmaceutical Sciences, Arden, Nigel; Nuffield Department of Orthopaedics,
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	General practice / Family practice
Keywords:	Rheumatology < INTERNAL MEDICINE, PRIMARY CARE, RHEUMATOLOGY

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

Authors

Christopher J Edwards *consultant rheumatologist*[1,2], Jennifer Campbell *research scientist*[3], Tjeerd Van Staa *head of research*[3,4], Nigel K Arden *professor of rheumatology*[2,5].

[1]Department of Rheumatology, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, SO16 6YD; [2]University of Southampton, Southampton, United Kingdom SO16 6YD; [3]General Practice Research Database, Medicines and Healthcare products Regulatory Agency, London, United Kingdom SW1W 9SZ; [4]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; [5]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, United Kingdom OX3 7HE.

Correspondence to: Christopher J Edwards cedwards@soton.ac.uk

Abstract

Objectives: To describe current DMARD 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 01/01/1995 and 31/03/2010 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 one 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 under-treatment, 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.

Key words: *Rheumatoid arthritis, DMARDs, General Practice Research Database, regional variation.*

Article summary

Article focus:

- Over recent years there have been fundamental changes in the approach to treatment of rheumatoid arthritis (RA) with a move towards early and more aggressive treatment
- Disease-modifying anti-rheumatic 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 under-treated 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 was 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 health-care costs [2]. A recent report from the National Audit Office (NAO) 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 anti-rheumatic 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, 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 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 5 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 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 general practitioner 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 computerized 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 level.

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 01/01/1995 and 31/03/2010. 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 01/01/1995 (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 one 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 (i.e. index date) to the date of censoring (i.e. 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 (i.e., prevalent cases) and also RA patients with a first-ever record of RA at least 1 year after start of GPRD data collection (i.e. 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 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;

sulfasalazine; 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 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 9-fold increase in prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) in the 6 months prior to diagnosis.

Prescription practice by region and time period for incident patients

General trends

The data was 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 months 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 was 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) to 73.6% (Scotland). A general trend for increased prescription of DMARDs/methotrexate between 3–12 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–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 19.29–49.06% between 1995–1999; from 36.09–60.17% between 2000–2005; and from 45.32–73.6% between 2006–April 2010. The regional difference in the proportion of patients prescribed DMARD at 12 months ranged from 24–30% 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 five years was analysed to evaluate time from diagnosis to treatment with either DMARD and/or methotrexate. For 5,513 patients prescribed a DMARD, the median time from diagnosis to treatment was 50 days (interquartile range [IQR] 0–1,826); for 3,754 patients prescribed methotrexate, the median time from diagnosis to treatment was 119 days (IQR 0–1,826); while for 1,310 patients prescribed combination DMARD the median time from diagnosis to treatment was 560 days (IQR 0–1,826).

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 ten-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 under-treatment 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.

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, 15, 16, 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–April 2010 for regions in England (i.e. excluding Wales, Scotland and Northern Ireland), the proportion of RA patients receiving DMARDs at 12 months between 2006–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 NHS 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 emphasize 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 1,133 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 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 management of RA persists after almost two 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 post-NICE recommendations, these appear to reflect a general upward trend rather than rapid implementation and uptake of NICE guidelines. However, it is too early for us to conclude with any accuracy whether the NICE guidance is influencing 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 publication of American College of Rheumatology (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 was 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 (BPI) / IMS Hospital Pharmacy Index (HPA) 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 (PCTs) 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 1995–2010 with increasing use of DMARDs which currently represent best clinical practice. Despite this improvement, RA remains under-treated 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 and publication of national clinical guidelines does not appear to have had a marked impact on standardising prescribing behaviour. 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.

Acknowledgements We thank Claire Housden and Kirsty Roberts (Roche Products Ltd) for procuring project funding and Ify Sargeant (ismedica Ltd) for medical writing support, funded by Roche Products Ltd.

Contributors: CJE, NKA, TvS and JC made primary contributions to study design, data collection, data analysis, interpretation of results, and writing the manuscript. All authors contributed to the interpretation of results and critical revision of the manuscript and approved the final manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. CJE is the guarantor.

Funding: This work was supported by Roche-Chugai who funded data generation and analysis by GPRD. Funding sources had no influence on the study design, interpretation of results, or decision to submit the article.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: financial support for the submitted work from Roche-Chugai; CJE has acted as speaker for and received research funding from Roche, UCB, Abbott, GSK and Pfizer; NKA has acted as speaker for and received research funding from Roche, Merck, Q-Med, NICOX, Flexion, Servier, GSK, Amgen and Lilley; GPRD (JC and TvS) has received funding from the MHRA, Wellcome Trust, Medical Research Council, NIHR Health Technology Assessment programme, Innovative Medicine Initiative, UK Department of Health, Technology Strategy Board, Seventh Framework Programme EU, various universities, contract research organisations and pharmaceutical companies. The department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (TvS) has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private-public funded Top Institute Pharma (www.tipharma.nl, includes co-funding from universities, government, and industry), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethical approval was not required

Data sharing: No additional data available.

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Table 1: *Proportion of patients prescribed DMARDs within 12 months vs. number diagnosed according to time period across all regions.*

Time period	No. of patients diagnosed with RA	No. of patients prescribed DMARD (%)	No. of patients prescribed methotrexate (%)	No. 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%

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

Authors

Christopher J Edwards *consultant rheumatologist*[1,2], Jennifer Campbell *research scientist*[3], Tjeerd Van Staa *head of research*[3,4], Nigel K Arden *professor of rheumatology*[2,5].

[1]Department of Rheumatology, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, SO16 6YD; [2]University of Southampton, Southampton, United Kingdom SO16 6YD; [3]General Practice Research Database, Medicines and Healthcare products Regulatory Agency, London, United Kingdom SW1W 9SZ; [4]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; [5]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, United Kingdom OX3 7HE.

Correspondence to: Christopher J Edwards cedwards@soton.ac.uk

Abstract

Objectives: To describe current DMARD 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 01/01/1995 and 31/03/2010 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 one 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 under-treatment, according to established best practice ~~and published national guidelines~~. 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.

Key words: *Rheumatoid arthritis, DMARDs, General Practice Research Database, regional variation.*

Article summary

Article focus:

- Over recent years there have been fundamental changes in the approach to treatment of rheumatoid arthritis (RA) with a move towards early and more aggressive treatment
- Disease-modifying anti-rheumatic 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 under-treated 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 was 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 health-care costs [2]. A recent report from the National Audit Office (NAO) 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 anti-rheumatic 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, 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 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 [~~12~~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 5 million currently active [~~12, 13~~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~~13~~]. All patients in the UK will be seen by a primary care physician or general practitioner 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 general practitioner the validation studies described show that a rheumatologist in secondary care will also have seen the vast majority of individuals [~~13~~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 computerized 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 level.

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 01/01/1995 and 31/03/2010. 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 01/01/1995 (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 one day of follow-up (n=35,911). We used the same Read codes as in the previous RA validation study [~~13~~12].

The period of follow-up was from the date of first RA record up (i.e. index date) to the date of censoring (i.e. 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 (i.e., prevalent cases) and also RA patients with a first-ever record of RA at least 1 year after start of GPRD data collection (i.e. 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 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;

sulfasalazine; 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 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 9-fold increase in prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) in the 6 months prior to diagnosis.

Prescription practice by region and time period for incident patients

General trends

The data was 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 months 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 was 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) to 73.6% (Scotland). A general trend for increased prescription of DMARDs/methotrexate between 3–12 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–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 ~~2~~1). Regional variation in DMARD prescribing at 12 months ranged from 19.29–49.06% between 1995–1999; from 36.09–60.17% between 2000–2005; and from 45.32–73.6% between 2006–April 2010. The regional difference in the proportion of patients prescribed DMARD at 12 months ranged from 24–30% 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 five years was analysed to evaluate time from diagnosis to treatment with either DMARD and/or methotrexate. For 5,513 patients prescribed a DMARD, the median time from diagnosis to treatment was 50 days (interquartile range [IQR] 0–1,826); for 3,754 patients prescribed methotrexate, the median time from diagnosis to treatment was 119 days (IQR 0–1,826); while for 1,310 patients prescribed combination DMARD the median time from diagnosis to treatment was 560 days (IQR 0–1,826).

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 ten-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 under-treatment 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.

