Can the publication of guidelines change the management of early rheumatoid arthritis? An interrupted time series analysis from the United Kingdom

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Abstract

Objective. To assess whether publication of national treatment guidelines improved the management of early RA in the UK.

Methods. Incident diagnoses of RA in persons aged over 18 years from 1995 to 2010 were identified from the Clinical Practice Research Datalink. Using a natural experimental study design, interrupted time series analysis was used to assess whether trends in the proportion of patients receiving DMARDs, within 3 and 12 months of diagnosis, changed following publication of British Society for Rheumatology guidelines in 2006.

Results. Between 1995 and 2010, 11 772 incident cases of RA were identified. There was a progressive increase in the proportion of patients prescribed any DMARD within 12 months from 43.3% in 1995 to 78.5% in 2010. After publication of the British Society for Rheumatology guidelines, the proportion of patients prescribed any DMARD within 12 months increased by 4.2% (P = 0.053). Prior to the guidance, prescribing was increasing by 1.64% per year, compared with 3.55% per year after publication (P < 0.001).

Conclusion. Guidelines published by a national body can improve the proportion of patients receiving DMARD treatment in the first year after diagnosis of RA.

Key words: rheumatoid arthritis, DMARDs, guidelines, epidemiology, natural experiment.

Introduction

RA is a chronic autoimmune disease causing pain and inflammation in the joints [1]. The disease is progressive, ultimately leading to joint destruction and deformity, and systemic, so it can affect many other parts of the body [2]. Each year ~26 000 people are newly diagnosed with RA in the UK [2]. RA is associated with substantial morbidity, mortality and health care costs [3]. A third of patients lose their jobs within 2 years of diagnosis [4]. The economic impact is substantial, with the total cost of disease in the UK estimated at between £3.8 and £4.75 billion per year [5].
DMARDs can control disease activity, reduce joint erosions and improve quality of life. Intervention with treatment in the early stages of disease is essential [6] to slow disease progression and joint destruction [7]. Many RA treatment guidelines have been published and updated: for example British Society for Rheumatology (BSR) [8]; ACR [9]; National Institute for Health and Clinical Excellence [5]; EULAR [10]. UK guidance recommends a combination of DMARDs (MTX 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 [5]. The BSR guideline focuses on early RA alone, whereas the other guidelines also consider established RA.

Despite the proven efficacy of DMARDs, a large number of patients with RA receive therapy late in the disease course or not at all [11]. It remains unclear whether publication of guidelines directed towards the management of early RA can alter prescribing practice. The importance of early and more aggressive treatment is emphasized, as there is strong evidence that this is when the disease is most responsive to treatment [6], termed the window of opportunity [10]. The aim of this study was to assess whether trends in the proportion of patients receiving DMARDs changed following publication of the 2006 BSR guidelines.

**Methods**

**Study design**

Natural experimental study design [12]. The Clinical Practice Research Datalink (CPRD) Group has obtained ethical approval from the National Research Ethics Service Committee for all purely observational research using anonymized CPRD data (i.e. studies that do not include patient involvement. The study has been approved by the Independent Scientific Advisory Committee for Medicines and Healthcare Products Regulatory Agency Database Research) (protocol number 12_055R2).

**Study population and setting**

We obtained data from the CPRD. The CPRD comprises the entire computerized medical records of a sample of patients attending general practitioners in the UK, covering a population of 6.5 million patients from 433 contributing practices chosen to be representative of the wider UK population. CPRD records contain all clinical and referral events in both primary and secondary care, in addition to comprehensive demographic information, prescription data and hospital admissions. Data are stored using Read and Oxford Medical Information System codes for diseases that are cross-referenced to the International Classification of Diseases.

A first-ever clinical or referral record of RA occurring from 1995 until the end of 2010 was identified using Read codes. The validity of an RA diagnosis in CPRD is high [13] when using ACR diagnostic criteria as the standard. We used the same diagnostic groups as in the previous RA validation study [13], and included patients with more than one medical code for RA on different dates. The study population included incident patients (those with a first-ever record of RA at least 1 year after start of data collection). Using these criteria we identified 11 772 patients.

**Ascertainment of outcome**

Prescription of a DMARD (MTX, other DMARD, any DMARD) within 3 months and 1 year of RA diagnosis date. Data on outcomes are measured at equally spaced (quarterly) intervals over the period of interest (1 January 1995 to 31 December 2011).

**Primary exposure**

The exposure (intervention) is the date the BSR guideline was published in 2006.

**Statistical analyses**

Interrupted time series analysis (longitudinal quasi-experimental design) [14] was used to evaluate the impact of the BSR guidelines on DMARD use. Segmented linear regression models are used to estimate changes in levels and trends of rates in DMARD use after BSR guidance (intervention) publication. Regression diagnostics were performed to confirm assumptions underlying the model and to test for evidence of serial autocorrelation and seasonality. We used Stata version 13.1 for all analyses.

**Results**

Trends in the prescribing of DMARDs have increased substantially over time. In 1995, only 3.9% of patients were prescribed MTX within 3 months of RA diagnosis (10.2% in 12 months). This compares with 37.7% within 3 months (64.6% within 12 months) for patients diagnosed in the final quarter of 2010. For receipt of any DMARD within 3 months, this increased from 28.3% to 58.5% over the follow-up period (within 12 months from 43.3% to 78.5%).

