Author's response to reviews

Title: The presence of KIR2DS4 full-length gene decreases a chance of rheumatoid arthritis patients to respond to methotrexate treatment

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Our answers to the Reviewers' comments:

Reviewer: Jeng-Hsien Yen

- In addition to MTX, is there any other DMARD combined in this study?
All patients did not receive other DMARD. Now, it has been stated in the text.

- The definitions for good and poor responses may be inadequate. It is not easy to achieve complete remission in the treatment of RA. Therefore, it is not adequate to use whether remission or not as the response criteria. Furthermore, the definition for remission of RA is not DAS28 < 2.4. It is suggested to use EULAR response criteria in this study.

In our opinion, DAS28 remains common parameter to MTX therapy efficiency assessment, and is still used in clinical practice as well as in research analyses. DAS28 are used in the following timely papers, e.g.:


4. Dhir V, Sandhu A, Gupta N, Dhawan V, Sharma S, Sharma A. Low serum levels of myeloid progenitor inhibitory factor-1 predict good response to


However, we agree that DAS28 #2.5 is not a definition for remission of RA. Now, we assumed DAS28 #2.5 represents good response to MTX, but does not indicate the remission of RA symptoms.

Reviewer: Tony Bjourson

1. It has been reported that there is a lack of response to methotrexate in 30-40% of treated patients and that there is a scarcity of clinically reliable markers of response to methotrexate. The authors clearly state that they aim to examine the association of carriership of specific KIR genes with response to methotrexate. However, if this paper aims to address this unmet clinical need, they should state this in the introduction section and state how their work meets this need in the conclusion section.

This is, as the reviewer admits, “clearly stated” both in the Introduction:

“As KIR and KIR ligand genotypes affect immune response, and seem to impact on response to RA treatment using anti-TNF-# agents [13], we wondered whether these genotypes might also influence the outcome of MTX therapy of RA.”

- and in the Discussion:

“This report confirms that almost one third of patients affected by rheumatoid arthritis does not respond to low-dose MTX treatment [Maillefert et al, 2010, Copone et al, 2000, Dervieux et al, 2004, Marchespi et al, 2003]. This phenomenon causes that the discovery of (bio)markers of response to the drug are still required for clinical practice. Here, we found a negative association of KIR2DS4f gene with a response of RA patients to MTX treatment.”

- as well as in the Conclusion:

“This study reports that the presence of KIR2DS4 full-length gene decreases a
probability of patients affected by rheumatoid arthritis to respond to methotrexate therapy. (...) Therefore, KIR typing may help to predict a response to MTX therapy, especially for patients with moderate rheumatoid arthritis.”

3. The data appears to be sound - in this report the response and non-response to methotrexate was approximately 57.3% and 42.6% respectively, in general agreement with previous studies, this could also be stated.


5. Are the discussion and conclusions well balanced and adequately supported by the data?
   Discretionary revision
   We hope that the discussion is balanced better now.

7. Discretionary revision - state the percentage of rheumatoid arthritis patients that are methotrexate responders and non-responders generally and how that compares with their findings.
   It has been stated in Discussion section, as suggested.

8. Do the title and abstract accurately convey what has been found? Yes, an appropriate title that adequately reflects the aims of the research and the content of the paper.
   Minor Essential Revisions
   Abstract is modified according to content.

9. Is the writing acceptable? Yes - the writing is generally good. There are a number of grammatical errors throughout that should be corrected prior to publication.
   We hope we have sufficiently corrected grammatical errors in our text.