PEER REVIEW HISTORY

ARTICLE DETAILS

TITLE (PROVISIONAL)	Regional and temporal variation in the treatment of rheumatoid arthritis across the UK: a descriptive register-based cohort study
AUTHORS	Edwards, Christopher; Campbell, Jennifer; van Staa, Tjeerd; Arden, Nigel

VERSION 1 - REVIEW

REVIEWER	Dr Patrick Kiely Consultant Rheumatologist St Georges Healthcare NHS Trust London UK Member of ERAN.
REVIEW RETURNED	11-Jul-2012

THE STUDY	The data collection period is inappropriate to infer whether or not recent guidelines have influenced clinical practice
RESULTS & CONCLUSIONS	The data is interesting in its own right, but does not answer the research question relating to influence of guidelines on current practice. See my comment to the authors
GENERAL COMMENTS	This is a powerful study reporting the changing patterns of use of DMARDs (mono, combination and Methotrexate specifically) with time and across regions of the UK. Interesting and important observations have been made which are worthy of publication. The way the data is interpreted needs revision Major criticisms. 1. The 15 year period (1995 – 2010) that has been studied essentially ends at the time that EULAR and UK clinical guidelines were published. The authors cite European recommendations (2010) and NICE guidance (2009). Only the American ACR guidelines of 2002 were released mid way through the study period. It seems to me to be premature to make conclusions concerning the take up of these guidelines in routine UK practice, and thus in the 'Article Focus' the statement ' We ... reveal whether the latest knowledge on how RA should be treated has been translated into actual clinical practice' is unfounded based on the time period of data analysis. Equally the authors' conclusion that 'publication of national clinical guidelines does not appear to have had a marked impact on standardising prescribing behaviour' cannot be made from the data studied. I agree that the data demonstrate a 'general upward trend' over the 15 years, but this has nothing to do with these guidelines as they came out at the end of the study period, and you have not presented a sub-analysis of the data from 2010 alone, to see if this shows a 'rapid implementation and uptake of NICE guidelines'. Now (i.e. 2012, 2 – 3 years post NICE and EULAR guidelines) is the time to start to look for this evidence.

	2. The source of information concerning which drugs a patient is receiving seems to be dependent upon the GP issuing the prescription. If this is the case then it is possible that this analysis might fail to register prescriptions for DMARDs issued on a hospital prescription. This is an important study weakness because GPs do refuse to prescribe some DMARDs on grounds of unfamiliarity, cost, monitoring implications and lack of confidence in taking responsibility for adverse effects. The focus on Methotrexate toxicity and monitoring by the NPSA has brought DMARD prescribing to the attention of GPs in the last 5 years, and some DMARDs (eg Leflunomide or even Methotrexate) are never prescribed by GPs. This is particularly the case in urban areas where distances make it easy for patients to access secondary care. You allude to this in the very last paragraph but I am not confident that 'by 12 months it seems likely that most prescribing will be via the GP', certainly not uniformly so across all regions. This method of data collection is likely to underestimate Methotrexate and other DMARD use, detracting from the ability to make inter-regional comparisons of prescribing behaviour. 3. The time to starting a DMARD is critical to long term outcome. As such it is a shame that this aspect of the data analysis has not been broken down into the 3 time intervals 95-99, 00-05, 06-10. This is arguably as critical as the actual choice of DMARD – starting any DMARD quickly is better/as good as DMARD combination therapy started late. Others have published on this in the UK from much smaller cohorts (ERAS, ERAN, Birmingham group) and sub analysis of the FINRACo study made the same observation. The current study has the potential to report on this aspect of RA care over time, from a much larger cohort than hitherto published. Although you cant measure [symptom onset to first DMARD] the time interval from [RA diagnosis to first DMARD] reflects important aspects of the referral, triage and treatment behaviour of GPs/rheumatologists and is a surrogate for well organised care. Minor points 1. The Ulster data is interesting because access to anti-TNF agents is very poor in this province. Whether this reflects a more aggressive use of DMARDs is a point of speculation and discussion. 2. There is no Figure 2 in the version I have been given to review 3. Reference 1 seems an unusual choice for substantiation of the statement: 'RA is a chronic systemic autoimmune disease, the most common form of chronic joint inflammation'

REVIEWER	Zufferey, Pascal DAL, CHUV, Service de rhumatologie
REVIEW RETURNED	03-Aug-2012

THE STUDY	As a non British rheumatologist, I am not necessarily aware of the way the British wealth system works and therefore to understand the paper some precisions are needed. How many of your patients with the diagnosis of RA have seen outside their GPs by a rheumatologist during the following period? IF yes, were there temporal or regional trends? Did the rheumatologists confirm the diagnosis, and did they give any recommendation about treatment? If the authors do not have all these information, they should discuss it in more detail because these data could explain many of the temporal and regional discordances.

