Author's response to reviews

Title: Clinical and radiological dissociation of anti-TNF plus MTX treatment in early rheumatoid arthritis in routine care. Results from the ABRAB study

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Author's response to reviews: see over
Dear Editor,

Please find attached our article on the efficacy of anti-TNF + MTX therapy on dissociation of clinical activity and radiological progression in early rheumatoid arthritis. To our knowledge this is the first publication on this phenomenon in clinical routine care. Formerly this manuscript was sent to Arthritis Research and Therapy. After reviewing our paper some notifications and comments have been made and it was recommended to send it to BMC Musculoskeletal Disorders. The appropriate revisions requested by the peer reviewers of Arthritis Research and Therapy have been performed and so your medical Editor can consider the manuscript for publication.

Next you can find the two reviewers’ comments and below them our reflections from point to point on it. The modified sections have been highlighted in our article with bold italic style.

Reviewer I.
„This is a nicely written and presented manuscript reporting outcomes of standard of care therapies in a relatively small observational cohort of patients in the early stages of rheumatoid arthritis. The question of distinctions in outcome between cohorts of patients treated with MTX alone or with combination anti-TNF and MTX therapy has been addressed many times in the contexts of various patient cohorts and at different stages of the evolution of RA. Studies have been published based on randomised, controlled clinical trials as well as observational cohorts. Nonetheless, this study adds to the body of literature on this topic and the findings are consistent with previously reported data. In essence, key findings are that with respect to the outcomes assessed, the MTX and anti-TNF combination gives rise to favourable radiographic outcomes over treatment with methotrexate alone, but with respect to symptoms and signs and remission criteria, both treatment strategies in early arthritis are broadly comparable with respect to outcomes.

Reviewer II.
„The authors provide interesting evidence for the existence of a dissociation between disease activity and radiological progression in patients treated with anti-TNF in combination with MTX, as opposed to patients treated with MTX alone. Especially Figure 3 convincingly presents the difference in progression between responders and nonresponders in the two treatment groups. The novelty of this study lies in the daily practice setting; however, as the authors acknowledge in their conclusions, daily practice settings are at high risk for bias. As the two treatment groups differ in many ways, the effect might not be attributed to the dissociation alone. I have the following concerns:
1. The major limitation of this study is that the patients in group A and B are not comparable with regards to disease duration and past treatment and are consequently at different stages in their disease
process. Table 1 presents the baseline SvH score, which is 5 points higher in group B compared to group A. From literature we know that the rate of radiographic progression may be highest at the early stages of the disease. So in theory, group B has already been through a period of rapid radiographic progression and is now stabilising, while group A is just commencing that period. On the other hand, one might argue that the patients in group B have a worse prognosis compared to the patients in group A, as they have already failed one or two DMARDs, in which case the halt of progression in group B is even more newsworthy. I miss this reflection on the results in the discussion of the manuscript.

2. Although the authors state that there are no statistical differences between the two groups in baseline characteristics, the difference in age is remarkable, especially since you would expect the patients on aTNF+MTX to be older instead of 5 years younger, as they have already failed one or 2 DMARDs.

3. I miss information on disease duration of the two groups to be able to interpret the above; this should be presented in Table 1.

Minor comments:

4. The limitations are currently presented in the conclusion paragraph. I would move the limitations to the discussion paragraph, so that the conclusions contain only conclusions.

5. Figure 3: as opposed to the table and other figures, this graph presents the two treatment groups (A and B) on the y-axes and the progression on the x-axes. I would suggest to switch these in order to improve readability.

6. Table 1: most variables do not need a precision of 2 digits

Our reflections on the reviewers’ comments are the follows

1. All patients in both groups are early RA patients thus all can be in the same phase of radiological progression. The baseline radiological score between the two groups is different in numbers but without statistical significance. Van der Heijde modified Sharp (vdHS) method scores values between 0-448, so on this scale numerical difference of 5 points at the baseline radiological status probably does not mean any different stage of disease process. Nevertheless the anti-TNF + MTX treated Group B patients could have worse prognosis on radiological progression because of their earlier failure of one or two different DMARDs.

2. We agree that there is a numerical difference of age between the two groups but it is statistically not significant. Even in case of statistical significance this difference would not exclude the comparability of the groups.

3. We provided precise information on the disease duration of the two groups in Table 1. (highlighted)

4. The limitations of the study in the conclusions have been moved to the discussion paragraph (highlighted)
5. Figure 3 was modified after the suggestion of the reviewer (earlier version of Figure 3 is also uploaded, named Figure3_earlier)

6. The precision of 2 digits was reduced to 1 at the variables in Table 1. (can’t be highlighted)

Hopefully the revised paper will be considered suitable for publication in your journal. Thank you very much for your efforts,
yours sincerely

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