Reviewer's report

Title: Serum levels of reactive oxygen metabolites at 12 weeks during tocilizumab therapy are predictive of 52 weeks-disease activity score-remission in patients with rheumatoid arthritis

Version: 1 Date: 21 Jul 2019

Reviewer: David Liew

Reviewer's report:

Dear Dr Nakajima and colleagues,

Thank you for your manuscript and the chance to read it. This is an interesting study which aims to achieve a laudable aim: that is, a biomarker for response from tocilizumab in RA, given that response may be delayed and conventional inflammatory markers are unhelpful. The data may therefore be of interest to a broad rheumatological audience, even despite other recent publications addressing a similar problem (which you have addressed in your manuscript). This manuscript nevertheless would benefit from consideration of substantive changes before publication.

Major points:
Please detail how the cut-off value was determined (e.g. was this an ideal cut point determined from a Youden's J statistic, based on the DAS28-ESR remission data?). The ROC presumably refers to ROM at 12 weeks, please include this in both the body text and figure caption (and also within Table 4). Also do not refer to AUC for ROC as 'not statistically significant' unless it is being compared to another ROC, even if the correlation or the difference between mean scores is not statistically significant. If discussing ROCs for CRP and MMP-3, please mention the AUC, particularly given that the ROC for CRP appears to visually closely match the ROC for ROM.

Please express within the 'Results' section the variables identified by stepwise method in the multivariable logistic regression. Did it include bDMARD naïve status and prednisolone exposure status? If not, it should be explicitly stated that these did not affect the association.

Does the disconcordance between the associations correlating to CDAI and DAS28-ESR remission affect the generalisability/application of your observations, especially given that your discussion implies that the DAS28-ESR result is in part an artefact of the disease activity estimation? Please include in discussion.

It appears that ROS may or may not actually represent an index of disease activity, as it may not necessarily be involved causally but may merely be present in patients who respond to disease. It may be worth explicitly highlighting that this is a biomarker predictive of future response rather than an index of disease activity, particularly as in the second part of the background you move quickly from talking about CRP and ESR (traditionally primarily thought of as indices of disease activity) to talking about the need for novel biomarkers, without signposting the difference.
Minor points:

Background:
Given that the role of ROM (and oxidative stress in general) in the pathogenesis of RA are not commonly known to the lay rheumatology reader, you might consider a hypothesising introductory sentence at the beginning of the relevant paragraph in the 'Background' (first page of Background, line 51) to explain the biological plausibility behind your study.
You might reconsider the wording in the final sentence of the 'Background' in order to not incorporate results prior to the 'Results' (i.e. avoid stating that you "verified that ROM is a useful biomarker to monitor the treatment process during TCZ therapy" prior to describing the study results").

Methods:
Conventionally, background characteristics of the cohort (and reference to the corresponding Table 1) would be included in the 'Results' - there does not seem to be a necessary rationale for the inclusion of this in 'Methods'.

Results:
The section order makes this harder to follow. Strongly consider moving the discussion about ROM kinetics (which makes up the core part of the section 'Changes in ROM serum levels in the DAS-remission and non-remission groups at 52 weeks of treatment') after the comparisons of parameters at 4 and 12 weeks, to give rationale as to why the kinetics of ROM serum levels by DAS28 remission is of specific interest.
Suggest expressing sensitivity and specificity as percentages.

Tables:
With the table captions, make it clear that 'remission' is remission at 52 weeks, and 'non-remission' is non-remission at 52 weeks - this may otherwise be less clear given the time frame titling the tables.

Figures:
Figure 2: please do not stagger the remission/non-remission points so greatly as it is not visually apparent that the data points relate to the same time point (i.e. the 'non-remission' and 'remission' week 0 data point are highly staggered). This would actually make the difference between the two groups more apparent.

I look forward to your response, and thank you once again for your submission.

Best wishes,

David Liew
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?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

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