	The lack of precision about RA diagnosis is also disturbing. How many of the RA were RF and anti CCP +. Many sero-negative RA disappear during the first two years and this could explain why so many patients did not need any DMARDS after one year in this cohort. The author never talk about biologic treatments. With a follow-up of one year, some aggressive RA not responding to the classical DMARD should have been eligible for such treatments, but of course they should therefore be also referred the a secondary center . Are those patients excluded? If yes does the cohort really represent the British RA population? As you can notice this paper is not really clear for a non British reader. Moreover, the fact that the diagnosis is based essentially on the GP's opinion and the treatment initiated and followed by them without the help of a referent rheumatologist is quite strange as this practice is more than unusual in many countries.

VERSION 1 – AUTHOR RESPONSE

Reviewer 1
Major criticisms.
1. The 15 year period (1995 – 2010) that has been studied essentially ends at the time that EULAR and UK clinical guidelines were published. The authors cite European recommendations (2010) and NICE guidance (2009). Only the American ACR guidelines of 2002 were released mid way through the study period. It seems to me to be premature to make conclusions concerning the take up of these guidelines in routine UK practice, and thus in the 'Article Focus' the statement ' We ... reveal whether the latest knowledge on how RA should be treated has been translated into actual clinical practice' is unfounded based on the time period of data analysis. Equally the authors' conclusion that 'publication of national clinical guidelines does not appear to have had a marked impact on standardising prescribing behaviour' cannot be made from the data studied. I agree that the data demonstrate a 'general upward trend' over the 15 years, but this has nothing to do with these guidelines as they came out at the end of the study period, and you have not presented a sub-analysis of the data from 2010 alone, to see if this shows a 'rapid implementation and uptake of NICE guidelines'. Now (i.e. 2012, 2 – 3 years post NICE and EULAR guidelines) is the time to start to look for this evidence.

We agree that it is very difficult to make strong statements about the uptake of the UK NICE guidance on the treatment of RA given the time points studied in our work. However, we believe that the papers main objective is to comment on how knowledge on the best possible treatment of RA is being translated into everyday prescribing. With this in mind we describe our objective as being to consider DMARD prescribing, "….with respect to best practice….". With this in mind we have made changes to reflect the fact that is would be unreasonable to expect large changes to have occurred in DMARD prescribing as a result of EULAR and NICE guidance given the period of time we have studied. We plan to look again shortly. The changes have been made to the abstract conclusion, para 2 of the introduction, and in the second para page 9 of the discussion.

2. The source of information concerning which drugs a patient is receiving seems to be dependent upon the GP issuing the prescription. If this is the case then it is possible that this analysis might fail to register prescriptions for DMARDs issued on a hospital prescription. This is an important study weakness because GPs do refuse to prescribe some DMARDs on grounds of unfamiliarity, cost, monitoring implications and lack of confidence in taking responsibility for adverse effects. The focus

on Methotrexate toxicity and monitoring by the NPSA has brought DMARD prescribing to the attention of GPs in the last 5 years, and some DMARDs (eg Leflunomide or even Methotrexate) are never prescribed by GPs. This is particularly the case in urban areas where distances make it easy for patients to access secondary care. You allude to this in the very last paragraph but I am not confident that 'by 12 months it seems likely that most prescribing will be via the GP', certainly not uniformly so across all regions. This method of data collection is likely to underestimate Methotrexate and other DMARD use, detracting from the ability to make inter-regional comparisons of prescribing behaviour.

This is a very important point. One of the great strengths of the GPRD is the accuracy of prescribing data as long as it prescribed in primary care. We appreciate the points made by reviewer 1 in this regard. However, despite concerns we believe that the majority of DMARD prescribing is being picked up. This is due to validation work performed previously (ref 13) in which the author (CE) looked at the original records of 400 individuals with RA and JIA, the IMS British Pharmaceutical Index information that suggests 90% of DMARDs are prescribed in primary care (ref 15) and a recent survey that we have undertaken with this question in mind. We have surveyed all 118 PCTs via the PCT pharmacist in England to understand the use of shared care guidelines, DMARD prescribing and blood monitoring. This work has been prepared as a letter to the journal Rheumatology. Of the 118 PCTs contacted 70 (59%) responded. Of these, 77% stated that MTX prescribing was performed by GPs by 6 months and a further 19% when the dose was stable. All regions of England were represented. We have described this further in final paragraph of the discussion.

3. The time to starting a DMARD is critical to long term outcome. As such it is a shame that this aspect of the data analysis has not been broken down into the 3 time intervals 95-99, 00-05, 06-10. This is arguably as critical as the actual choice of DMARD – starting any DMARD quickly is better/as good as DMARD combination therapy started late. Others have published on this in the UK from much smaller cohorts (ERAS, ERAN, Birmingham group) and sub analysis of the FINRACo study made the same observation. The current study has the potential to report on this aspect of RA care over time, from a much larger cohort than hitherto published. Although you cant measure [symptom onset to first DMARD] the time interval from [RA diagnosis to first DMARD] reflects important aspects of the referral, triage and treatment behaviour of GPs/rheumatologists and is a surrogate for well organised care.