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 [~~16, 17, 18, 19~~14, 15, 16, 17]. However previous studies indicate that many patients receive insufficient treatment [~~20~~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–April 2010 for regions in England (i.e. excluding Wales, Scotland and Northern Ireland), the proportion of RA patients receiving DMARDs at 12 months between 2006–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 NHS 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 emphasize the importance of early and appropriate intervention in RA to optimise patient outcomes [10, ~~21~~19]. A meta-analysis assessing the long-term impact of early treatment on radiographic progression in RA which included 1,133 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 [~~22~~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 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, ~~23~~21] however, the results from our study demonstrate that RA is often suboptimally treated and that regional variation in the management of RA persists after almost two 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 post-NICE recommendations, these appear to reflect a general upward trend rather than rapid implementation and uptake of NICE guidelines. However, it is too early for us to conclude with any accuracy whether the NICE guidance is influencing 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 publication of American College of Rheumatology (ACR) treatment recommendations indicates that at best only around 50% of RA patients with active disease receive care consistent with the current recommendations [~~25~~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 was obtained. The GPRD is representative of patients and practices throughout the UK [~~14~~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 [~~13~~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 [~~14~~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 (BPI) / IMS Hospital Pharmacy Index (HPA) 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 [~~15~~24]. We have recently performed a survey of primary care trust (PCTs) 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 1995–2010 with increasing use of DMARDs which currently represent best clinical practice. Despite this improvement, RA remains under-treated according to clinical recommendations and guidelines in the UK [10] and elsewhere [~~24~~25]. In addition regional variation in DMARD and methotrexate prescribing persists across the UK and publication of national clinical guidelines does not appear to have had a marked impact on standardising prescribing behaviour.

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.

Acknowledgements We thank Claire Housden and Kirsty Roberts (Roche Products Ltd) for procuring project funding and Ify Sargeant (ismedica Ltd) for medical writing support, funded by Roche Products Ltd.

Contributors: CJE, NKA, TvS and JC made primary contributions to study design, data collection, data analysis, interpretation of results, and writing the manuscript. All authors contributed to the interpretation of results and critical revision of the manuscript and approved the final manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. CJE is the guarantor.

Funding: This work was supported by Roche-Chugai who funded data generation and analysis by GPRD. Funding sources had no influence on the study design, interpretation of results, or decision to submit the article.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: financial support for the submitted work from Roche-Chugai; CJE has acted as speaker for and received research funding from Roche, UCB, Abbott, GSK and Pfizer; NKA has acted as speaker for and received research funding from Roche, Merck, Q-Med, NICOX, Flexion, Servier, GSK, Amgen and Lilley; GPRD (JC and TvS) has received funding from the MHRA, Wellcome Trust, Medical Research Council, NIHR Health Technology Assessment programme, Innovative Medicine Initiative, UK Department of Health, Technology Strategy Board, Seventh Framework Programme EU, various universities, contract research organisations and pharmaceutical companies. The department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (TvS) has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private-public funded Top Institute Pharma (www.tipharma.nl, includes co-funding from universities, government, and industry), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethical approval was not required

Data sharing: No additional data available.

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Table 1: *Proportion of patients prescribed DMARDs within 12 months vs. number diagnosed according to time period across all regions.*

Time period	No. of patients diagnosed with RA	No. of patients prescribed DMARD (%)	No. of patients prescribed methotrexate (%)	No. 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%

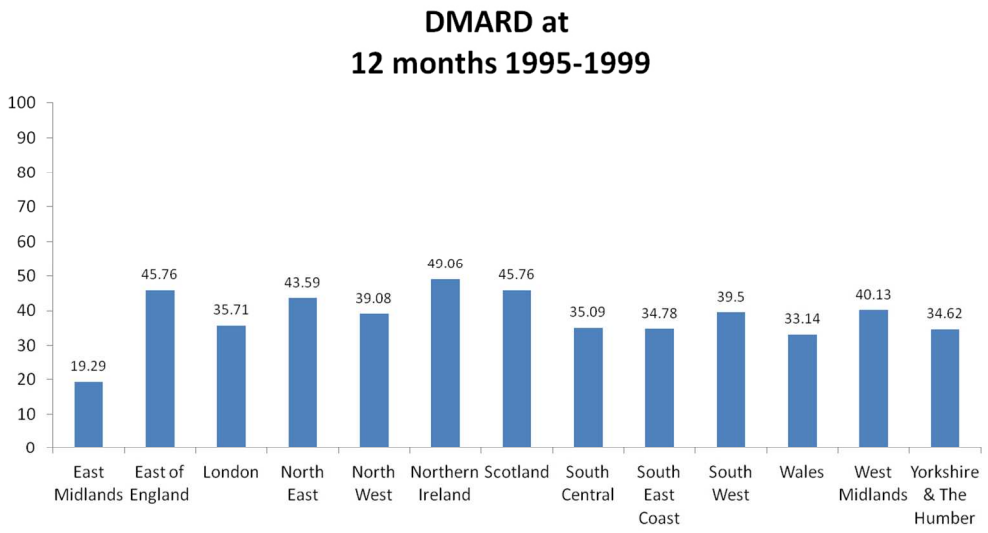

Figure 1a: Percentage of patients prescribed DMARDs at 12 months by region for the time period 1995–1999.
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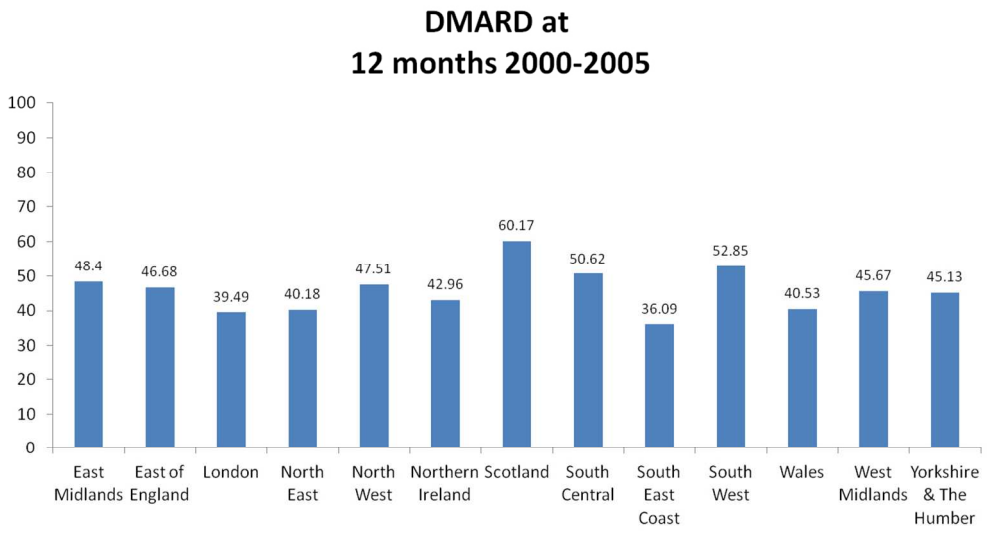

Figure 1b: Percentage of patients prescribed DMARDs at 12 months by region for the time period 2000–2005.
228x125mm (150 x 150 DPI)

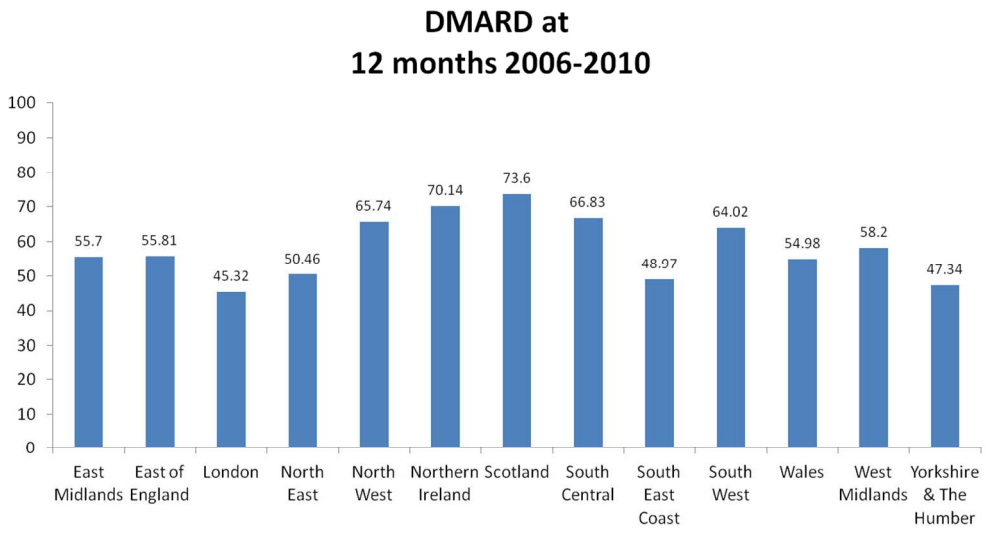

Figure 1c: Percentage of patients prescribed DMARDs at 12 months by region for the time period 2006–2010.
228x125mm (150 x 150 DPI)

Appendix 1

Each RA patient was matched by age, gender and practice to three patients without a record of inflammatory disease such as RA, juvenile arthritis, ankylosing spondylitis, enteropathic arthritis, reactive arthritis, inflammatory arthritis [seronegative], systemic lupus erythematosus [SLE], Sjogren's syndrome, mixed connective tissue disease [MCTD], polymyositis/dermatomyositis, scleroderma, polymyalgia rheumatica, giant cell arteritis, vasculitis [Wegeners], microscopic polyangiitis [MPA], Churg-strauss syndrome, polyarteritis nodosa [PAN], Takayasu arteritis, inflammatory bowel disease, sarcoidosis and psoriasis.

