Reviewer’s report

Title: Tissue metabolite of type I collagen, C1M, and CRP predicts structural progression of rheumatoid arthritis

Version: 0 Date: 12 Sep 2018

Reviewer: Janet Huebner

Reviewer's report:

The study by Bay-Jensen, et al reports on the utility of high serum levels of biomarkers C1M and C3M, compared to CRP and RF, for their prognostic value of structural disease progression and the potential to be used as tools for enrichment of clinical trials. This elegant assessment of biomarkers reflecting different aspects of disease pathogenesis (inflammation and autoimmunity vs tissue metabolism) suggest that C1M may be a useful tool for the much needed enrichment of clinical populations for disease progression, resulting in significant reductions of patients needed and costs of conducting the trial.

Major concerns:

1) C1M and CRP appear to have performed similarly and there was no indication that C1M provided any additional prognostic value over that of CRP for the purposes of enrichment of clinical trials. The authors themselves state (p12, line 36) that they saw "very similar patterns for C1M and CRP which could indicate that the markers would perform equally well in enrichment for patients with a structural progressive disease." However, since these two markers are indicative of different processes (inflammation vs tissue metabolism), is it possible for the authors to provide some additional discussion about the value of C1M as a biomarker of type I collagen metabolism and how that relates to RA disease progression? What unique information can C1M provide?

2) There is a bias in the patient selection that would result in enrichment for structural progressors since the OSK clinical trials included RA patients who were not only selected partly based on high CRP levels, as the authors indicate, but who also had an inadequate response to treatments (MTX, DMARDS, anti-TNF). Please include this as an additional limitation.

3) The power calculation is based only on C1M, but one would assume, as the authors stated, that similar reductions would be possible by using CRP. It would be powerful to know how patients selected based on high C1M vs high CRP differ and how individual biomarkers may
be useful in trials assessing different therapeutic treatments focused on different disease processes.

Minor Concerns:

1) P6, line 10 and p11, line 37: Although type I and type III collagen may be among the most abundant in the body, type III collagen is not the most abundant in the joint.

2) P7, line 33: please clarify the method by which radiographic progression was defined specifically, '…changes >0.23 units linear extrapolated from >0.5 units/year'.

3) There are several grammatical errors that require correction

4) P8, line 41: "A pooled dataset of 474 placebo and MTX-treated patients.." does this mean that only some of the placebo patients were MTX-treated or all of them? If all, I would suggest re-writing as follows: 474 placebo (MTX-treated).

5) P8, line 46: please clarify by changing to the following - "Of the 474 patients, 181 patients with inadequate response to the therapy went into escape at week 12…"

6) P10, line 13. The authors state that the overlap between patients identified by C1M and CRP was 80%, but it would be useful to know what percentage, if any, were uniquely identified by C1M.

7) P13, line 10. Insert (see supplement) after 'reduce patient numbers by 50%.'

8) In tables, please include the units of measure for biomarker concentrations

9) In methods or supplement - please include metrics of ELISA based assay for C1M and C3M (inter- and intra-assay CVs; percent measurable, etc)

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

Yes

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes
Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
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