Author’s response to reviews

Title: REAL WORLD LONG-TERM IMPACT OF INTENSIVE TREATMENT ON DISEASE ACTIVITY, DISABILITY AND HEALTH-RELATED QUALITY OF LIFE IN RHEUMATOID ARTHRITIS

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Author’s response to reviews:

Dear Editorial Team

Thank you for your comments regarding our article ‘Real world long-term impact of intensive treatment on disease activity, disability and health-related quality of life in rheumatoid arthritis’.

We have considered and responded to each comment individually. Although the text is below, I have uploaded a 'response to reviewers' file which also includes the additional supplementary tables and figures.
REVIEWER 1

General

The authors have performed an observational study based on electronic medical records of a cohort of RA patients. As with all observational studies, there are methodological problems which the authors have discussed in the Discussion. However, just discussing it cannot overcome some of the limitations of the data.

Comment 1

One of the major problems is that patients are being compared at different time points in their disease course. So, to give an overall average DAS28 for patients that may be 15 years into their disease together with someone who is only 1 year into their disease may not be representative of true disease activity in the group. Could there be an analysis to take into account of duration of disease prior to the start of the study?

Response 1

Our aim was to assess temporal changes in specialist care rather than the course of RA as specialist practice involves managing RA patients across a range of disease durations. However, the impact of disease duration is an issue of interest. We have undertaken some additional analyses in the patients followed for three years or more assessing the impact of disease duration. Dividing these patients into those with disease durations of less than 5 years and those with more than 5 years showed no evidence that DAS28 scores were different over time; we have provided an additional supplementary figure summarising this finding. However, there two differences between these groups: (a) sustained remission was more frequently seen in patients with less than 5 years duration (12% versus 3%; Chi-squared 10.8; DF=1; P=0.001); (b) flares were more frequently seen in patients with more than 5 years duration (78% versus 62%). We have added this information in the revised text.

Revision 1

Impact Of Disease Duration (End Of Results)

Dividing patients followed for three years or more into those with disease durations of less than 5 years and those with more than 5 years showed no evidence that DAS28 scores were different over time between them (Supplementary Figure 1) However, there two differences between them (a) sustained remission was more frequently seen in patients with less than 5 years duration (12% versus 3%; Chi-squared 10.8; DF=1; P=0.001); (b) flares were more frequently seen in patients with more than 5 years duration (78% versus 62%; Chi-squared 11.9; DF=1; P=0.001).
Supplementary Figure 1 Changes In Mean DAS28 Over Time In Patients Seen Within Five Years Of RA Onset Or Later

Comment 2

Another major concern is that the number of patients seen at least once a year for 3 years is less than 50% of the total - only 753 out of 1693. Why were the others not seen so regularly? What was the average time between assessments/clinic visits? The authors state that the patients had "intensive management", which is not the case if they are seen less than once a year.

Response 2

The patients fall into two groups: those seen for more than 3 years and those seen for less than 3 years; more than half of the patients were not followed for more than three years. The median time between assessments for all patients (n=1,693) was 3 (IQR: 1–6) months and the mean was 5.3 (SD 6.6) months. In those patients seen for more than 3 years, the median time between assessments was 4 (IQR 2-6) months and mean was 5.0 (SD: 5.5) months. The mean time of follow up for patients followed for less than 3 years was 1.1 years (mean 2.98 visits), and 4.9 years (12.5 visits) for those followed > 3 years.

The reasons patients did not remain under follow-up for over three years are likely to be complex. Death is likely to explain why some patients were not followed up, there are many other factors involved. London has a highly mobile population and patients frequently move within London or outside the capital. RA patients often have comorbid diseases and these can result in their moving to other London hospitals for their care. Patients may also often stop attending specialist units; the information on this latter point is incomplete but historical studies suggest nearly half of RA patients may not be under specialist care receiving DMARDs during the course of their disease (Treasure E, Scott DL, Katona PM, Toon P. Arthritis in inner city general practices. Br J Gen Pract 1990; 40: 81-2., Edwards CJ, Arden NK, Fisher D, Saperia JC, Reading I, Van Staa TP, Cooper C. The changing use of disease-modifying anti-rheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database. Rheumatology 2005; 44: 1394-8).

