Author’s response to reviews

Title: Ramosetron for the treatment of irritable bowel syndrome with diarrhea: a systematic review and meta-analysis of randomized controlled trials

Authors:

Qingqing Qi (qiqingqing@sina.com)
Yan Zhang (muyeyuanzhu@gmail.com)
Feixue Chen (chenfeixueok@126.com)
Xiuli Zuo (zuoxiuli@sina.com)
Yanqing Li (liyanqing@sdu.edu.cn)

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Author’s response to reviews:

Dear Editor:

Firstly, we are deeply sorry for our delay of the revised manuscript. Thank you for giving us the precious opportunity for a revision of our manuscript. We appreciate very much the comments and suggestions from the reviewers and editors. Those comments are all valuable and very helpful for revising and improving our manuscript. We have studied the reviewers’ comments very carefully and tried our best to improve the manuscript. The followings are our point-by-point responses to the original reviewers’ remarks.

Reviewer reports:

Reviewer #1:

1. The meta-analysis is done very methodically and systematically. However, I do have concerns regarding the generalizability of the results. The authors correctly point out that the study involves only Japanese patients. Even after that is taken into account, it should be noted that the 4 randomized control trials eventually included are actually just by 2 groups of investigators.

Response:
We greatly appreciate your valuable comments and admire your profound knowledge. As you have mentioned, our study involves only Japanese patients, and the 4 randomized control trials eventually included are actually by 2 groups of investigators. These limitations might influence the generalizability of our results. However, we systematically searched the Pubmed, MEDLINE, EMBASE and the Cochrane Library, and included studies strictly according to the study selection criteria. All the included trials had high quality. What is more, there are relative large amounts of participants enrolled in each trial, which could partly compensate the relative small absolute number of clinical trials included in this meta-analysis. As you have emphasized, further clinical trials are necessary to establish a more powerful evidence for the use of ramosetron in IBS-D, and to reveal the efficacy of ramosetron in a broader population worldwide.

2. Secondly, meta-analyses are done with the intent of pooling data together to resolve conflicting signals from existing literature. In this case it appears that all the 4 studies included already show consistent benefits of the drug in question, so I am not sure what the authors intend to achieve. In its current form, it only serves the purpose of a useful review article. The only instance among all the Forest plots, where the total risk ratio is different from one of the included studies, is in the case of Total Adverse events, and even in that case, it is not significant. The overall results are expected because of the obviously apparent results of the included RCTs.

Response:

Thank you very much for your careful review. We totally agree with you that meta-analyses are done with the intent of pooling data together to resolve conflicting signals from existing literature. Although it appears that all the 4 studies included in our meta-analysis already show consistent benefits of the drug, there is still no evidence for the efficacy of ramosetron for IBS-D based on the systematic review and meta-analysis. What is more, the efficacy of ramosetron on the treatment of both male and female IBS-D population, and the safety data of ramosetron, need to be clearly elucidated. Therefore, we performed this systematic review and meta-analysis of randomized, controlled trials comparing ramosetron with placebo in the treatment of IBS-D, and finally we provide more accurate and comprehensive results to systematically evaluate the efficacy and safety of ramosetron in the treatment of abdominal symptoms and bowel function in IBS-D.

3. Thirdly, due to the difference in the sample size of the component RCTs, a sensitivity analysis should be performed to ensure one of the studies is not having an undue influence on the final relative risk. One way to do this would be to exclude each of the studies at a time
and re-analyze the remaining. In this case, I anticipate that although the relative risk might change, the conclusions will be the same.

Response:

Thank you very much for your professional suggestion. In our revised manuscript, we perform the sensitivity analysis by excluding each of the studies at a time and re-analyze the remaining studies as your suggestion. As you have anticipated, although the relative risk changed, the conclusions are the same after the sensitivity analysis. We have added the related results in the revised manuscript. (Methods section, line 19-21, page 8; Results section, line 2-7, page 13; Results section, Table 2, page 30)

4. Lastly, even though the included studies are randomized control trials, the authors have not used a formal scale for study assessment (e.g the Newcastle Ottawa scale) to comment on study quality. The authors have also not commented on the coefficient of agreement between the authors in the section where 'disagreements were resolved by discussion'—Page 6, Line 14.

