Author’s response to reviews

Title: Does rituximab improve clinical outcomes of patients with thyroid-associated ophthalmopathy? A systematic review and meta-analysis

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Author’s response to reviews:

Dear Roberta Scherer:

We appreciated for your and the reviewers’ helpful and valuable comments concerning our manuscript (BOPH-D-17-00470R1). We have made corrections according to the reviewer’s comments. We believe that the quality of the revised manuscript has been improved based on reviewers’ comments. Our detailed point-by-point responses to the reviewer’s comments are as following:

1. The research question should be explicitly stated. An explicit question includes the PICO characteristics (participants, interventions, comparison (if applicable), outcomes and study design), or in the case of cohort/observational studies, the participants, interventions, and outcomes and types of studies. From my reading of the review, it appears your question is “In persons with thyroid-associated ophthalmopathy, does rituximab increase the mean clinical activity score one month or more after treatment? The population (persons with TAO), intervention (RTX) and outcome (CAS activity after one month) are all defined.

Response: We appreciate your suggestion. We have stated the research question as “we did a systematic review and aimed to check whether the CAS activity improved one month or more after RTX treatment for persons with TAO.” in the Introduction Part of the revised manuscript.
2. The methods for screening and selecting the included studies need to be provided. You said that two persons completed the electronic searches. Were these done independently? What happened if the title/abstract was unclear? How were discrepancies resolved? Was the intended method to first review the abstracts in duplicate and then download the full length articles for detailed review of adherence to eligibility criteria – this is typically what is done.

Response: Thanks for this suggestion. We have revised the methods for screening and selecting the included studies. For example, “To assess the evidence on this issue, a broad literature search was independently initiated by Changjun Wang and Qingyao Ning through the PubMed, EMBASE, and SCOUPS databases for articles published up to July 3, 2017 (Appendix 1).” We also added that “Discrepancy was finally resolved by another reviewer (Juan Ye).” Please see them in the Search strategy Part of the revised manuscript.

3. I appreciate that you used GRADE for assessment of quality by OUTCOME. However, PRISMA request that information about the STUDY is provided (items 12 and 19 specifically mention by individual study). Instruments such as the Cochrane risk of bias tool (for trials) or the NewCastle Ottawa tool (for observational studies) are used and then the results of these are used to inform the GRADE assessment. A table with the risk of bias for each study should be included in addition to the table provided showing GRADE assessment (Table S2). Describing the assessment again requires you to say who evaluated the ‘quality’ of the studies and whether this was done in duplicate with disagreements handled by consensus. It is really great to see that you used some assessment of quality to interpret the study results – good step!

Response: Thanks for this suggestion. We have provided Cochrane risk of bias tool for trials and the Newcastle-Ottawa Scale tool for observational studies to inform the GRADE assessment. Please see them in the Table S1-S2, Figure S1-S2 of the revised manuscript.

4. It does appear that you looked for subgroups for heterogeneity, but do not include this information in the methods section. In the methods section, you simply state that state that you used a random effects model if the I2 was higher than 50%. In addition to this, you should indicate that you did look for clinical heterogeneity before doing any statistical testing.

Response: We appreciate this suggestion. We have added the sentence that “We performed subgroup analysis for heterogeneity according to CAS, proptosis, TRAbs, TSH and IL-6.” Please see them in the Statistical Analysis Part of the revised manuscript.
5. Per PRISMA, please state the role, if any, your funding source had in designing or conducting this review, or state that they had no role.

Some minor comments:

SCOPUS (not SCOUPS) is incorrectly spelled

Cohort (not corhort) is incorrectly spelled in Table 1

Response: We appreciate your suggestion. We have revised and stated that “Supported by grants from the Medicine and Health Science Technology Project of Zhejiang Province (2015KYA113) the Scientific Research Foundation of Traditional Chinese Medicine of Zhejiang Province (2015ZB031) the National Natural Science Foundation of China (81670888), National key research and development program (2016YFC1100403). These funding had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.” Please see them in the Funding Part of the revised manuscript. We also revised incorrect spelling including SCOPUS and Cohort. Please see them in Table 1 of the revised manuscript.