We have clarified this issue by providing further information in the results section and have commented on the points in the revised discussion.

Revision 2 (Results - Patients Studied)

All Patients
Between 2005 and 2015, 1,693 RA patients were entered into the database. Most were female (1,262, 75%) and Caucasian (1,134, 67%). Their mean age was 55 years and mean disease duration was 11 years. The median time between assessments was 3 (IQR: 2–6) months and the mean was 5.3 (SD 6.6) months. Details of the patients are shown in Table 1. Numbers of patients with data in each calendar year are shown in Supplementary Table 1 (included in manuscript).

Patients Followed Over Three Or More Years

752 patients were seen at least annually over three years or more. Their baseline features were similar to those of the overall group (Table 1). The median time between assessments was 3.5 (IQR 1-5) months and mean was 5.0 (SD: 5.5) months.

Revision 2 (Discussion)

A fifth limitation is the definition of flares; other definitions were all developed some time after our study started and are difficult to apply retrospectively. A sixth limitation is that many patients did not remain under follow-up for over three years. The reasons for this are likely to be complex; death is one factor; London has a highly mobile population and patients frequently move within London or outside the capital; RA patients often have comorbid diseases and these can result in their moving to other hospitals for their care; and patients may stop attending specialist units, with historical studies suggest nearly half of RA patients may not be under specialist care receiving DMARDs during the course of their disease (Treasure E, Scott DL, Katona PM, Toon P. Arthritis in inner city general practices. Br J Gen Pract 1990; 40: 81-2 - Edwards CJ, Arden NK, Fisher D, Saperia JC, Reading I, Van Staa TP, Cooper C. The changing use of disease-modifying anti-rheumatic drugs in individuals with rheumatoid arthritis from the United Kingdom General Practice Research Database. Rheumatology 2005; 44: 1394-8). Finally, our cohort predominantly included patients with established disease rather than new referrals with early RA.

Comment 3

Following on from comment 2, it is not clear exactly what "intensive management" meant.

a. From the graphs, the mean DAS28 in 2015 was still above 3.2, so the average was still moderate disease activity. This is similar in those followed for more than 3 years, they also ended up with an average DAS28 of >3.2. Was there an explicit treatment target? If so, how many patients reached the target?
b. Although there was an increase in the number of patients in remission (Results page 7), was this persistent remission, or remission at any one time point? I would suggest that it would be difficult to have a definite figure if over 50% of the patients were not followed-up consistently.

Response 3

Our results show that over time DAS28 scores have fallen and more patients achieve remissions. Although only about 30% of patients were in remission in 2015 despite the increases in treatment intensity, this is somewhat better than the impact of starting certolizumab in patients with moderate RA in the CERTAIN trial (Smolen JS, Emery P, Ferraccioli GF, Samborski W, Berenbaum F, Davies OR, Koets W, Purcaru O, Bennett B, Burkhardt H. Certolizumab pegol in rheumatoid arthritis patients with low to moderate activity: the CERTAIN double-blind, randomised, placebo-controlled trial. Ann Rheum Dis 2015; 74: 843-50) and was comparable to the rates in the Canadian Treat To Target study of Pope et al (Pope JE, Haraoui B, Rampakakis E, Psaradellis E, Thorne C, Sampalis JS; Optimization of Adalimumab Trial Investigators. Treating to a target in established active rheumatoid arthritis patients receiving a tumor necrosis factor inhibitor: results from a real-world cluster-randomized adalimumab trial. Arthritis Care Res 2013; 65: 1401-9).