Appendix 2: Medications usage by region and by time period

Region	Time period	No. of patients diagnosed	No. of patients prescribed DMARD at 3 months (%)	No. of patients prescribed DMARD at 6 months (%)	No. of patients prescribed DMARD at 12 months (%)	No. of patients prescribed methotrexate at 3 months (%)	No. of patients prescribed methotrexate at 6 months (%)	No. of patients prescribed methotrexate at 12 months (%)	No. of patients prescribed combination DMARDs at 3 months (%)	No. of patients prescribed combination DMARDs at 6 months (%)	No. of patients prescribed combination DMARDs at 12 months (%)
East Midlands	1995_1999	197	22 (11.17%)	31 (15.74%)	38 (19.29%)	1 (0.51%)	2 (1.02%)	7 (3.55%)	. (.%)	. (.%)	. (.%)
	2000_2005	219	57 (26.03%)	84 (38.36%)	106 (48.40%)	20 (9.13%)	44 (20.09%)	58 (26.48%)	. (.%)	. (.%)	4 (1.83%)
	2006_April 2010	149	63 (42.28%)	75 (50.34%)	83 (55.70%)	27 (18.12%)	38 (25.50%)	49 (32.89%)	. (.%)	4 (2.68%)	7 (4.70%)
East of England	1995_1999	236	68 (28.81%)	92 (38.98%)	108 (45.76%)	18 (7.63%)	22 (9.32%)	31 (13.14%)	. (.%)	. (.%)	2 (0.85%)
	2000_2005	512	157 (30.66%)	204 (39.84%)	239 (46.68%)	64 (12.50%)	85 (16.60%)	113 (22.07%)	2 (0.39%)	2 (0.39%)	16 (3.13%)
	2006_April 2010	353	143 (40.51%)	178 (50.42%)	197 (55.81%)	86 (24.36%)	111 (31.44%)	129 (36.54%)	13 (3.68%)	16 (4.53%)	23 (6.52%)
London	1995_1999	154	33 (21.43%)	44 (28.57%)	55 (35.71%)	11 (7.14%)	14 (9.09%)	18 (11.69%)	1 (0.65%)	1 (0.65%)	1 (0.65%)
	2000_2005	314	80 (25.48%)	102 (32.48%)	124 (39.49%)	43 (13.69%)	60 (19.11%)	76 (24.20%)	1 (0.32%)	3 (0.96%)	7 (2.23%)
	2006_April 2010	331	91 (27.49%)	123 (37.16%)	150 (45.32%)	65 (19.64%)	91 (27.49%)	116 (35.05%)	9 (2.72%)	15 (4.53%)	26 (7.85%)
North East	1995_1999	39	9 (23.08%)	12 (30.77%)	17 (43.59%)	1 (2.56%)	2 (5.13%)	5 (12.82%)	. (.%)	. (.%)	. (.%)
	2000_2005	112	28 (25.00%)	41 (36.61%)	45 (40.18%)	6 (5.36%)	13 (11.61%)	18 (16.07%)	. (.%)	. (.%)	1 (0.89%)
	2006_April 2010	109	30 (27.52%)	43 (39.45%)	55 (50.46%)	17 (15.60%)	25 (22.94%)	35 (32.11%)	1 (0.92%)	1 (0.92%)	7 (6.42%)

Region	Time period	No. of patients diagnosed	No. of patients prescribed DMARD at 3 months (%)	No. of patients prescribed DMARD at 6 months (%)	No. of patients prescribed DMARD at 12 months (%)	No. of patients prescribed methotrexate at 3 months (%)	No. of patients prescribed methotrexate at 6 months (%)	No. of patients prescribed methotrexate at 12 months (%)	No. of patients prescribed combination DMARDs at 3 months (%)	No. of patients prescribed combination DMARDs at 6 months (%)	No. of patients prescribed combination DMARDs at 12 months (%)
North West	1995_1999	284	70 (24.65%)	96 (33.80%)	111 (39.08%)	21 (7.39%)	28 (9.86%)	34 (11.97%)	. (.%)	. (.%)	1 (0.35%)
	2000_2005	583	215 (36.88%)	253 (43.40%)	277 (47.51%)	85 (14.58%)	111 (19.04%)	135 (23.16%)	8 (1.37%)	11 (1.89%)	23 (3.95%)
	2006_April 2010	470	247 (52.55%)	286 (60.85%)	309 (65.74%)	151 (32.13%)	178 (37.87%)	201 (42.77%)	28 (5.96%)	44 (9.36%)	60 (12.77%)
Northern Ireland	1995_1999	53	22 (41.51%)	24 (45.28%)	26 (49.06%)	4 (7.55%)	5 (9.43%)	6 (11.32%)	1 (1.89%)	2 (3.77%)	4 (7.55%)
	2000_2005	135	42 (31.11%)	53 (39.26%)	58 (42.96%)	21 (15.56%)	28 (20.74%)	38 (28.15%)	1 (0.74%)	2 (1.48%)	5 (3.70%)
	2006_April 2010	144	84 (58.33%)	97 (67.36%)	101 (70.14%)	69 (47.92%)	80 (55.56%)	87 (60.42%)	6 (4.17%)	6 (4.17%)	9 (6.25%)
Scotland	1995_1999	59	22 (37.29%)	25 (42.37%)	27 (45.76%)	2 (3.39%)	4 (6.78%)	5 (8.47%)	. (.%)	. (.%)	. (.%)
	2000_2005	231	101 (43.72%)	126 (54.55%)	139 (60.17%)	16 (6.93%)	18 (7.79%)	30 (12.99%)	2 (0.87%)	3 (1.30%)	7 (3.03%)
	2006_April 2010	322	206 (63.98%)	228 (70.81%)	237 (73.60%)	75 (23.29%)	94 (29.19%)	112 (34.78%)	14 (4.35%)	22 (6.83%)	33 (10.25%)
South Central	1995_1999	114	32 (28.07%)	37 (32.46%)	40 (35.09%)	12 (10.53%)	13 (11.40%)	18 (15.79%)	. (.%)	1 (0.88%)	1 (0.88%)
	2000_2005	324	123 (37.96%)	145 (44.75%)	164 (50.62%)	69 (21.30%)	90 (27.78%)	111 (34.26%)	11 (3.40%)	18 (5.56%)	35 (10.80%)
	2006_April 2010	401	215 (53.62%)	253 (63.09%)	268 (66.83%)	163 (40.65%)	192 (47.88%)	207 (51.62%)	33 (8.23%)	52 (12.97%)	67 (16.71%)

Region	Time period	No. of patients diagnosed	No. of patients prescribed DMARD at 3 months (%)	No. of patients prescribed DMARD at 6 months (%)	No. of patients prescribed DMARD at 12 months (%)	No. of patients prescribed methotrexate at 3 months (%)	No. of patients prescribed methotrexate at 6 months (%)	No. of patients prescribed methotrexate at 12 months (%)	No. of patients prescribed combination DMARDs at 3 months (%)	No. of patients prescribed combination DMARDs at 6 months (%)	No. of patients prescribed combination DMARDs at 12 months (%)
South East Coast	1995_1999	115	20 (17.39%)	29 (25.22%)	40 (34.78%)	6 (5.22%)	10 (8.70%)	17 (14.78%)	. (.%)	. (.%)	. (.%)
	2000_2005	327	73 (22.32%)	96 (29.36%)	118 (36.09%)	48 (14.68%)	63 (19.27%)	83 (25.38%)	2 (0.61%)	2 (0.61%)	6 (1.83%)
	2006_April 2010	290	101 (34.83%)	130 (44.83%)	142 (48.97%)	72 (24.83%)	95 (32.76%)	104 (35.86%)	7 (2.41%)	9 (3.10%)	16 (5.52%)
South West	1995_1999	200	51 (25.50%)	66 (33.00%)	79 (39.50%)	13 (6.50%)	20 (10.00%)	26 (13.00%)	1 (0.50%)	1 (0.50%)	5 (2.50%)
	2000_2005	316	133 (42.09%)	149 (47.15%)	167 (52.85%)	55 (17.41%)	63 (19.94%)	90 (28.48%)	2 (0.63%)	2 (0.63%)	14 (4.43%)
	2006_April 2010	378	180 (47.62%)	212 (56.08%)	242 (64.02%)	110 (29.10%)	139 (36.77%)	164 (43.39%)	11 (2.91%)	21 (5.56%)	30 (7.94%)
Wales	1995_1999	169	46 (27.22%)	55 (32.54%)	56 (33.14%)	5 (2.96%)	12 (7.10%)	17 (10.06%)	. (.%)	. (.%)	1 (0.59%)
	2000_2005	338	92 (27.22%)	112 (33.14%)	137 (40.53%)	28 (8.28%)	42 (12.43%)	53 (15.68%)	. (.%)	1 (0.30%)	2 (0.59%)
	2006_April 2010	271	112 (41.33%)	136 (50.18%)	149 (54.98%)	69 (25.46%)	88 (32.47%)	105 (38.75%)	2 (0.74%)	4 (1.48%)	13 (4.80%)
West Midlands	1995_1999	152	40 (26.32%)	50 (32.89%)	61 (40.13%)	2 (1.32%)	5 (3.29%)	12 (7.89%)	. (.%)	2 (1.32%)	3 (1.97%)
	2000_2005	497	140 (28.17%)	201 (40.44%)	227 (45.67%)	43 (8.65%)	82 (16.50%)	102 (20.52%)	. (.%)	. (.%)	6 (1.21%)
	2006_April 2010	366	147 (40.16%)	185 (50.55%)	213 (58.20%)	89 (24.32%)	123 (33.61%)	146 (39.89%)	8 (2.19%)	15 (4.10%)	29 (7.92%)
Yorkshire & The Humber	1995_1999	156	33 (21.15%)	47 (30.13%)	54 (34.62%)	7 (4.49%)	12 (7.69%)	16 (10.26%)	. (.%)	. (.%)	. (.%)
	2000_2005	277	90 (32.49%)	107 (38.63%)	125 (45.13%)	37 (13.36%)	49 (17.69%)	67 (24.19%)	2 (0.72%)	7 (2.53%)	13 (4.69%)
	2006_April 2010	169	50 (29.59%)	65 (38.46%)	80 (47.34%)	33 (19.53%)	42 (24.85%)	58 (34.32%)	1 (0.59%)	2 (1.18%)	5 (2.96%)

