Journal of Clinical Question

**Decision Letter (JCQ-2026-0034)**

**From:** [redacted]
**To:**
**CC:**
**BCC:**

**Subject:** Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0034

**Body:** 17-Oct-2026

Dear Professor Shimada:

Manuscript ID JCQ-2026-0034 entitled "Efficacy and Safety of B-Cell-Targeted and Conventional Immunomodulatory Therapies for IgG4-Related Disease: A Systematic Review and Meta-Analysis of Randomized Trials" which you submitted to the Journal of Clinical Question, has been reviewed. The comments of the reviewer(s) are included at the bottom of this letter.

The reviewer(s) have recommended publication, but also suggest some revisions to your manuscript. Therefore, I invite you to respond to the reviewer(s)' comments and revise your manuscript.

To submit your revised manuscript, follow the below steps.
1. Access to https://mc.manuscriptcentral.com/jcq and log into the site.
2. Click "Author" at the top left of the screen at "Home" page.
3. Click "Manuscripts with Decisions" on Author Dashboard page.
4. Click "create a revision" on the manuscript you are going to revise.
5. The system creates your revision manuscript form. Provide your comments about the revised points at the response field, fill in on each field step by step as same as you did for the original submission, and submit your revised manuscript.
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Your manuscript number has been appended to denote a revision.

You will be unable to make your revisions on the originally submitted version of the manuscript. Instead, revise your manuscript using a word processing program and save it on your computer. Please also highlight the changes to your manuscript within the document by using the track changes mode in MS Word or by using bold or colored text.

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When submitting your revised manuscript, you will be able to respond to the comments made by the reviewer(s) in the space provided. You can use this space to document any changes you make to the original manuscript. In order to expedite the processing of the revised manuscript, please be as specific as possible in your response to the reviewer(s).

IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.

Because we are trying to facilitate timely publication of manuscripts submitted to the Journal of Clinical Question, your revised manuscript should be uploaded as soon as possible. If it is not possible for you to submit your revision in a reasonable amount of time, we may have to consider your paper as a new submission.

Once again, thank you for submitting your manuscript to the Journal of Clinical Question and I look forward to receiving your revision.

Sincerely,
Richard S. Isaacs
Editor in Chief
Journal of Clinical Question

[Editor's Comments]
Associate Editor
Comments to the Author:
(There are no comments.)

[Reviewer(s)' Comments]

Reviewer: 1

Comments to the Author
The authors conducted a systematic review and pairwise meta-analysis of randomized controlled trials (RCTs) to assess the efficacy and safety of conventional immunomodulatory and B-cell-targeted treatments. They found that both treatments improved remission and reduced relapse compared with their respective controls. However, due to limited statistical power and differences in study settings including the definitions of several parameters, it was not achievable to make a valid comparison between the drugs under evaluation, which limits the significance and novelty of the present study.

Reviewer: 2

Comments to the Author
This manuscript addresses a clinically relevant question regarding the efficacy and safety of conventional immunomodulatory and B-cell-targeted therapies for IgG4-related disease. The inclusion of five randomized controlled trials provides useful evidence for clinical decision-making. However, several methodological and reporting issues require clarification before the manuscript can be considered for publication.
Table 1 is referenced in the Results section but was not included in the materials provided for review. Please ensure that the table is available and contains the characteristics of all five included RCTs.
The Methods section describes independent data extraction by two reviewers but does not specify whether title/abstract screening and full-text eligibility assessments were performed independently. Please clarify the study selection procedure and how disagreements were resolved.
The potential influence of Chen et al., particularly its per-protocol data, warrants further investigation. Please verify the reported sensitivity analysis for adverse events and consider additional sensitivity analyses for remission and relapse.
The Introduction describes glucocorticoid exposure as being evaluated descriptively, whereas the Results report a statistical comparison between treatments (P = 0.061). Please clarify that this analysis was exploratory to maintain consistency across sections.

**Date Sent:** 17-Oct-2026

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**Author's Response to Decision Letter for (JCQ-2026-0034)**

**Efficacy and Safety of B-Cell-Targeted and Conventional Immunomodulatory Therapies for IgG4-Related Disease: A Systematic Review and Meta-Analysis of Randomized Trials**

Dear Reviewers,
Thank you for the opportunity to revise our manuscript for consideration in the Journal of Clinical Question. We appreciate the careful evaluation and constructive comments from you and the reviewers. We have addressed each point and made focused revisions to improve the clarity of the methods, the interpretation of treatment comparisons, and the reporting of sensitivity analyses.
In particular, we have emphasized the limitations of indirect comparisons, clarified independent study screening and consensus procedures, added sensitivity analyses excluding Chen et al. for remission and relapse, and identified the comparison of additional glucocorticoid exposure as exploratory. We have also ensured that Table 1 accompanies the manuscript and reconciled relevant reporting across the main text and supplementary material.