The target was achieving remission or low disease activity, in line with treat to target recommendations. In the patients followed for 3 years or more 9% had sustained remission, 50% had remission at one or more time-points without being sustained, 16% had sustained low disease activity or remission and 58% had point low disease activity or remission at one or more time-points without being sustained.

We have included these points within the revised paper.

Revision 3

Based on the presence of remission the patients were subdivided into 3 sub-groups: 68 (9%) were always in remission, 376 (50%) had one or more episodes of remission without being sustained, and 308 never achieved remission. There were substantial differences between these groups (Table 2). In addition 16% had sustained low disease activity or remission and 58% had point low disease activity or remission at one or more time-points without being sustained.

Comment 4

Table one should compare the overall group, those followed-up annually for at least 3 years, and those who did not have regular follow-up, as we would want to check that those not regularly
followed up did not have characteristics that were different from those who were regularly followed up.

Response 4

There were no clinically important nor significant differences between patients followed for 3 years and the other patients. We have added an additional column to the Table to show the data.

Revision 4 (see revised Table 1 in manuscript)

Comment 5

The authors need to clarify how they arrived at the mean values in all the figures - DAS28, ESR, TJC, SJC, remission, active disease etc. In the figures, there is only 1 time point per year, so were all the values just averaged? How were the repeated values from individual patients analysed? Was there a statistical correction for the analysis of repeated values from single individuals?

Response 5

Our statistical analyses used mixed effects maximum likelihood regression models to assess changes over time; these take into account repeated measures in individual patients.

The figures currently show the mean data for each year irrespective of the number of times individual patients were seen in the year. We have had detailed discussions on the best way to present this data. The mean values for each year are simple for the average clinician to understand and we therefore believed this approach was more useful. We have also prepared figures which show the data based on trend analyses, which take into account repeated measures from the same patient. We thought these may be more confusing to the average clinician, who would not necessarily be familiar with the statistical methods. We have added them as supplementary data; they show a similar pattern.

Revision 5: Methods (Analyses)

Descriptive analyses used numbers of patients and percentages and mean scores with standard deviations or 95% confidence intervals (CI). We calculated mean data for each patient seen during each year. We used mixed models to examine the changes in DAS28 and its components over time. We also used trend analysis to take into account repeated measures from the same patient. Subgroups were compared by Chi-Squared analyses or by one-way analysis of variance.

Revision 5: Results

Patients Followed Over Three Or More Years
There were 4,345 annual measures of DAS28 in the 752 patients with at least three annual clinic visits. Their mean DAS28 scores showed similar falls over time (Figure 1). Mean DAS28 scores fell 12% from 3.95 (95% CI 3.73, 4.17) to 3.48 (95% CI 3.22, 3.74). Trend analysis, which takes into account repeated measures, showed similar changes (Supplementary Table 2 included in manuscript).

Comment 6
The information on medication usage should be included. For example, how many patients were on biologics in 2005, compared to 2015, for the whole cohort. Is the improvement in the disease activity/remission due to increased use of biologics? There should be some adjustment for drug use in the analysis.

Response 6
Initially 55% of patients were taking DMARD monotherapies and 19% biologics; by 2015 this had changed to 35% of patients taking DMARD monotherapies and 42% biologics (Supplementary table 3). We believe the increased use of biologic treatments resulted in the reductions in DAS28 scores and greater number of remissions, though observational data cannot provide definitive proof for a link. Adjusting for treatment use is complex. For example, the patients with persistently high DAS28 scores often had received relatively little suppressive treatment, reflecting issues related to patient choice, adverse events and comorbidities. Patients with persisting remission also often received relatively little suppressive treatment, reflecting potential treatment tapering. Such complexities make it impractical to adjust for treatment intensity. We have added a comment on this point in the revised paper (see response to Comment 7).