Appendix 3: Baseline characteristics for the incident RA patients (N=15,259)

Characteristic	Incident RA Patients (N=15,259)	Matched Controls (N=45,777)	Crude Odds Ratio (95% CI)
Age 18–29 years	418 (2.7%)	1,254 (2.7%)	*
Age 30–39 years	1,139 (7.5%)	3,417 (7.5%)	*
Age 40–49 years	2,035 (13.3%)	6,105 (13.3%)	*
Age 50–59 years	3,387 (22.2%)	10,161 (22.2%)	*
Age 60–69 years	3,513 (23.0%)	10,539 (23.0%)	*
Age 70–79 years	3,136 (20.6%)	9,408 (20.6%)	*
Age 80+ years	1,631 (10.7%)	4,893 (10.7%)	*
Female gender (%)	10,565 (69.2%)	31,695 (69.2%)	*
Year of diagnosis: 1995	589 (3.9%)	1,767 (3.9%)	*
1996	563 (3.7%)	1,689 (3.7%)	*
1997	659 (4.3%)	1,977 (4.3%)	*
1998	709 (4.6%)	2,127 (4.6%)	*
1999	780 (5.1%)	2,340 (5.1%)	*
2000	981 (6.4%)	2,943 (6.4%)	*
2001	1,171 (7.7%)	3,513 (7.7%)	*
2002	1,321 (8.7%)	3,963 (8.7%)	*
2003	1,308 (8.6%)	3,924 (8.6%)	*
2004	1,306 (8.6%)	3,918 (8.6%)	*
2005	1,204 (7.9%)	3,612 (7.9%)	*
2006	1,195 (7.8%)	3,585 (7.8%)	*
2007	1,113 (7.3%)	3,339 (7.3%)	*
2008	1,068 (7.0%)	3,204 (7.0%)	*
2009	1,098 (7.2%)	3,294 (7.2%)	*
2010	194 (1.3%)	582 (1.3%)	*
Length of follow-up (mean, years)	5.2	4.9	*
Smoking status[1] Non smoker (%)	6,453 (42.3%)	22,052 (48.2%)	Reference
Ex smoker (%)	3,747 (24.6%)	9,230 (20.2%)	1.45 (1.38 - 1.53)
Smoker (%)	3,798 (24.9%)	8,862 (19.4%)	1.51 (1.43 - 1.58)
History of a presenting symptom (any)[2]	10,091 (66.1%)	15,015 (32.8%)	4.99 (4.77 - 5.22)
Joint pain (%)	9,275 (60.8%)	13,118 (28.7%)	4.73 (4.53 - 4.95)
Swollen tender joints (%)	1,587 (10.4%)	1,543 (3.4%)	3.53 (3.27 - 3.81)
Morning stiffness (%)	701 (4.6%)	465 (1.0%)	4.77 (4.22 - 5.38)
Previous prescribing of[3]:			
Steroid injections	704 (4.6%)	316 (0.7%)	7.30 (6.36 - 8.39)
Prednisolone	2,732 (17.9%)	990 (2.2%)	10.03 (9.26 - 10.86)
NSAIDs	10,698 (70.1%)	10,305 (22.5%)	8.95 (8.54 - 9.38)
Analgesics/ opioids	1,801 (11.8%)	1,275 (2.8%)	4.84 (4.48 - 5.23)
H2 antagonists and PPIs	3,971 (26.0%)	5,302 (11.6%)	2.89 (2.75 - 3.03)
Statins	1,847 (12.1%)	5,348 (11.7%)	1.05 (0.99 - 1.12)
Aspirin	1,975 (12.9%)	5,726 (12.5%)	1.05 (0.99 - 1.11)
Antihypertensives	4,581 (30.0%)	12,573 (27.5%)	1.16 (1.11 - 1.22)
Diabetic medications	745 (4.9%)	2,013 (4.4%)	1.12 (1.03 - 1.22)

*Patients were matched on this variable.

[1]Smoking status not known in 1,261 (8.3%) and 5,633 (12.3%) of RA patients and matched controls, respectively.

[2] Medical records were analysed in the 5 years before index date.

[3] Prescriptions were analysed in the six months before index date.

Appendix 4: Incidence rates and point prevalence of RA in the GPRD 2009

Region	Person years at risk (years)	Incident RA cases 2009	Incidence rate per 100,000 persons (30/06/09)	GPRD Population 2009	RA Cases 2009	Point Prevalence per 100,000 persons (30/06/09)
North East	85016.28	34	0.400	84831	491	5.788
North West	534355.5	146	0.273	544693	2,930	5.379
Yorkshire & The Humber	123289.3	34	0.276	123910	770	6.214
East Midlands	123771.1	31	0.250	130367	781	5.991
West Midlands	363201.7	111	0.306	374308	2,074	5.541
East of England	377678	96	0.254	389617	2,041	5.238
South West	349426.3	125	0.358	354863	1,918	5.405
South Central	474538	106	0.223	483299	2,250	4.656
London	514153.7	113	0.220	519717	1,877	3.612
South East Coast	381501.3	89	0.233	387344	1,718	4.435
Northern Ireland	121126.8	35	0.289	124176	725	5.838
Scotland	339703.9	97	0.286	343287	1,676	4.882
Wales	331040.5	81	0.245	338133	1,787	5.285

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Done – page 1 and 2 of PDF proof**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Done – page 2 of PDF proof**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Done – page 3 of PDF proof**
Objectives	3	State specific objectives, including any prespecified hypotheses **Done – page 3 of PDF proof**
Methods		
Study design	4	Present key elements of study design early in the paper **Done – page 4 of PDF proof**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Done – page 4 of PDF proof**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Done – page 4 of PDF proof**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **Done – page 4 of PDF proof**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Done – page 4 of PDF proof**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Done – page 4 of PDF proof**
Bias	9	Describe any efforts to address potential sources of bias **Done – page 8, 23 and 24 of PDF**
Study size	10	Explain how the study size was arrived at **(Not applicable – this is a descriptive study without definition of any a-priori hypothesis)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(Not applicable)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **(Not applicable)**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed

		Done – page 5 and 23 of PDF proof
		(b) Give reasons for non-participation at each stage **(Not applicable)**
		(c) Consider use of a flow diagram **(Not applicable)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Done – page 5 and 23 of PDF proof**
		(b) Indicate number of participants with missing data for each variable of interest **(Not applicable)**
		(c) Summarise follow-up time (eg, average and total amount) **Done – page 4 of PDF proof**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Done – page 5 and 6 of PDF proof**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **(Not applicable)**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **(Not applicable)**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Done – pages 6, 7 and 8 of PDF proof**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Done – pages 8 and 9 of PDF proof**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Done – pages 6–10 of PDF proof**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Done – pages 6–10 of PDF proof**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Done – page 11 of PDF proof**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

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

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2012-001603.R2
Article Type:	Research
Date Submitted by the Author:	11-Sep-2012
Complete List of Authors:	Edwards, Christopher; University Hospital Southampton NHS Foundation Trust, Rheumatology Campbell, Jennifer; General Practice Research Database, Medicines and Healthcare products Regulatory Agency, van Staa, Tjeerd; General Practice Research Database, Medicines and Healthcare products Regulatory Agency, ; Utrecht Institute for Pharmaceutical Sciences, Arden, Nigel; Nuffield Department of Orthopaedics,
Primary Subject Heading:	Rheumatology
Secondary Subject Heading:	General practice / Family practice, Pharmacology and therapeutics
Keywords:	Rheumatology < INTERNAL MEDICINE, PRIMARY CARE, RHEUMATOLOGY

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

Authors

Christopher J Edwards *consultant rheumatologist*[1,2], Jennifer Campbell *research scientist*[3], Tjeerd Van Staa *head of research*[3,4], Nigel K Arden *professor of rheumatology*[2,5].

