**Author’s response to reviews**

**Title:** Evaluating the therapeutic efficacy of the Chinese herbal medicine, Yishen Tongbi decoction, in patients with active rheumatoid arthritis: Protocol for a randomized, controlled, noninferiority trial

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**Author’s response to reviews:**

Dear Oscar Bortolami and reviewers:

Thank you for your letter and the reviewers’ comments on our manuscript entitled “Evaluating the therapeutic efficacy of the Chinese herbal medicine, Yishen Tongbi decoction, in patients with active rheumatoid arthritis: Protocol for a randomized, double-blind, prospective controlled trial” (TRLS-D-19-00917). Those comments are very helpful for revising and improving our paper, as well as the important guiding significance to other research. We have studied the comments carefully and made corrections which we hope meet with approval. The main corrections are marked in red in the manuscript and the responds to the reviewers’ comments are as follows.

Replies to the Associate Editor’s comments:

i. It is not clear whether the study is a superiority or non inferiority. From sample size you mention non inferiority. However it is not clear which will be the non inferiority margin and the rationale for choosing it.

Response : In the new title and the part of Research design, we pointed out that this study is a non-inferiority study. In the section of sample size, we added a non-inferiority margin of -0.1 and some relevant references.
ii. It is not clear which will be the primary analysis and how non inferiority will be assessed (e.g. upper/lower confidence limit greater/lower than the non inferiority margin). For additional details see CONSORT for non inferiority design (Piaggio2016)

Response: In the part of Statistical analyses, we clarified that the good response rate of CDAI in the Chinese medicine group is not lower than the one of CDAI in the western medicine group by a margin of $-0.1$, indicating that the efficacy of traditional Chinese medicine is not inferior to western medicine.

iii. As a reviewer point out creating responder/non responders from a continuous outcome can create a loss on statistical efficiency (Senn2009)

Response: In the treatment of rheumatoid arthritis, the “Treat to Target” has been widely recognized and accepted by rheumatologists since 2014, which requires doctors to set goals, striving to achieve this goal during the treatment. The target was defined as clinical remission or at least low-disease activity since these states has conveyed the best and second-best outcomes in RA[1]. Therefore, we pay more attention to the response rate than the reduction of the indicator value. The vast majority of clinical studies in the treatment of rheumatoid arthritis use the response rates as endpoints indicator[2-4]. In recent years, CDAI has become increasingly important in the evaluation of the disease activity for rheumatoid arthritis, so we decided to treat CDAI good response as the primary outcome of efficacy [5-8].

references


iv. Please consider the use of ANCOVA (i.e. using baseline assessment as covariate) has having more power than a t test (Van Breukelen2006)

Response: After knowing the advantages of ANCOVA, we determined to use ANCOVA instead of t-test as the analyses method.

Replies to the reviewers’ comments:

Reviewer #1:

1. For all patients, it is necessary to specify medications in use including NSAIDs and corticosteroid before and during the trial.

Response: Treatment can be maintained if the patient has taken a steady dose of a corticosteroid or a non-steroidal anti-inflammatory drug before the trial.

2. For the exclusion criteria, are there any requirements in the white blood cell count, level of alanine aminotransferase, aspartate minotransferase and serum creatinine since the drugs may be cause liver or renal damage.
Response: We have added the above description to the exclusion criteria. The content is as follows: White blood cell (WBC) < $3.5 \times 10^9$/L, Hemoglobin (Hb) < 100 g/L, Alanine Aminotransferase (ALT) or Aspartate Aminotransferase (AST) $\geq 1.5$ times the upper limit of normal value (ULN), Serum creatinine (Scr) $>$ the upper limit of normal value.

3. The definition of serious adverse event: RA also may cause disability and inability to work. How to distinguish from drug-related adverse events?

Response: We have reinterpreted the disability and inability working in serious adverse events to rule out the joint damages caused by rheumatoid arthritis itself.

4. What's the limitation of this trial?

Response: We have added the limitations of the trial at the end of the article. The content is as follows: Our research also has some limitations. First, there are some subjective indicators in the study that are evaluated by patients and doctors. Thus, these results may be influenced by their preferences. We can only let doctors maintain a relatively-uniform standard for evaluation, further teaching patients how to evaluate disease situation correctly. Secondly, during the research process, patients may have difficulty in adhering to the 24-week study because of various reasons, so we need to strengthen the follow-up, and communicate with patients in time to minimize the loss rate.

Reviewer #2:

1. Please include the detailed amount of each ingredient in Yishen Tongbi decoction, and constituents for placebo of both TCM and MTX.

Response: In the interventions section, we have a detailed amount of each ingredient in Yishen Tongbi decoction, and constituents for the placebo of both TCM and MTX.

2. Please add references for Action of TCM, and the previous studies in Sample size section.

Response: We have also added both references for ‘Action of TCM’, and the previous studies in the Sample size section.

3. Please explain the reason to give folic acid for patients of RA.

Response: We have explained the reasons why we give folic acid for patients of RA in the part of interventions. The content is as follows: Systematic evaluation shows that the folic acid...
supplementation during methotrexate treatment can reduce the adverse reactions, such as gastrointestinal side effects and liver damage.

4. As for outcomes, please explain why you use proportion of patients who achieve good response rather just the change of score.

Response: In the treatment of rheumatoid arthritis, the “Treat to Target” has been widely recognized and accepted by rheumatologists since 2014, which requires doctors to set goals, striving to achieve this goal during the treatment. The target was defined as clinical remission or at least low-disease activity since these states has conveyed the best and second-best outcomes in RA[1]. Therefore, we pay more attention to the response rate than the reduction of the indicator value. The vast majority of clinical studies in the treatment of rheumatoid arthritis use the response rates as endpoints indicator[2-4]. In recent years, CDAI has become increasingly important in the evaluation of the disease activity for rheumatoid arthritis, so we decided to treat CDAI good response as the primary outcome of efficacy [5-8].

references


7. Anderson JK, Zimmerman L, Caplan L, Michaud K. Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score With 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score Without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). Arthritis care & research. 2011;63(S11):S14-S36.


5. Use standardized terminology for feng, shi, etc.

Response: We have deleted these unstandardized terminologies.

Once again, thank you very much for your constructive comments and suggestions which would help us in depth to improve the quality of the paper.

Kind regards,

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