Publication of BSR guidance appeared to have a significant impact on DMARD prescribing for patients with newly diagnosed RA (Fig. 1). Immediately after publication of guidance, the proportion of patients prescribed any DMARD within 12 months increased by 4.2% (P = 0.053). Prior to publication of the guideline, this proportion was increasing by 1.64% per year; however, after publication it was increasing by 3.55% per year (P < 0.001). The effect of the guideline was stronger for MTX (Fig. 2), for which prescriptions within 12 months increased by 5.0% after publication (P = 0.009), and the trend in proportions changed from an increase of 2.56% per year prior to publication, to 4.73% per year afterwards (P < 0.001).

**Discussion**

Over the past 15 years within the UK, there has been a substantial increase in DMARD prescribing for patients with early RA. In 1995, only 43.3% of patients received a DMARD within 12 months of diagnosis, compared with 78.5% in 2010. Publication of the BSR guideline
had a significant impact on DMARD prescribing and led to a sharp increase in the upward trend in prescribing rates, particularly for MTX. DMARDs are slow-acting drugs that can take weeks or even months to produce a clinical response, so it is vital that patients are established on this disease-modifying therapy as soon as possible.

There are a number of potential explanations for the substantial increasing trend in the use of DMARDs early.

BSR: British Society for Rheumatology.
in the course of RA over the 15-year period of this study. Internationally, many other RA treatment guidelines have been published and updated, including: the ACR in 2008 [9] (updated in 2012 [15]); the National Institute for Health and Clinical Excellence clinical guideline 79 in 2009 [5] and EULAR in 2010 [10, 16] (updated in 2013 [17]). These guidelines have been disseminated at national and international conferences to health professionals attending as part of their continuous medical education. Increasing trends in DMARD use will have also been influenced by the growing body of research evidence demonstrating the efficacy of DMARDs [6, 7], and the availability of better tools for early diagnosis that act as prognostic factors for RA [9] (such as: RF; anti-CCP antibodies; ESR; CRP level). The availability of DMARD therapies has also changed over the past decade, with the introduction of new and highly effective DMARDs emerging, and the ability to achieve better efficacy by using high-dose and combination therapies [10].

One of the strengths of this study is the data on which it is based. CPRD covers ~5% of general practices across all of the UK and is broadly representative of the UK population as a whole. The large sample size and high degree of generalizability enables population-level inferences to be made. Coding of the diagnosis of RA is a potential limitation. However, previous studies have shown the validity of an RA diagnosis in CPRD to be high [13]. In the UK, patients are prescribed DMARDs in primary care by their general practitioner while being managed by a rheumatologist in secondary care. As the first prescription is usually prescribed by the rheumatologist, the prescribing patterns at 12 months are likely to be more accurate in this study. One limitation is that it is not possible to study biologic drug usage within CPRD (biologics are given by injection or intravenously); this could also explain the low proportion of patients receiving DMARDs. However, we only included incident patients. The national guidelines recommend DMARDs as first-line therapy in early RA, with progression to a biologic for patients with inadequate response; a large proportion of patients do not need biologic therapy in the first 2 years of disease [18].

We used an interrupted time series (quasi-experimental design), taking advantage of a natural experimental approach [12] to evaluate the impact of a population-level intervention. This is a strong study design as it provides an unbiased estimate of the difference pre- and post-intervention, and it has high external validity as it occurs in a natural setting. There are many possible explanations for the overall increasing trend in the use of DMARDS for early RA over the study period, including the publication of national and international guidelines, the influence of medical education through attendance at conferences and lectures, the availability of better diagnostic tools for early diagnosis and the increased availability of DMARD therapies. Set in this context, our study shows that in the UK, the publication of BSR guidelines had a significant impact, and led to a sharp increase in this upward trend in prescribing rates, particularly for MTX.

Our findings of an increasing trend in levels of prescribing are consistent with those of large national databases from other countries, including the USA [19], Canada [20] and Germany [21], and confirm the trend towards early and more aggressive treatment. Our data suggest that currently 78.5% receive a DMARD within 12 months of diagnosis. DMARDs are not suitable for all RA patients, such as those with contraindications and women trying to conceive, and it has been suggested that ~80% is a realistic estimate of patients eligible for DMARD therapy [11]. This is consistent with estimates from a United States study, where 15% of patients with a clinical diagnosis of RA were not receiving DMARDs, with Canadian administrative data showing 16% not receiving DMARDs [22] and estimates in Germany being between 13 and 19% [21].

This study provides strong evidence that national guidelines can be effective in changing the management of incident patients with early RA. Our findings support evidence of the effectiveness of guidelines observed in other countries. Data from the Swedish RA register from 1997 to 2001 [23] identified an increasing trend in DMARD prescribing driven by publication of the Swedish guidelines in 1998. Data on an incident RA cohort of seniors from Ontario physician billing data for 1997–2006 [20] demonstrated that for periods before (2001–2003) and after (2004–2006) the Canadian Rheumatology Association guideline, they observed a significant increase in DMARD use from 40% to 50%.

There has been a massive growth in the number of treatment guidelines published for RA and subsequently updated. Production of guidelines consumes an enormous amount of resource, so it is important to understand whether they are effective. This study provides evidence that the publication of a BSR guideline aimed at early RA has been effective in increasing the numbers of patients with RA being quickly prescribed DMARDs. Within the UK, nearly 80% of patients now receive a DMARD within a year of diagnosis and benefit from treatment to control their disease progression and maintain physical function [6].

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