[1]Department of Rheumatology, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, SO16 6YD; [2]University of Southampton, Southampton, United Kingdom SO16 6YD; [3]General Practice Research Database, Medicines and Healthcare products Regulatory Agency, London, United Kingdom SW1W 9SZ; [4]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; [5]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, United Kingdom OX3 7HE.

Correspondence to: Christopher J Edwards cedwards@soton.ac.uk

Abstract

Objectives: To describe current DMARD 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 01/01/1995 and 31/03/2010 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 one 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 under-treatment, 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.

Key words: *Rheumatoid arthritis, DMARDs, General Practice Research Database, regional variation.*

Article summary

Article focus:

- Over recent years there have been fundamental changes in the approach to treatment of rheumatoid arthritis (RA) with a move towards early and more aggressive treatment
- Disease-modifying anti-rheumatic 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 under-treated 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 was 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 health-care costs [2]. A recent report from the National Audit Office (NAO) 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 anti-rheumatic 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, 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 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 5 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 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 general practitioner 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 computerized 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 level.

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 01/01/1995 and 31/03/2010. 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 01/01/1995 (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 one 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 (i.e. index date) to the date of censoring (i.e. 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 (i.e., prevalent cases) and also RA patients with a first-ever record of RA at least 1 year after start of GPRD data collection (i.e. 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 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;

sulfasalazine; 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 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 9-fold increase in prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) in the 6 months prior to diagnosis.

Prescription practice by region and time period for incident patients

General trends

The data was 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 months 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 was 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) to 73.6% (Scotland). A general trend for increased prescription of DMARDs/methotrexate between 3–12 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–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 19.29–49.06% between 1995–1999; from 36.09–60.17% between 2000–2005; and from 45.32–73.6% between 2006–April 2010. The regional difference in the proportion of patients prescribed DMARD at 12 months ranged from 24–30% 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 five years was analysed to evaluate time from diagnosis to treatment with either DMARD and/or methotrexate. For 5,513 patients prescribed a DMARD, the median time from diagnosis to treatment was 50 days (interquartile range [IQR] 0–1,826); for 3,754 patients prescribed methotrexate, the median time from diagnosis to treatment was 119 days (IQR 0–1,826); while for 1,310 patients prescribed combination DMARD the median time from diagnosis to treatment was 560 days (IQR 0–1,826).

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 ten-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 under-treatment 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.

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, 15, 16, 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–April 2010 for regions in England (i.e. excluding Wales, Scotland and Northern Ireland), the proportion of RA patients receiving DMARDs at 12 months between 2006–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 NHS 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 emphasize 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 1,133 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 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 management of RA persists after almost two 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 publication of American College of Rheumatology (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 was 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 (BPI) / IMS Hospital Pharmacy Index (HPA) 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 (PCTs) 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 1995–2010 with increasing use of DMARDs which currently represent best clinical practice. Despite this improvement, RA remains under-treated 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.

Acknowledgements We thank Claire Housden and Kirsty Roberts (Roche Products Ltd) for procuring project funding and Ify Sargeant (ismedica Ltd) for medical writing support, funded by Roche Products Ltd.

Contributors: CJE, NKA, TvS and JC made primary contributions to study design, data collection, data analysis, interpretation of results, and writing the manuscript. All authors contributed to the interpretation of results and critical revision of the manuscript and approved the final manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. CJE is the guarantor.

Funding: This work was supported by Roche-Chugai who funded data generation and analysis by GPRD. Funding sources had no influence on the study design, interpretation of results, or decision to submit the article.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: financial support for the submitted work from Roche-Chugai; CJE has acted as speaker for and received research funding from Roche, UCB, Abbott, GSK and Pfizer; NKA has acted as speaker for and received research funding from Roche, Merck, Q-Med, NICOX, Flexion, Servier, GSK, Amgen and Lilley; GPRD (JC and TvS) has received funding from the MHRA, Wellcome Trust, Medical Research Council, NIHR Health Technology Assessment programme, Innovative Medicine Initiative, UK Department of Health, Technology Strategy Board, Seventh Framework Programme EU, various universities, contract research organisations and pharmaceutical companies. The department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (TvS) has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private-public funded Top Institute Pharma (www.tipharma.nl, includes co-funding from universities, government, and industry), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethical approval was not required

Data sharing: No additional data available.

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Table 1: *Proportion of patients prescribed DMARDs within 12 months vs. number diagnosed according to time period across all regions.*

Time period	No. of patients diagnosed with RA	No. of patients prescribed DMARD (%)	No. of patients prescribed methotrexate (%)	No. 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%

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

Authors

Christopher J Edwards *consultant rheumatologist*[1,2], Jennifer Campbell *research scientist*[3], Tjeerd Van Staa *head of research*[3,4], Nigel K Arden *professor of rheumatology*[2,5].

[1]Department of Rheumatology, University Hospital Southampton NHS Foundation Trust, Southampton, United Kingdom, SO16 6YD; [2]University of Southampton, Southampton, United Kingdom SO16 6YD; [3]General Practice Research Database, Medicines and Healthcare products Regulatory Agency, London, United Kingdom SW1W 9SZ; [4]Utrecht Institute for Pharmaceutical Sciences, Utrecht University, Utrecht, the Netherlands; [5]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal Sciences, University of Oxford, United Kingdom OX3 7HE.

Correspondence to: Christopher J Edwards cedwards@soton.ac.uk

Abstract

Objectives: To describe current DMARD 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 01/01/1995 and 31/03/2010 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 one 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 under-treatment, according to established best practice ~~and published national guidelines~~. 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.

Key words: *Rheumatoid arthritis, DMARDs, General Practice Research Database, regional variation.*

Article summary

Article focus:

- Over recent years there have been fundamental changes in the approach to treatment of rheumatoid arthritis (RA) with a move towards early and more aggressive treatment
- Disease-modifying anti-rheumatic 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 under-treated 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 was 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 health-care costs [2]. A recent report from the National Audit Office (NAO) 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 anti-rheumatic 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, 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 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 [~~12~~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 5 million currently active [~~12, 13~~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~~13~~]. All patients in the UK will be seen by a primary care physician or general practitioner 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 general practitioner the validation studies described show that a rheumatologist in secondary care will also have seen the vast majority of individuals [~~13~~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 computerized 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 level.

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 01/01/1995 and 31/03/2010. 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 01/01/1995 (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 one day of follow-up (n=35,911). We used the same Read codes as in the previous RA validation study [~~13~~12].

The period of follow-up was from the date of first RA record up (i.e. index date) to the date of censoring (i.e. 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 (i.e., prevalent cases) and also RA patients with a first-ever record of RA at least 1 year after start of GPRD data collection (i.e. 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 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;

sulfasalazine; 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 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 9-fold increase in prescribing of non-steroidal anti-inflammatory drugs (NSAIDs) in the 6 months prior to diagnosis.

Prescription practice by region and time period for incident patients

General trends

The data was 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 months 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 was 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) to 73.6% (Scotland). A general trend for increased prescription of DMARDs/methotrexate between 3–12 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–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 ~~2~~1). Regional variation in DMARD prescribing at 12 months ranged from 19.29–49.06% between 1995–1999; from 36.09–60.17% between 2000–2005; and from 45.32–73.6% between 2006–April 2010. The regional difference in the proportion of patients prescribed DMARD at 12 months ranged from 24–30% 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 five years was analysed to evaluate time from diagnosis to treatment with either DMARD and/or methotrexate. For 5,513 patients prescribed a DMARD, the median time from diagnosis to treatment was 50 days (interquartile range [IQR] 0–1,826); for 3,754 patients prescribed methotrexate, the median time from diagnosis to treatment was 119 days (IQR 0–1,826); while for 1,310 patients prescribed combination DMARD the median time from diagnosis to treatment was 560 days (IQR 0–1,826).

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 ten-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 under-treatment 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.