We agree but have been concerned about the reliability of the first diagnosis of the RA recorded by the GP and the introduction of DMARD prescribing in primary care. For the reasons discussed in major point 2 from reviewer 1 there is difficulty in defining when the GP has full responsibility for DMARD prescribing. We are currently working on making this information more accurate in a more up to date dataset from GPRD.

Minor points
1. The Ulster data is interesting because access to anti-TNF agents is very poor in this province. Whether this reflects a more aggressive use of DMARDs is a point of speculation and discussion.
We agree. This is a very interesting point and we have included the concept in the second para of page 9 in the discussion.

2. There is no Figure 2 in the version I have been given to review.
This is a typographical error and should refer to Figure 1: this has been corrected (para 4 of the results section)

3. Reference 1 seems an unusual choice for substantiation of the statement: 'RA is a chronic systemic autoimmune disease, the most common form of chronic joint inflammation'
We agree. A new reference has been included. Choy EH & Panayi GS NEJM 2001, 22, 344, 907-16

Reviewer 2

1) How many of your patients with the diagnosis of RA have seen outside their GPs by a rheumatologist during the following period?
IF yes, were there temporal or regional trends? Did the rheumatologists confirm the diagnosis, and did they give any recommendation about treatment?
If the authors do not have all these information, they should discuss it in more detail because these data could explain many of the temporal and regional discordances.

Many thanks for your comments. The GPRD is a well-established database for observing the treatment and outcomes of individuals with chronic disease. Its strengths are its large size and the fact that the patients included do not all come from highly selected tertiary centres. There has been extensive validation of the diagnosis of chronic diseases including RA in this dataset. This is described in the references 12, 13 and 14. This has been described in the 3 paragraph of the introduction and in the final paragraph of the discussion. From previous work described in reference 13 it is likely that the vast majority of RA patients described will have been seen by a rheumatologist in secondary care. We have also added an explanation in the 3rd paragraph of the introduction to make this clearer.

2) The lack of precision about RA diagnosis is also disturbing. How many of the RA were RF and anti CCP +. Many sero-negative RA disappear during the first two years and this could explain why so many patients did not need an DMARDS after one year in this cohort. Moreover, the fact that the diagnosis is based essentially on the GP's opinion and the treatment initiated and followed by them without the help of a referent rheumatologist is quite strange as this practice is more than unusual in many countries.

We hope this point has been addressed in the answer to question 1. In addition, we re-enforce the fact that RF and anti-CCP was not available in this large study of 34,000 individuals with RA. However, extensive validation has been carried out comparing the clinical diagnosis with the previous ACR diagnostic criteria for RA. We have described this in the 3rd paragraph of the introduction.

3) The author never talk about biologic treatments.
With a follow-up of one year, some aggressive RA not responding to the classical DMARD should have been eligible for such treatments, but of course they should therefore be also referred the a secondary center . Are those patients excluded? If yes does the cohort really represent the British RA population?

Thank you for making this point. RA patients receiving biologic therapy are not excluded from the GPRD. Primary care physicians would perform the prescribing of most therapy in the UK. Biological therapies are excluded from this and we have no record of this prescribing in the GPRD. For this reason we have concentrated on the use of DMARDs. We have clarified this in the last paragraph of the discussion.

VERSION 2 – REVIEW

REVIEWER	Kiely, Patrick St George's Hospital, London
REVIEW RETURNED	04-Sep-2012

GENERAL COMMENTS	Most of my previous comments are satisfactorily acknowledged or answered. I remain unhappy with the statement in the discussion that 'there has been an encouraging increase in DMARD and methotrexate prescribing post NICE recommendations' and in the final conclusion 'publication of national clinical guidelines does not appear to have had a marked impact on standardising prescribing behaviour' - you cant conclude this from the time interval 2006-2010 as NICE guidelines were published in 2009 and EULAR guidelines in 2010. There is no post guidelines group. These conclusions must be removed. The sentence in the discussion could read 'Although there has been an encouraging increase in DMARD and methotrexate prescribing over the time periods studied, it is too early to conclude whether the more recently published NICE (2009) and EULAR (2010) guidelines have influenced DMARD prescribing in the UK'. The statement in the Conclusions starting 'and publication of national clinical guidelines.....' should be deleted.

VERSION 2 – AUTHOR RESPONSE

Reviewer 1

Most of my previous comments are satisfactorily acknowledged or answered.
I remain unhappy with the statement in the discussion that 'there has been an encouraging increase in DMARD and methotrexate prescribing post NICE recommendations' and in the final conclusion 'publication of national clinical guidelines does not appear to have had a marked impact on standardising prescribing behaviour' - you cant conclude this from the time interval 2006-2010 as NICE guidelines were published in 2009 and EULAR guidelines in 2010. There is no post guidelines group. These conclusions must be removed.

The sentence in the discussion could read 'Although there has been an encouraging increase in DMARD and methotrexate prescribing over the time periods studied, it is too early to conclude whether the more recently published NICE (2009) and EULAR (2010) guidelines have influenced DMARD prescribing in the UK'.
The statement in the Conclusions starting 'and publication of national clinical guidelines.....' should be deleted.

We agree and have deleted the statement in the conclusion and changed the sentence as suggested.