Author's response to reviews

Title: The association between C-reactive protein and the likelihood of progression to joint replacement in people with rheumatoid arthritis: a retrospective observational study.

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Author's response to reviews: see over
The association between C-reactive protein and the likelihood of progression to joint replacement in people with rheumatoid arthritis

Authors’ responses to reviewers’ comments

Reviewer ONE (Eero A Belt)

1. How the authors have got different CRP categories? Methods and figures should present the same data and categories.

The manuscript details two sub studies which examine the association between CRP and TJR in two separate ways.

In the first, we test the burden of inflammation as measured by mean CRP between diagnosis and endpoint (TJR or censor) and the progression to TJR. In this section of the study we did not set an a priori hypothesis of what CRP level represented a particular level of disease severity. The key data for this analysis is presented in Table 2 with log mean CRP used as a continuous covariate in the Cox regression model. For the purposes of illustrating this relationship in a survival curve (Figure 1) we categorized log mean CRP by tertile, arbitrarily named by their order as ‘low’, ‘medium’, and ‘high’.

In the second sub-study we sought to analyse the effect of change in inflammatory status over a given period and progression to TJR. In this instance we decided to use an a priori classification of CRP status based on population norms which classify 10mg/L as the 95th percentile. Levels above this are regarded by the American Heart Association and Centers for Disease Control as ‘highly elevated’.

We believe the concordance of results using either a statistical classification (tertiles of mean CRP) and an a priori population classification (for CRP change) serve to strengthen the manuscript. A statement has been added to the discussion to this effect.

2. Limitations of the use of CRP levels as an indicator for the risk of joint replacement. Other factors may be on the background. Deficient clinical data e.g. the count of tender and swollen joints

A statement has been added to the discussion to this effect.

3. Surgery itself increases CRP values, this should be shortly discussed

A statement has been added to the discussion to this effect.
4. It should be discussed that the median time from RA diagnosis to joint replacement is only 4 years in contrast to literature, where much longer periods are presented (e.g. Wolfe and Zwillich Arthritis Rheum 1998 and Palm et al Clin Exp Rheumatol 2002;20:392-4)

The data are concordant with the higher end of the UK-based ERAS study for which the median time from RA diagnosis to first joint replacement was 36 months. Our data represent a much longer period of observation than the ERAS study during which joint replacement practice is likely to have changed.

The suggested references are included for comparative purposes.

5. It should be discussed if these patients have already previously had replacement surgery. How do CRP values behave when one individual joint is replaced? May be there is no influence at all on the CRP levels.

As described in the methods, the analysed patients were those in whom first rheumatoid presentation was preceded by a six month wash-in period of known contact with the surgery. Therefore is it highly unlikely that any of these cases had previously undergone replacement surgery. The study endpoint was total replacement of any major joint.

The subsequent influence of joint replacement surgery on CRP was outside the scope of this study and has not been investigated.

Reviewer TWO (Joachim Kalden)

1. It would have been of interest to know if the percentage of patients who did not show a major decrease in CRP or presented major changes in the CRP over the observation period, ended up with a total joint replacement.

We refer the reviewer to Table 3 in which for patients whose CRP remained persistently elevated (>10mg/L; Acute-Acute) over a one year observation period the hazard ratio of TJR was 2.19 (95%CI 1.04 to 4.64; p=0.040) compared to cases whose CRP remained ≤10mg/L (Subacute-Subacute).

2. In addition, it would be of interest if this group of patients were undergoing different therapeutic regimes as compared to RA patients not ending up with a joint replacement. I am not sure if this would be possible. At least this possibility should be included in the discussion.

This is the subject of current investigation. A reference is made in the discussion to this.
Reviewer THREE (Andrew P Andonopoulos)

1. The way they are written, the terms acute and sub-acute appear as if referred to CRP status. This is not correct. These terms apply to clinical conditions and not to laboratory values. They should therefore be used as indicative of acute or subacute disease status.

Comment accepted. We have changed all references of acute and subacute to high and low respectively.

2. Furthermore, the arbitrary cutoff at the level of 10mg/L of CRP, to indicate acute or sub-acute disease, is rather inappropriate. This is more important especially for values just or slightly above 10mg/L, which may not reflect significant disease activity, as values well above this level would. This point, to our opinion, is particularly important, and we would suggest that the authors use wider ranges of CRP values to categorize disease activity (**).

In this instance we decided to use an a priori classification of CRP status based on population norms which classify 10mg/L as the 95th percentile\textsuperscript{1,2}. Levels above this are regarded by the American Heart Association and Centers for Disease Control as ‘highly elevated’.

In the first part of the study we attempt to quantify burden of inflammation using log mean CRP observed between diagnosis (or onset of symptoms) and study endpoint. The entire range of values contributes to the Cox modeling in this instance.

In the second part of the analysis we attempt to classify direction of change in CRP when observed over fixed period. The reviewer will appreciate how this limits the statistical power of the cohort and that further classification of disease status would have resulted in groups too small to usefully analyse.

In this regard we have not sought to explicitly characterize disease activity by the accepted measures (e.g. count of swollen or tender joints) and acknowledge we are unable to do in this primary care dataset.

We believe the concordance of results using either a statistical classification (tertiles of mean CRP [Figure 1]) and an a priori population-based classification (for CRP change) serve to strengthen the manuscript.

3. In lines 11-12, the way it is written the phrase suggests that the analysis was associated with a 36% increase in the hazard ratio of surgery. It should be corrected to indicate that the increase (itself) in log mean CRP is associated with the risk.