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 [~~16, 17, 18, 19~~14, 15, 16, 17]. However previous studies indicate that many patients receive insufficient treatment [~~20~~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–April 2010 for regions in England (i.e. excluding Wales, Scotland and Northern Ireland), the proportion of RA patients receiving DMARDs at 12 months between 2006–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 NHS 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 emphasize the importance of early and appropriate intervention in RA to optimise patient outcomes [10, ~~21~~19]. A meta-analysis assessing the long-term impact of early treatment on radiographic progression in RA which included 1,133 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 [~~22~~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 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, ~~23~~21] however, the results from our study demonstrate that RA is often suboptimally treated and that regional variation in the management of RA persists after almost two 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. ~~post-NICE recommendations, these appear to reflect a general upward trend rather than rapid implementation and uptake of NICE guidelines. However, it is too early for us to conclude with any accuracy whether the NICE guidance is influencing 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 publication of American College of Rheumatology (ACR) treatment recommendations indicates that at best only around 50% of RA patients with active disease receive care consistent with the current recommendations [~~25~~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 was obtained. The GPRD is representative of patients and practices throughout the UK [~~14~~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 [~~13~~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 [~~14~~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 (BPI) / IMS Hospital Pharmacy Index (HPA) 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 [~~15~~24]. We have recently performed a survey of primary care trust (PCTs) 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 1995–2010 with increasing use of DMARDs which currently represent best clinical practice. Despite this improvement, RA remains under-treated according to clinical recommendations and guidelines in the UK [10] and elsewhere [~~24~~25]. In addition regional variation in DMARD and methotrexate prescribing persists across the UK ~~and publication of national clinical guidelines does not appear to have had a marked impact on standardising prescribing behaviour~~.

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.

Acknowledgements We thank Claire Housden and Kirsty Roberts (Roche Products Ltd) for procuring project funding and Ify Sargeant (ismedica Ltd) for medical writing support, funded by Roche Products Ltd.

Contributors: CJE, NKA, TvS and JC made primary contributions to study design, data collection, data analysis, interpretation of results, and writing the manuscript. All authors contributed to the interpretation of results and critical revision of the manuscript and approved the final manuscript. All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. CJE is the guarantor.

Funding: This work was supported by Roche-Chugai who funded data generation and analysis by GPRD. Funding sources had no influence on the study design, interpretation of results, or decision to submit the article.

Competing interests: All authors have completed the Unified Competing Interest form at www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: financial support for the submitted work from Roche-Chugai; CJE has acted as speaker for and received research funding from Roche, UCB, Abbott, GSK and Pfizer; NKA has acted as speaker for and received research funding from Roche, Merck, Q-Med, NICOX, Flexion, Servier, GSK, Amgen and Lilley; GPRD (JC and TvS) has received funding from the MHRA, Wellcome Trust, Medical Research Council, NIHR Health Technology Assessment programme, Innovative Medicine Initiative, UK Department of Health, Technology Strategy Board, Seventh Framework Programme EU, various universities, contract research organisations and pharmaceutical companies. The department of Pharmacoepidemiology & Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (TvS) has received unrestricted funding for pharmacoepidemiological research from GlaxoSmithKline, Novo Nordisk, the private-public funded Top Institute Pharma (www.tipharma.nl, includes co-funding from universities, government, and industry), the Dutch Medicines Evaluation Board, and the Dutch Ministry of Health; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Ethical approval was not required

Data sharing: No additional data available.

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Table 1: *Proportion of patients prescribed DMARDs within 12 months vs. number diagnosed according to time period across all regions.*

Time period	No. of patients diagnosed with RA	No. of patients prescribed DMARD (%)	No. of patients prescribed methotrexate (%)	No. 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%

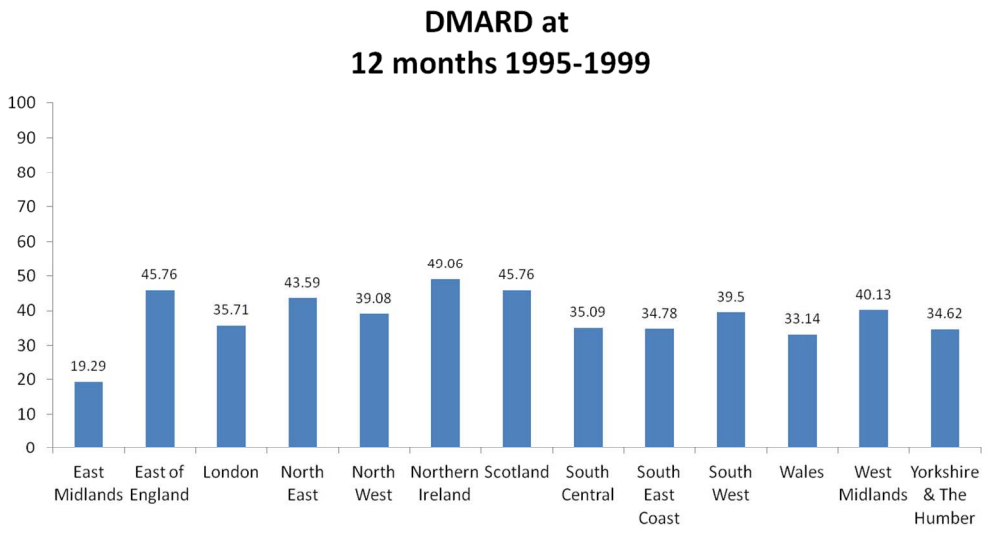

Figure 1a: Percentage of patients prescribed DMARDs at 12 months by region for the time period 1995–1999.
228x125mm (150 x 150 DPI)

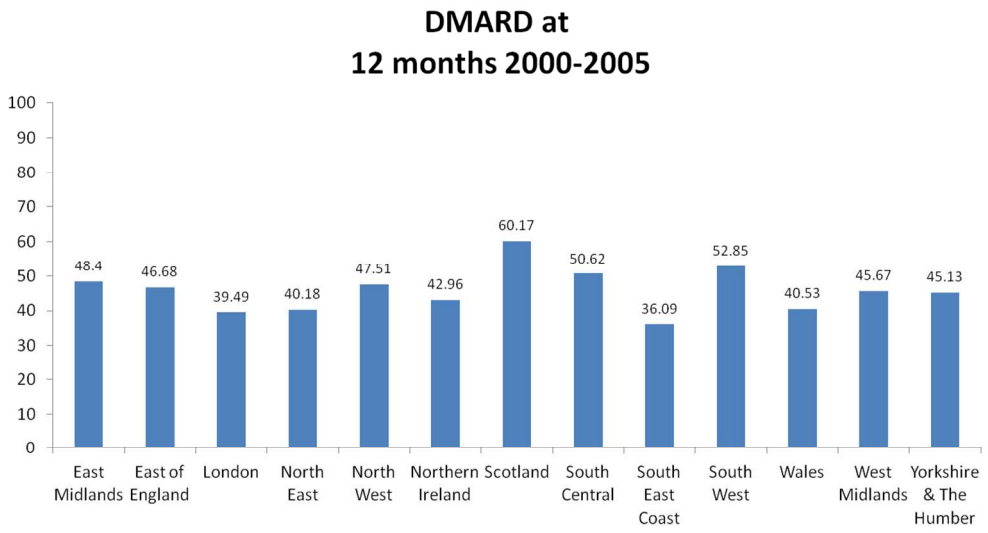

Figure 1b: Percentage of patients prescribed DMARDs at 12 months by region for the time period 2000–2005.
228x125mm (150 x 150 DPI)

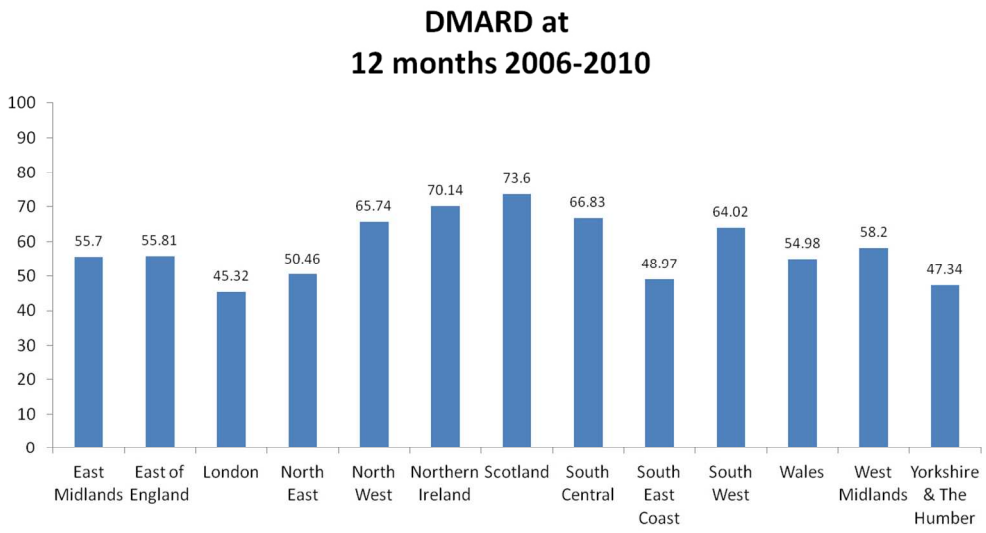

Figure 1c: Percentage of patients prescribed DMARDs at 12 months by region for the time period 2006–2010.
228x125mm (150 x 150 DPI)

Appendix 1

Each RA patient was matched by age, gender and practice to three patients without a record of inflammatory disease such as RA, juvenile arthritis, ankylosing spondylitis, enteropathic arthritis, reactive arthritis, inflammatory arthritis [seronegative], systemic lupus erythematosus [SLE], Sjogren's syndrome, mixed connective tissue disease [MCTD], polymyositis/dermatomyositis, scleroderma, polymyalgia rheumatica, giant cell arteritis, vasculitis [Wegeners], microscopic polyangiitis [MPA], Churg-strauss syndrome, polyarteritis nodosa [PAN], Takayasu arteritis, inflammatory bowel disease, sarcoidosis and psoriasis.