Reviewer 1
Comment 1
The authors conducted a systematic review and pairwise meta-analysis of randomized controlled trials (RCTs) to assess the efficacy and safety of conventional immunomodulatory and B-cell-targeted treatments. They found that both treatments improved remission and reduced relapse compared with their respective controls. However, due to limited statistical power and differences in study settings including the definitions of several parameters, it was not achievable to make a valid comparison between the drugs under evaluation, which limits the significance and novelty of the present study.
Response. We appreciate this important concern. We have revised the Discussion to distinguish treatment effects estimated against the respective randomized control groups from direct comparisons among active treatments. We now emphasize that the between-category differences in remission, relapse, and adverse events were not statistically significant, and that differences in study populations, background glucocorticoid regimens, and outcome definitions limit the interpretation of indirect comparisons. We have also clarified the contribution of this updated review, particularly the inclusion of the 2026 phase 3 obexelimab trial and the outcome-specific safety and exploratory flare-rate analyses. The limitations and Conclusion continue to state that the available evidence does not establish superiority of one treatment over another in the absence of head-to-head trials. (Page 13, lines 2–13; page 14, lines 14–22; page 15, lines 1–7.)
Reviewer 2
Comment 1
Table 1 is referenced in the Results section but was not included in the materials provided for review. Please ensure that the table is available and contains the characteristics of all five included RCTs.
Response. Thank you for identifying this omission from the review materials. Table 1 is included in the revised manuscript and summarizes all five randomized trials, including their interventions, comparators, analyzed sample sizes, baseline characteristics, follow-up durations, and glucocorticoid regimens. The table footnote also distinguishes the 60 participants randomized in Chen et al. from the 57 participants included in its per-protocol analysis. (Page 10, lines 11–13; page 19, Table 1.)
Comment 2
The Methods section describes independent data extraction by two reviewers but does not specify whether title/abstract screening and full-text eligibility assessments were performed independently. Please clarify the study selection procedure and how disagreements were resolved.
Response. We have clarified the study selection procedures in the Methods. Two reviewers independently screened titles and abstracts and assessed the eligibility of full-text reports. We have also specified that disagreements arising during study selection or data extraction were resolved by consensus. (Page 8, lines 1–10.)
Comment 3
The potential influence of Chen et al., particularly its per-protocol data, warrants further investigation. Please verify the reported sensitivity analysis for adverse events and consider additional sensitivity analyses for remission and relapse.
Response. We agree that the use of per-protocol data in Chen et al. warrants assessment of its influence. In addition to the previously reported adverse-event sensitivity analysis excluding Chen et al. (RR, 1.01; 95% CI, 0.98–1.04; $I^2 = 0\%$), we conducted separate sensitivity analyses for remission and relapse. After exclusion, the pooled estimates remained statistically significant for remission (RR, 1.74; 95% CI, 1.35–2.23; $I^2 = 24.7\%$) and relapse (RR, 0.38; 95% CI, 0.24–0.62; $I^2 = 54.8\%$). These findings are now reported in the corresponding Results subsections. The Results and Table 1 also identify the per-protocol denominators used for Chen et al. (Page 10, lines 11–21; page 11, lines 1–14; page 19, Table 1.)
Comment 4
The Introduction describes glucocorticoid exposure as being evaluated descriptively, whereas the Results

report a statistical comparison between treatments (P = 0.061). Please clarify that this analysis was exploratory to maintain consistency across sections.
Response. We have revised the Introduction and Statistical Analysis subsections to make clear that the additional glucocorticoid-exposure comparison was exploratory. The P value of 0.061 reflects a test for differences between trial-level treatment effects, not a direct randomized comparison between inebilizumab and obexelimab. We have retained the caveat that the two trials defined additional glucocorticoid exposure differently, limiting the interpretation of this comparison. (Page 6, lines 6–8; page 9, lines 15–17; page 12, lines 3–7.)

We hope that the revised manuscript and the additional analyses adequately address the reviewers' concerns. Thank you for your consideration of our revised submission.
Sincerely,
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