The statement is corrected.

4. In line 14, “Repeated CRP observations around one year apart”: Does this mean that CRP values were recorded once a year? If yes, this does not accurately reflect the disease activity status of the patients during the observation periods. They should have had more than one CRP determinations per year (**).

We refer the reviewer to the methods section. Cases were selected in whom, following the first-ever CRP observation, we observed at least one CRP observation in a period between 9 and 15 months later. Some cases may have had multiple observations during the intervening period, although this was not explicitly quantified. As the reviewer correctly states, the quality of data in this primary care dataset is unlikely to be reflective of specialist rheumatology practice. Despite this, strong associations emerge.
5. The studies referenced by the authors #2, 3 and 4 have been published prior to the introduction of anti-TNF treatments, therefore they do not reflect the current status of the long term prognosis of RA. The same may be true for reference #1. No one of the patients in that study had received biologics (**).

Whilst this is true, in the UK the biologics (adalimumab, etanercept and infliximab) have only recently (September 2007) been approved by NICE for the routine management of RA, and then only after trials of at least two DMARDs. In 2007 primary care prescriptions for adalimumab and etanercept accounted for 0.4% of all DMARDs, making their presence on practice databases vanishingly small. Their long-term benefit on relevant endpoints such as TJA will not be established until a substantial body of practice data has accrued. Until then surrogates of the disease process including inflammatory markers can give an indication of the likely prognosis when these agents are used. The present analysis attempts to answer whether one of these surrogates, CRP, has value in the prognosis of TJA. The efficacy of the biologics in reducing progression to TJA is neither made nor implied.

6. In page 4, lines 1-2: ESR and CRP are not biochemical parameters.

Sentence revised.

7. Line 7 of the same page: Reference #12 does not refer to orthopedic prognosis in RA but to cardiovascular prognosis in dialysis patients. Therefore the authors, just before citing that reference and at the end of the sentence, should write: “as has been true for evaluation of the effect of such changes upon the risk of cardiovascular disease in other patient groups (12).”

Sentence revised. Thankyou.

8. Multiple copy-editing suggestions.

All incorporated. Thankyou.

9. Third paragraph: The authors say that they included CRP changes “where at least two observations were recorded approximately one year apart (±90 days in order to recruit sufficient cases)”. This statement may imply that the majority of their cases had hardly any CRP observations within 9-15 months, which, if true, is rather inappropriate in the follow up of a chronic inflammatory disease such as RA. Furthermore, the mean values obtained from these CRP observations may not be reflecting the CRP evolution over the observation period. Following that, the authors claim that the baseline CRP values and those of follow up were defined as the average or mean of the values obtained within 90 days of the observation. They should provide some information about the average number of CRP determinations over the observation periods (**).

More detail provided.

10. Page 9, First Paragraph: It is very unclear how many CRP determinations in average corresponded to each case subjected to joint replacement. If the 24,023 CRP observations corresponded to the 125 cases with joint arthroplasty (which was performed after an average of 49 months following diagnosis of RA), this roughly would suggest that each such case had an average of 4 CRP measurements per month. Is that true?? If yes, it should be stated. If not, then the authors should better provide more accurate data and in a more understandable way (**).

Text amended for clarity.
11. Also, the fact that “Among 7,121 cases with newly diagnosed rheumatoid arthritis, 3,576 had at least one valid CRP measurement….” indicates that the remaining 3,545 did not have any CRP determination. Is that true?? If yes, this indicates a poor follow up practice of the RA cohort studied (**).

The cases without CRP were historically older (median year diagnosis was 1997 CF. 2001 for those analysed). Given secular changes in practice, especially the more widespread and earlier use of DMARDs, it was prudent to exclude these older cases as they would no longer be representative of current TJA prognoses.

12. Page 10, 2nd paragraph: It is stated that “Repeated CRP observations at one year were available for 1,287 subjects, of whom 54 experienced at least one major joint replacement”. It is unclear whether these figures ascertain statistical significance to the results. This is extremely important, because it is this cohort of 1287 individuals (of whom 54 ended up with arthroplasty) which provides “novel and meaningful” information to the study, i.e. the effect of CRP evolution upon the end point of joint replacement. Perhaps the authors should focus on this group only, because the data on the remaining, with only one CRP determination, offer nothing new, since they represent cross-sectional study results. (***)

The reviewer has misunderstood the data. Among the first sample analysed (2,421 cases), 76% had more than one CRP measurement. We disagree with the reviewer that the results from the first analysis (log mean CRP) offer nothing new. Given the majority of cases selected have more than one CRP determination our use of the average value may be interpreted as an approximation of inflammatory burden between index and endpoint. At the time of writing we are not aware of any similar findings from routinely collected data. We also present data to show that CRP does not appear to change in a time-dependent manner in this cohort.

In the sub-sample described, only cases with CRP measurements repeated around one-year after the first measurement were included. Table 3 illustrates the CPHM model including CRP change as a factor and we have explicitly stated the level of statistical significance in the results section on page 10 but have reworded the text for added clarity.

13. 3rd Paragraph: The authors should change the sentence, because what they really mean is that: the hazard of TJR in the preexisting acute (AA) cases was twice that of stable sub-acute (SS) cases.

Text amended. Thankyou.

14. Finally, in the discussion section, the authors should be somewhat less adamant about the “striking” correlation of mean CRP change with TJR outcome, keeping in mind the limitations of their study (**).

Text amended.

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