Response:

We greatly appreciate your careful review and we are sorry for the unclear statement. In our study, we assessed the quality of included studies using the Cochrane Risk of Bias assessment tool.[1] According to the Cochrane Handbook for Systematic Reviews of Interventions, risk of bias assessment tool could be used for study quality assessment of randomized control trials. The same assessment method could be found in previous meta-analysis.[2-5] Thank you very much for your kind comments and we have revised some sentences in our revised manuscript to make the statement more clear. (Methods section, line 2-4, page 8)

In our study, two reviewers independently performed the study search process and disagreements were resolved by discussion. In fact, in this section of our study the coefficient of agreement between the authors was 1.0, which meant that there was no disagreement between the two authors. The reason for this was that both authors strictly followed the search criteria we established in this section. They used the same search terms in the same databases with no language or document type restrictions. All bibliographies of the identified relevant studies were also checked carefully to identify any additional studies. After scanning titles and abstracts of articles selected from the initial search, we read through the full text of eligible articles. We are sorry for our unclear statement in this section and we have revised our manuscript according to your comments in the revised manuscript. (Results section, line 10-17, page 10)
References:


5. Overall, although I feel that the study adds somewhat to the existing literature by combining the limited existing literature on Ramosetron, a more appropriate time to do this study would be when we have more (and possibly conflicting) data on Ramosetron.

Response:

Thank you very much for your kind comments and professional suggestions. We have studied your comments carefully and tried our best to revise our manuscript following your suggestions, all of which could help to improve our manuscript. As you have mentioned that this study did add somewhat to the existing literature by combining the existing literature on Ramosetron. We hope that you could be satisfied with our revised manuscript.

Reviewer #2:

I have read with interest the systematic review and metaanalysis by Qi et al where the authors studied the safety and efficacy of Ramosetron in patients with diarrhea predominant IBS.
1. Introduction may be shortened. Lines 2,3,4 on page 5 can be removed from the introduction.

Response:

Thank you very much for your kind comments. We have removed the contents of lines 2,3,4 on page 5 to shorten the introduction as your suggestion. (Background section, line 1-4, page 5)

2. Since most outcomes are subjective and were likely measured on an ordinal scale i.e. relief of abdominal discomfort, diarrhea etc. and were analyzed as dichotomous outcomes in the meta-analysis, the authors should clarify whether definitions for symptom relief were consistent across studies. Were subjective outcomes measured using standardized/validated tools in different studies? If not, the authors should discuss how this could impact interpretation of their study findings in the limitations section of the paper.

Response:

We greatly appreciate your valuable comments and admire your profound knowledge. Although most outcomes in the included studies are subjective and were measured on an ordinal scale, and were analyzed as dichotomous outcomes in the meta-analysis, the definitions for symptom relief were consistent across studies. In all included studies, the monthly responder was defined as a patient who had experienced “Completely relieved” or “Considerably relieved” for at least 2 weeks of the 4-week treatment, and the monthly responder rate of “symptom relief in IBS” was analyzed in these studies. What is more, in these different studies subjective outcomes were measured using standardized and validated tools. Severity of abdominal pain and discomfort was assessed daily on a 5-point scale (0: none, 1: mild, 2: moderate, 3: severe, 4: intolerable), and stool form data was scored on a 7-point ordinal scale according to the Bristol Stool Form Scale. Above consistent definitions for symptom relief and standardized and validated tools used for subjective outcomes measurement all make the pooled estimates in our meta-analysis robust and convincing. Thank you very much for your professional suggestions and we have revised our manuscript following your suggestion in our manuscript. (Discussion section, line 3-15, page 17)

3. The authors present a subgroup analysis of outcomes according to sex. Was there an interaction of sex with treatment allocation for safety and efficacy outcomes?

Response:

Thank you very much for your comments and we are sorry for the unclear statement. In our meta-analysis, we pooled the dichotomous data of relief of overall IBS symptoms. For both male and female patients, ramosetron could lead to significant relief of overall IBS symptoms (RR 1.94; 95%CI 1.58, 2.38 vs RR 1.49; 95%CI 1.25, 1.79. respectively). These results suggested
that there was no interaction of sex with treatment allocation for safety and efficacy outcomes. In our meta-analysis, we present a subgroup analysis of outcomes according to sex because the 5-HT3 receptor antagonist alosetron has been approved for only female patients with IBS-D. Many possible factors, including sexual cycle, biobehavioral responses to stress, differences in roles and emotions between males and females, may affect gender differences in the response to treatments with alosetron and ramosetron.