Revision 6 (Results – Changes in treatment and remission status)
Initially 55% of patients were taking DMARD monotherapies and 19% biologics. DMARD monotherapy fell progressively, with increasing use of biologic therapies; by 2015 this had changed to 35% of patients taking DMARD monotherapies and 42% biologics. Simar changes in biologics use were seen in patients followed over three or more years (Supplementary Table 3 included in manuscript).

Comment 7
A comment: It would seem intuitive that those in remission would be on less medication compared to those with active disease, as drugs will be tapered once patients are in remission. It would be interesting to see if those who went into remission were on biologics prior to achieving
remission, and what proportion of those achieving remission had had biologics. Is this information available?

Response 7

The results show patients with persisting remission receive more combination DMARDs and fewer biologics. It is possible that this is because of biologic tapering in patients in persistent remission, though it is difficult to be certain on this point. We have added a comment on this issue in the revised paper.

With respect to analysing treatments before patients achieved persisting remission, such complex statistical assessments are not possible with this dataset. In a prospective research study, when patients are seen at regular pre-determined intervals, it might be possible to consider such issues. But in a “real life” context, when data is collected from individual patients at variable time-points, such analyses are impractical. Historical pre-biologic observational studies always reported a small proportion of patients entering remission without receiving any suppressive treatment. Trials also show biologics increase remission rates in active disease. However, in an observational study it is impossible to be certain whether patients have achieved remission because they had mild disease or because they received biologic treatment.

Revision 7 (Discussion)

The presence of intermittent and persistent remissions had a substantial relationship with both treatment and disease outcomes. Patients with remissions were more likely to be male and Caucasian with shorter disease duration, which reflects previous experience predicting RA outcomes [32-34]. There were also differences in treatment intensity with patients in persisting remission having less intensive treatment and, in particular, fewer biologics. It is possible patients in sustained remission had any biologic treatment tapered and stopped.

REVIEWER 2

General Comment

This is an interesting and valuable study, particularly as it is based on real world clinical data and includes a large number of patients. It adds to the literature on temporal trends in RA. The figures included in the manuscript are particularly helpful in understanding the trends.

General Response

We are grateful for the encouraging view of the referee.
Main Comment

My main concern is that, based on the information included in the current manuscript, I think the conclusion in the abstract and some statements in discussion are too strong regarding the effect of intensive management on temporal trends in disease. "Intensive management reduces disease activity and disability levels in routine practice." (abstract) This is an observational study and cause and effect cannot be assumed. Particularly given that it is not clear at what time point and to what extent intensive management was instituted within the cohort (see below). The data do show an upward trend for use of combination therapy and biologics over time and a reduction in disease activity but I don't think one can conclusively be attributed to the other. I think that the statement would need to be altered.

Main Response

We accept the perspective of the referee and have modified the abstract and discussion accordingly.

Revision 8 (Abstract)

Conclusions: Over 10 years an intensive management strategy in a routine practice setting increased combination DMARD and biologic use: disease activity levels declined; this association is in keeping with a causal relationship. Patients who achieved remission, even transiently, had better functional outcomes than patients never achieving remission.

Comment Methods Section - Details On Treatment Strategy

The authors report that an intensive management approach was instituted during the follow up period and that UK guidance was followed. I suspect that details of this are available within the references but the link provided for the best practice award doesn't seem to work. It would be helpful to have the following information clarified in the methods and/or supplementary data if it is available:

- What the departmental policy on intensive disease management was
- When was the policy (or policies) instituted
- Is there any evidence to demonstrate how well the policy was adhered to within routine practice in the department?