Appendix 2: Medications usage by region and by time period

Region	Time period	No. of patients diagnosed	No. of patients prescribed DMARD at 3 months (%)	No. of patients prescribed DMARD at 6 months (%)	No. of patients prescribed DMARD at 12 months (%)	No. of patients prescribed methotrexate at 3 months (%)	No. of patients prescribed methotrexate at 6 months (%)	No. of patients prescribed methotrexate at 12 months (%)	No. of patients prescribed combination DMARDs at 3 months (%)	No. of patients prescribed combination DMARDs at 6 months (%)	No. of patients prescribed combination DMARDs at 12 months (%)
East Midlands	1995_1999	197	22 (11.17%)	31 (15.74%)	38 (19.29%)	1 (0.51%)	2 (1.02%)	7 (3.55%)	. (.%)	. (.%)	. (.%)
	2000_2005	219	57 (26.03%)	84 (38.36%)	106 (48.40%)	20 (9.13%)	44 (20.09%)	58 (26.48%)	. (.%)	. (.%)	4 (1.83%)
	2006_April 2010	149	63 (42.28%)	75 (50.34%)	83 (55.70%)	27 (18.12%)	38 (25.50%)	49 (32.89%)	. (.%)	4 (2.68%)	7 (4.70%)
East of England	1995_1999	236	68 (28.81%)	92 (38.98%)	108 (45.76%)	18 (7.63%)	22 (9.32%)	31 (13.14%)	. (.%)	. (.%)	2 (0.85%)
	2000_2005	512	157 (30.66%)	204 (39.84%)	239 (46.68%)	64 (12.50%)	85 (16.60%)	113 (22.07%)	2 (0.39%)	2 (0.39%)	16 (3.13%)
	2006_April 2010	353	143 (40.51%)	178 (50.42%)	197 (55.81%)	86 (24.36%)	111 (31.44%)	129 (36.54%)	13 (3.68%)	16 (4.53%)	23 (6.52%)
London	1995_1999	154	33 (21.43%)	44 (28.57%)	55 (35.71%)	11 (7.14%)	14 (9.09%)	18 (11.69%)	1 (0.65%)	1 (0.65%)	1 (0.65%)
	2000_2005	314	80 (25.48%)	102 (32.48%)	124 (39.49%)	43 (13.69%)	60 (19.11%)	76 (24.20%)	1 (0.32%)	3 (0.96%)	7 (2.23%)
	2006_April 2010	331	91 (27.49%)	123 (37.16%)	150 (45.32%)	65 (19.64%)	91 (27.49%)	116 (35.05%)	9 (2.72%)	15 (4.53%)	26 (7.85%)
North East	1995_1999	39	9 (23.08%)	12 (30.77%)	17 (43.59%)	1 (2.56%)	2 (5.13%)	5 (12.82%)	. (.%)	. (.%)	. (.%)
	2000_2005	112	28 (25.00%)	41 (36.61%)	45 (40.18%)	6 (5.36%)	13 (11.61%)	18 (16.07%)	. (.%)	. (.%)	1 (0.89%)
	2006_April 2010	109	30 (27.52%)	43 (39.45%)	55 (50.46%)	17 (15.60%)	25 (22.94%)	35 (32.11%)	1 (0.92%)	1 (0.92%)	7 (6.42%)

Region	Time period	No. of patients diagnosed	No. of patients prescribed DMARD at 3 months (%)	No. of patients prescribed DMARD at 6 months (%)	No. of patients prescribed DMARD at 12 months (%)	No. of patients prescribed methotrexate at 3 months (%)	No. of patients prescribed methotrexate at 6 months (%)	No. of patients prescribed methotrexate at 12 months (%)	No. of patients prescribed combination DMARDs at 3 months (%)	No. of patients prescribed combination DMARDs at 6 months (%)	No. of patients prescribed combination DMARDs at 12 months (%)
North West	1995_1999	284	70 (24.65%)	96 (33.80%)	111 (39.08%)	21 (7.39%)	28 (9.86%)	34 (11.97%)	. (.%)	. (.%)	1 (0.35%)
	2000_2005	583	215 (36.88%)	253 (43.40%)	277 (47.51%)	85 (14.58%)	111 (19.04%)	135 (23.16%)	8 (1.37%)	11 (1.89%)	23 (3.95%)
	2006_April 2010	470	247 (52.55%)	286 (60.85%)	309 (65.74%)	151 (32.13%)	178 (37.87%)	201 (42.77%)	28 (5.96%)	44 (9.36%)	60 (12.77%)
Northern Ireland	1995_1999	53	22 (41.51%)	24 (45.28%)	26 (49.06%)	4 (7.55%)	5 (9.43%)	6 (11.32%)	1 (1.89%)	2 (3.77%)	4 (7.55%)
	2000_2005	135	42 (31.11%)	53 (39.26%)	58 (42.96%)	21 (15.56%)	28 (20.74%)	38 (28.15%)	1 (0.74%)	2 (1.48%)	5 (3.70%)
	2006_April 2010	144	84 (58.33%)	97 (67.36%)	101 (70.14%)	69 (47.92%)	80 (55.56%)	87 (60.42%)	6 (4.17%)	6 (4.17%)	9 (6.25%)
Scotland	1995_1999	59	22 (37.29%)	25 (42.37%)	27 (45.76%)	2 (3.39%)	4 (6.78%)	5 (8.47%)	. (.%)	. (.%)	. (.%)
	2000_2005	231	101 (43.72%)	126 (54.55%)	139 (60.17%)	16 (6.93%)	18 (7.79%)	30 (12.99%)	2 (0.87%)	3 (1.30%)	7 (3.03%)
	2006_April 2010	322	206 (63.98%)	228 (70.81%)	237 (73.60%)	75 (23.29%)	94 (29.19%)	112 (34.78%)	14 (4.35%)	22 (6.83%)	33 (10.25%)
South Central	1995_1999	114	32 (28.07%)	37 (32.46%)	40 (35.09%)	12 (10.53%)	13 (11.40%)	18 (15.79%)	. (.%)	1 (0.88%)	1 (0.88%)
	2000_2005	324	123 (37.96%)	145 (44.75%)	164 (50.62%)	69 (21.30%)	90 (27.78%)	111 (34.26%)	11 (3.40%)	18 (5.56%)	35 (10.80%)
	2006_April 2010	401	215 (53.62%)	253 (63.09%)	268 (66.83%)	163 (40.65%)	192 (47.88%)	207 (51.62%)	33 (8.23%)	52 (12.97%)	67 (16.71%)

Region	Time period	No. of patients diagnosed	No. of patients prescribed DMARD at 3 months (%)	No. of patients prescribed DMARD at 6 months (%)	No. of patients prescribed DMARD at 12 months (%)	No. of patients prescribed methotrexate at 3 months (%)	No. of patients prescribed methotrexate at 6 months (%)	No. of patients prescribed methotrexate at 12 months (%)	No. of patients prescribed combination DMARDs at 3 months (%)	No. of patients prescribed combination DMARDs at 6 months (%)	No. of patients prescribed combination DMARDs at 12 months (%)
South East Coast	1995_1999	115	20 (17.39%)	29 (25.22%)	40 (34.78%)	6 (5.22%)	10 (8.70%)	17 (14.78%)	. (.%)	. (.%)	. (.%)
	2000_2005	327	73 (22.32%)	96 (29.36%)	118 (36.09%)	48 (14.68%)	63 (19.27%)	83 (25.38%)	2 (0.61%)	2 (0.61%)	6 (1.83%)
	2006_April 2010	290	101 (34.83%)	130 (44.83%)	142 (48.97%)	72 (24.83%)	95 (32.76%)	104 (35.86%)	7 (2.41%)	9 (3.10%)	16 (5.52%)
South West	1995_1999	200	51 (25.50%)	66 (33.00%)	79 (39.50%)	13 (6.50%)	20 (10.00%)	26 (13.00%)	1 (0.50%)	1 (0.50%)	5 (2.50%)
	2000_2005	316	133 (42.09%)	149 (47.15%)	167 (52.85%)	55 (17.41%)	63 (19.94%)	90 (28.48%)	2 (0.63%)	2 (0.63%)	14 (4.43%)
	2006_April 2010	378	180 (47.62%)	212 (56.08%)	242 (64.02%)	110 (29.10%)	139 (36.77%)	164 (43.39%)	11 (2.91%)	21 (5.56%)	30 (7.94%)
Wales	1995_1999	169	46 (27.22%)	55 (32.54%)	56 (33.14%)	5 (2.96%)	12 (7.10%)	17 (10.06%)	. (.%)	. (.%)	1 (0.59%)
	2000_2005	338	92 (27.22%)	112 (33.14%)	137 (40.53%)	28 (8.28%)	42 (12.43%)	53 (15.68%)	. (.%)	1 (0.30%)	2 (0.59%)
	2006_April 2010	271	112 (41.33%)	136 (50.18%)	149 (54.98%)	69 (25.46%)	88 (32.47%)	105 (38.75%)	2 (0.74%)	4 (1.48%)	13 (4.80%)
West Midlands	1995_1999	152	40 (26.32%)	50 (32.89%)	61 (40.13%)	2 (1.32%)	5 (3.29%)	12 (7.89%)	. (.%)	2 (1.32%)	3 (1.97%)
	2000_2005	497	140 (28.17%)	201 (40.44%)	227 (45.67%)	43 (8.65%)	82 (16.50%)	102 (20.52%)	. (.%)	. (.%)	6 (1.21%)
	2006_April 2010	366	147 (40.16%)	185 (50.55%)	213 (58.20%)	89 (24.32%)	123 (33.61%)	146 (39.89%)	8 (2.19%)	15 (4.10%)	29 (7.92%)
Yorkshire & The Humber	1995_1999	156	33 (21.15%)	47 (30.13%)	54 (34.62%)	7 (4.49%)	12 (7.69%)	16 (10.26%)	. (.%)	. (.%)	. (.%)
	2000_2005	277	90 (32.49%)	107 (38.63%)	125 (45.13%)	37 (13.36%)	49 (17.69%)	67 (24.19%)	2 (0.72%)	7 (2.53%)	13 (4.69%)
	2006_April 2010	169	50 (29.59%)	65 (38.46%)	80 (47.34%)	33 (19.53%)	42 (24.85%)	58 (34.32%)	1 (0.59%)	2 (1.18%)	5 (2.96%)

