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-17-00470). 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. There is no explicit statement of the question being addressed in this review. The only place any statement is included is at the end of the introduction “…systematic review and meta-analysis of the therapy and aimed to quantify the efficacy of the drug on thyroid function and the clinical behavior of TAO.” An explicit question includes the PICO characteristics (participants, interventions, comparison, outcomes and study design).

Response: We appreciate your suggestion. We have revised the sentence as “we did a systematic review and meta-analysis and aimed to quantify the variation of the clinical behaviour and thyroid function before and after treatment with RTX for patients with TAO.” in the Introduction Part of the revised manuscript.
2. Is there a protocol published or registered for this review (i.e., in Prospero)?

Response: We are sorry that there is not a protocol published or registered for this review. However, we still appreciate you that we will do it for future review.

3. The inclusion criteria are not clearly defined. It is not at all clear what you mean by ‘…according to PRISMA’ when referring to inclusion criteria. PRISMA is a guideline for reporting all essential criteria for a systematic review. What population was included? One can assume that you included persons with thyroid associated ophthalmology, but how were they defined. What interventions were allowed – rituximab, but were there any concentration or other characterisics that were inclusion criteria. You have included outcomes, but these need to be defined more precisely. For example, how was clinical activity score (CAS) defined for inclusion in your review. If you used whatever definitions were provided by the investigators of included papers, that should be stated.

Response: Thanks for this suggestion. We have specifically described study selection, and defined clinical activity score (CAS) more precisely in Data extraction and quality assessment Part of the revised manuscript. For example, “The criteria deciding whether an article was included were as following: (1) cohort study or randomized controlled trial including RTX treatment for patients with TAO; (2) clinical data involving before-after RTX treatment would be available; (3) original articles including one or more parameters of CAS, TRAbs, proptosis, TSH, and IL-6 levels after clinical follow-up of at least 1 month.” “In this analysis, disease activity was estimated according to the seven-point CAS using Snellen chart based on the classical signs of inflammation (ocular pain, eyelid redness, eyelid swelling and fading eyesight)[11]. For each of included studies, CAS was calculated to examine the clinical improvement of these patients at the each ophthalmological visit.”

4. The outcomes need to be more clearly defined. Which is the primary outcome? Which are secondary outcomes? Also, keep in mind that a fully defined outcome includes 5 elements: domain (e.g., visual acuity), measurement (e.g., ETDRS chart); time frame (e.g., 1 month); metric (e.g., change from baseline); and method of aggregation (e.g., mean).

Response: Thanks for this suggestion. We have clearly defined the outcomes in Data extraction and quality assessment Part, and Statistical analysis Part of the revised manuscript. For example,” in view of mean CAS as the primary outcome, and mean of TRAbs, proptosis, TSH, IL-6 levels as secondary outcomes.”
5. Methods used for data extraction should be included – who extracted the data, was data extraction done in duplicate, what data collection forms were used, etc.

Response: We appreciate this suggestion. We have added these authors in Material and methods Part of the revised manuscript. Additionally, data collection forms were also attached in the supplementary files.

6. Similarly, who evaluated the ‘quality’ of the studies using GRADE? Again, how was this done, e.g., in duplicate with disagreements handled by consensus? Also, how were these data used to interpret the results of the meta-analyses?

Response: Thanks for this suggestion. We have provided these authors’ names, procedures, and explanations for GRADE in Data extraction and quality assessment, and Results Part of the revised manuscript.

7. For heterogeneity, instead of simply moving to a random effects model with high heterogeneity, one should first look for clinical heterogeneity – are the studies so different clinically that they should not be combined (e.g., one study included patients with clearly more severe disease than the others). Only if the studies are clinically similar is it reasonable to then consider using a random effects model.

Response: We appreciate this suggestion. In this study, we only included patients with TAO treated by RTX according to the predefined inclusion criteria. We appraised the between-study heterogeneity based on subgroups such as the primary outcome (CAS), and secondary outcomes (TRAbs, proptosis, TSH, IL-6 levels) in order to enable results precise using a random effects model if $I^2$ more than 50%.

8. Include the results from the Risk of Bias assessment – again, this could be a supplemental finding. Were the results of the risk of bias assessment used in any way to interpret the data? For each study, instead of simply presenting the GRADE summary, indicate why each study was downgraded – and present this information in a separate table (as a supplement).
Response: Thanks for this suggestion. We have interpreted the risk of bias assessment in Characteristics of eligible studies in the final analysis Part of the revised manuscript, and present the reasons of each subgroup in Table S1.

9. Table 1 – instead of retrospective or prospective, replace with study design (i.e., randomized controlled trial, prospective cohort, case control, retrospective cohort, cross-sectional etc. – the information that you included in Table S1). For randomized trials, indicate what the control group was. The formal name of the country is United States, not America. For age, indicate what measures are presented – one would need to assume you mean mean+ SD, but is the lower number in parentheses the IQR or the range? What does the number under smoking represent? Also include the outcomes that were measured in each study in this table – not necessarily the results, but which outcomes were included in which study. For Table S1, I do not understand what the ‘comparator.

Response: Thanks for your suggestion. We have updated Table to keep correspondence with Table S1. We also revised the formal name of the country America as United States, and labeled (Mean±SD) (Range). The number under smoking in Table 1 represents the number of population in smoking status. In addition, we include the outcomes that were measured in each study in Table 1. Because this analysis included before-after studies of RTX therapy for TAO, and we marked what the comparator was in Table S1.

10. Instead of including the Forest plot figures as supplemental information, include these in the text. Table 2 may not necessarily be needed then as it appears to be a summary of the information in the figures.

Response: Thank you for this suggestion. We have included Forest plot figures in the text, and replaced Table 2 as Table S2 for supplemental information.

11. Figures – please label the figures with the treatments compared and the time point to make it easier for the reader to find the figure corresponding to the text in the Results section.

Response: Thanks for this suggestion. We have labeled the figures and also provided figure legends at the end of the manuscript.
12. Per PRISMA, please include your funding source to conduct this review, or state that you had no funding

Response: We appreciate this suggestion. We have included funding source at the end of the manuscript.