Response

From the initiation of the cohort in 2005 there was an emphasis on disease control using combination DMARDs and biologics intensively. This emphasis increased in relation to NICE
Guidance on RA in general and on using biologics as these were published together with EULAR recommendations on treat to target. The treat to target approach in this cohort pre-dated NICE and EULAR recommendations. This contrasted with an alternative perspective on controlling symptoms highlighted in the report by Gullick et al (Gullick NJ, Oakley SP, Zain A et al. Goal-directed therapy for RA in routine practice is associated with improved function in patients with disease duration up to 15 years. Rheumatology 2012; 51: 759-61). In a routine practice setting it is impractical to review all clinical decisions against planned treatment strategies as many factors come into play in individual consultations. Previous audit data from the clinic showed that treatment was escalated in 58% patients with DAS28 > 2.6. In patient visits where treatment was not escalated, clinicians were asked to specify reasons for non-escalation; common reasons for non-escalation were patient choice (41%) and increase in therapy contraindicated due to co-morbid conditions (22%).

However, there is strong evidence of increasing intensity of care in patients with initial moderate disease with biologic use in these patients rising from under one quarter in 2005 to over one half by 2015. An additional figure has been provided as supplementary data.

Revision 9

Treatments (Methods)

Patients received treatment with DMARDs and biologics in line with existing English guidance about these treatments using a goal-directed strategy aiming for remission or low disease activity [27]. They received intensive DMARDs, often given in combination, and also had access to biologic therapies when they met the existing guidelines from the National Institute for Health and Care Excellence (NICE). These English guidelines have changed over time and the approach taken reflected the guidance existing at the time treatment decisions were made and guidance from EULAR about treat to target (Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010; 69: 631-7).

Changes in Treatment and Remission Status (Results)

The use of DMARD monotherapies, combination DMARDs and biologics changed over time (Figure 4). Initially 55% of patients were taking DMARD monotherapies and 19% biologics. DMARD monotherapy fell progressively, with increasing use of biologic therapies; by 2015 this had changed to 35% of patients taking DMARD monotherapies and 42% biologics. Similar changes in biologics use were seen in patients followed over three or more years (Supplementary Table 3).
Patients always in remission received fewer DMARD monotherapies and biologics and more combination DMARDs. Compared to patients with some or no remissions. There was strong evidence of increasing intensity of care in line with the intensive treatment strategy; in particular patients with initial moderate disease had increased biologic use rising from under one quarter in 2005 to over one half by 2015 irrespective of remission status (Supplementary Figure 2).

Supplementary Figure 2. Biologic Use In Patients With Initial Moderate Disease Activity And Remission Status

Comment Methods Section Inclusion/Exclusion Criteria

The authors report physician diagnosed RA patients within the clinic were included but were there any addition inclusion/exclusion criteria? E.g. did patients only need to contribute one visit or have a minimum amount of data recorded to be included?

Response

We included all patients in whom data was available in the electronic records. This meant including patients even if they only attended on a single occasion. We wished to provide a record of clinical practice experience in a real world setting and this means that patients often do not continue to attend for follow up. On balance we consider selecting patients would create complexities without any obvious benefit.

Comment Missing Data

There are often significant issues with missing data in routinely collected clinical datasets. The authors have included % missing data on baseline demographics but no detail on amount of missing data for disease measurements (DAS28, HAQ, EQ5D) at baseline or over time. What proportion of data was missing (suggest include in results section) and how was missing data handled?

Response

We appreciate that missing data is often challenging in observational studies. We have provided details in results section and amended the manuscript accordingly. We did not adjust specifically for missing data and did not use methods to impute it.

Revision 10 (Results - Patients Studied)

Details of the patients are shown in Table 1 and treatments are shown in Supplementary Table 1; overall DMARD monotherapy decreased and biologic use increased. Out of the total sample
337/1693 (19%) had at least one missing DAS28 during follow up. Similar proportions of HAQ and EQ5D data were missing (22% and 20% respectively).

Comment Results Section Incident vs Prevalent Cases

It would be helpful to understand more about the case-mix. Did the proportion of incidence/prevalent cases vary significantly over time? If so did variation influence the changes in DAS28? If this is not possible to examine, would suggest commenting further in the discussion section. If it is possible, would be really interesting to analyse trends in the 2 groups separately, to expand on milder disease phenotype/early referral versus better treatment debate (if the authors have the opportunity to do so).