Appendix 3: Baseline characteristics for the incident RA patients (N=15,259)

Characteristic	Incident RA Patients (N=15,259)	Matched Controls (N=45,777)	Crude Odds Ratio (95% CI)
Age 18–29 years	418 (2.7%)	1,254 (2.7%)	*
Age 30–39 years	1,139 (7.5%)	3,417 (7.5%)	*
Age 40–49 years	2,035 (13.3%)	6,105 (13.3%)	*
Age 50–59 years	3,387 (22.2%)	10,161 (22.2%)	*
Age 60–69 years	3,513 (23.0%)	10,539 (23.0%)	*
Age 70–79 years	3,136 (20.6%)	9,408 (20.6%)	*
Age 80+ years	1,631 (10.7%)	4,893 (10.7%)	*
Female gender (%)	10,565 (69.2%)	31,695 (69.2%)	*
Year of diagnosis: 1995	589 (3.9%)	1,767 (3.9%)	*
1996	563 (3.7%)	1,689 (3.7%)	*
1997	659 (4.3%)	1,977 (4.3%)	*
1998	709 (4.6%)	2,127 (4.6%)	*
1999	780 (5.1%)	2,340 (5.1%)	*
2000	981 (6.4%)	2,943 (6.4%)	*
2001	1,171 (7.7%)	3,513 (7.7%)	*
2002	1,321 (8.7%)	3,963 (8.7%)	*
2003	1,308 (8.6%)	3,924 (8.6%)	*
2004	1,306 (8.6%)	3,918 (8.6%)	*
2005	1,204 (7.9%)	3,612 (7.9%)	*
2006	1,195 (7.8%)	3,585 (7.8%)	*
2007	1,113 (7.3%)	3,339 (7.3%)	*
2008	1,068 (7.0%)	3,204 (7.0%)	*
2009	1,098 (7.2%)	3,294 (7.2%)	*
2010	194 (1.3%)	582 (1.3%)	*
Length of follow-up (mean, years)	5.2	4.9	*
Smoking status[1] Non smoker (%)	6,453 (42.3%)	22,052 (48.2%)	Reference
Ex smoker (%)	3,747 (24.6%)	9,230 (20.2%)	1.45 (1.38 - 1.53)
Smoker (%)	3,798 (24.9%)	8,862 (19.4%)	1.51 (1.43 - 1.58)
History of a presenting symptom (any)[2]	10,091 (66.1%)	15,015 (32.8%)	4.99 (4.77 - 5.22)
Joint pain (%)	9,275 (60.8%)	13,118 (28.7%)	4.73 (4.53 - 4.95)
Swollen tender joints (%)	1,587 (10.4%)	1,543 (3.4%)	3.53 (3.27 - 3.81)
Morning stiffness (%)	701 (4.6%)	465 (1.0%)	4.77 (4.22 - 5.38)
Previous prescribing of[3]:			
Steroid injections	704 (4.6%)	316 (0.7%)	7.30 (6.36 - 8.39)
Prednisolone	2,732 (17.9%)	990 (2.2%)	10.03 (9.26 - 10.86)
NSAIDs	10,698 (70.1%)	10,305 (22.5%)	8.95 (8.54 - 9.38)
Analgesics/ opioids	1,801 (11.8%)	1,275 (2.8%)	4.84 (4.48 - 5.23)
H2 antagonists and PPIs	3,971 (26.0%)	5,302 (11.6%)	2.89 (2.75 - 3.03)
Statins	1,847 (12.1%)	5,348 (11.7%)	1.05 (0.99 - 1.12)
Aspirin	1,975 (12.9%)	5,726 (12.5%)	1.05 (0.99 - 1.11)
Antihypertensives	4,581 (30.0%)	12,573 (27.5%)	1.16 (1.11 - 1.22)
Diabetic medications	745 (4.9%)	2,013 (4.4%)	1.12 (1.03 - 1.22)

*Patients were matched on this variable.

[1]Smoking status not known in 1,261 (8.3%) and 5,633 (12.3%) of RA patients and matched controls, respectively.

[2] Medical records were analysed in the 5 years before index date.

[3] Prescriptions were analysed in the six months before index date.

Appendix 4: Incidence rates and point prevalence of RA in the GPRD 2009

Region	Person years at risk (years)	Incident RA cases 2009	Incidence rate per 100,000 persons (30/06/09)	GPRD Population 2009	RA Cases 2009	Point Prevalence per 100,000 persons (30/06/09)
North East	85016.28	34	0.400	84831	491	5.788
North West	534355.5	146	0.273	544693	2,930	5.379
Yorkshire & The Humber	123289.3	34	0.276	123910	770	6.214
East Midlands	123771.1	31	0.250	130367	781	5.991
West Midlands	363201.7	111	0.306	374308	2,074	5.541
East of England	377678	96	0.254	389617	2,041	5.238
South West	349426.3	125	0.358	354863	1,918	5.405
South Central	474538	106	0.223	483299	2,250	4.656
London	514153.7	113	0.220	519717	1,877	3.612
South East Coast	381501.3	89	0.233	387344	1,718	4.435
Northern Ireland	121126.8	35	0.289	124176	725	5.838
Scotland	339703.9	97	0.286	343287	1,676	4.882
Wales	331040.5	81	0.245	338133	1,787	5.285

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Done – page 1 and 2 of PDF proof**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Done – page 2 of PDF proof**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Done – page 3 of PDF proof**
Objectives	3	State specific objectives, including any prespecified hypotheses **Done – page 3 of PDF proof**
Methods		
Study design	4	Present key elements of study design early in the paper **Done – page 4 of PDF proof**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **Done – page 4 of PDF proof**
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **Done – page 4 of PDF proof**
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed **Done – page 4 of PDF proof**
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable **Done – page 4 of PDF proof**
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group **Done – page 4 of PDF proof**
Bias	9	Describe any efforts to address potential sources of bias **Done – page 8, 23 and 24 of PDF**
Study size	10	Explain how the study size was arrived at **(Not applicable – this is a descriptive study without definition of any a-priori hypothesis)**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **(Not applicable)**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding
		(*b*) Describe any methods used to examine subgroups and interactions
		(*c*) Explain how missing data were addressed
		(*d*) If applicable, explain how loss to follow-up was addressed
		(*e*) Describe any sensitivity analyses **(Not applicable)**
Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed

		Done – page 5 and 23 of PDF proof
		(b) Give reasons for non-participation at each stage **(Not applicable)**
		(c) Consider use of a flow diagram **(Not applicable)**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Done – page 5 and 23 of PDF proof**
		(b) Indicate number of participants with missing data for each variable of interest **(Not applicable)**
		(c) Summarise follow-up time (eg, average and total amount) **Done – page 4 of PDF proof**
Outcome data	15*	Report numbers of outcome events or summary measures over time **Done – page 5 and 6 of PDF proof**
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included
		(*b*) Report category boundaries when continuous variables were categorized
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **(Not applicable)**
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **(Not applicable)**
Discussion		
Key results	18	Summarise key results with reference to study objectives **Done – pages 6, 7 and 8 of PDF proof**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Done – pages 8 and 9 of PDF proof**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Done – pages 6–10 of PDF proof**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Done – pages 6–10 of PDF proof**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Done – page 11 of PDF proof**

*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.