Response

This is an interesting issue.

We agree that the impact of disease duration is an issue of interest. We have undertaken some additional analyses in the patients followed for three years or more assessing the impact of disease duration. Dividing these patients into those with disease durations of less than 5 years and those with more than 5 years showed no evidence that DAS28 scores were different over time; we have provided an additional supplementary figure summarising this finding. There two differences between these groups: (a) sustained remission was more frequently seen in patients with less than 5 years duration (12% versus 3%); (b) flares were more frequently seen in patients with more than 5 years duration (78% versus 62%). We have added this information in the revised text.

As the study was not designed to evaluate the outcome of early RA patients seen soon after the onset of their disease within a specialist unit, it is impractical to evaluate the impact of very early treatment in our data.

The revision in relation to comment one from reviewer one deals with this point.

Comment Results Section Numbers At Each Time Point

It would help the reader to know number of patients contributing to the annual time points, even if only 2005, 2010, 2015 in the main manuscript and other years in supplemental data.

Response

We have provided this information in a supplementary table in the revised paper.
Revision 11 – Results - Patients studied
See Revision 2.

Comment Results Section Follow up
Although a separate analysis of patients with 3 or more years of follow up has been included, there is no mention of follow up time (either mean years follow up or number of visits per patient) for the whole population or the 3 year subgroup. I think it would be important to add this information in, particularly when interpreting those in remission always/sometimes/never in the 3-year group.

Response
The mean time of follow up for patients followed for less than 3 years was 1.1 years (mean 2.98 visits), and 4.9 years (12.5 visits) for those followed > 3 years.

Revision 12 (Results - Patients Studied)
The mean time of follow up for patients followed for less than 3 years was 1.1 years (mean 2.98 visits), and 4.9 years (12.5 visits) for those followed > 3 years.

Comment Results Section "Changes In Treatment And Remission Status"
Section states differences in medications between the remission groups but no values or significance levels detailed in the text.

Response
We have simplified this information in the revised paper but left it as a descriptive rather than a statistical analysis. We believe undertaking detailed statistical analyses of this treatment data is unlikely to prove informative.

Revision 13 - Changes in Treatment and Remission Status
See Revision 9.

Comment Discussion
There was no significant improvement observed between 2010 and 2015. Given that the NICE guidelines were published around 2009, is this an unexpected finding? It may be that the
intensive management was introduced much earlier in the department, leading to a stabilisation but would be interested to hear the author's thoughts on this in the discussion.

Response

Our results show treatment intensities increased throughout the study period but DAS28 scores stabilised in the final years and mean scores never fell below 3.4.

Studies such as QUEST-RA showed internationally that mean DAS28 scores are invariably over 3.0 (Sokka T, Kautiainen H, Pincus T, Toloza S, da Rocha Castelar Pinheiro G, Lazovskis J et al Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database. Ann Rheum Dis 2009; 68: 1666-72.); it seems likely that intensive treatment is limited in its ability to benefit all patients. The relationship of our findings to the timing of the NICE guidance is uncertain. We have commented on these issues in the revised paper.

Revision 14 (Discussion)

The implication is that intensive drug treatment alone is not sufficient and the use of other approaches to manage established RA needs to be extended. It is also possible there is a lower level of DAS28 which can be achieved by current drug treatments as international comparisons in the QUEST-RA study found no country achieved mean DAS28 scores below 3.0 (Sokka T, Kautiainen H, Pincus T, Toloza S, da Rocha Castelar Pinheiro G, Lazovskis J et al Disparities in rheumatoid arthritis disease activity according to gross domestic product in 25 countries in the QUEST-RA database. Ann Rheum Dis 2009; 68: 1666-72.). In addition the timing of NICE and other guidance may have influenced clinical practice, though we have not found any definite evidence to support this contention.

We hope that these changes will allow publication in BMC Rheumatology.

Yours sincerely

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