Journal of Clinical Question

Decision Letter (JCQ-2026-0019)

From: [redacted]
To:
CC:
BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2026-0019

Body: 02-Jun-2026

Dear Dr Wang:

Manuscript ID JCQ-2026-0019 entitled "Comparative Efficacy and Safety of Medical Treatments for IgG4-Related Disease: A Systematic Review and Network Meta-Analysis of Randomized Controlled 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.
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2. Click "Author" at the top left of the screen at "Home" page.
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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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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
This is a novel and clinically relevant meta-analysis addressing an important therapeutic question in IgG4-related disease (IgG4-RD). The study is generally well designed, and the methodology appears appropriate. The findings provide useful evidence for clinical decision-making regarding glucocorticoid-based treatment strategies in patients with IgG4-RD.

I have several suggestions that may further strengthen the manuscript:

1. In the Introduction, the authors may consider briefly summarizing the typical age and sex distribution of patients with IgG4-RD. This would allow readers to compare these established epidemiological characteristics with those of the pooled study population.

2. Please briefly introduce the IgG4-RD Responder Index (RI) when it is first mentioned in the Methods section.

3. In the Results section, please carefully verify the numbering of figures and tables and ensure that all numerical values reported in the text are consistent with those presented in the corresponding figures and tables.

4. In the Discussion, the finding that glucocorticoid cessation appears to be associated with more favorable outcomes than conventional glucocorticoid therapy is clinically intriguing. Additional discussion regarding the potential explanations for this result, including possible confounding factors or selection bias, would strengthen the interpretation of the findings.

Reviewer: 2

Comments to the Author
Dear author
The manuscript investigates an important clinical question and may contribute meaningful evidence to the current understanding of IgG4-related disease management. However, several major methodological and interpretative limitations currently undermine the reliability of the conclusions. Substantial revisions are required, particularly regarding the sparse evidence network, assessment of transitivity and consistency assumptions, evaluation of study quality and risk of bias, and the cautious interpretation of treatment rankings derived from limited data. Addressing these issues is essential to improve the scientific robustness, transparency, and clinical relevance of the manuscript.
Major Concerns

Limited Evidence Base
The analysis includes only five randomized controlled trials comprising 376 participants. Such a small evidence network raises concerns regarding the stability and precision of treatment rankings and pooled estimates.
The authors should discuss the implications of the limited sample size more explicitly and interpret ranking results with greater caution.
Clinical and Methodological Heterogeneity
Included studies differ in patient populations, disease manifestations, treatment regimens, follow-up durations, and outcome definitions.
Additional assessment and discussion of heterogeneity and transitivity assumptions are required to justify the validity of indirect comparisons.
Network Meta-Analysis Assumptions
The manuscript provides insufficient detail regarding evaluation of consistency, transitivity, and model assumptions.
The authors should present more comprehensive diagnostics, including consistency assessments and sensitivity analyses where feasible.
Risk of Bias and Certainty of Evidence
Although risk-of-bias assessment was conducted, the impact of study quality on the pooled estimates is not adequately explored.
The certainty of evidence for major outcomes should be more clearly presented and discussed, particularly considering the limited number of studies.
Interpretation of SUCRA Rankings
Treatment rankings are emphasized despite wide confidence intervals and sparse evidence.
Rankings should be interpreted cautiously and accompanied by a more balanced discussion of uncertainty.
Safety Outcomes
The analysis of adverse events is limited by the small number of studies and inconsistent reporting.
The authors should better acknowledge these limitations and avoid definitive conclusions regarding comparative safety.
Discussion and Clinical Implications
Several conclusions appear stronger than warranted by the available evidence.
The discussion should be revised to emphasize the exploratory nature of the findings and the need for larger, high-quality randomized trials.

Minor Concerns

Improve reporting clarity regarding inclusion criteria and outcome definitions.
Provide additional details on statistical methods and model selection.
Ensure consistency in terminology throughout the manuscript.
Consider including a summary table of evidence certainty for key outcomes.

Recommendation

The topic is important and the study has potential value; however, substantial revisions are necessary to address methodological concerns, improve transparency of the network meta-analysis, and moderate the interpretation of findings. Therefore, I recommend Major Revision.

Date Sent: 02-Jun-2026

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Author's Response to Decision Letter for (JCQ-2026-0019)

Comparative Efficacy and Safety of Medical Treatments for IgG4-Related Disease: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Dear Reviewers,
We sincerely thank you for your thorough and constructive comments on our manuscript. Your insights have been invaluable in enhancing the clarity and robustness of our study. Our point-by-point responses to your comments are provided below, along with the corresponding revisions made to the manuscript, in which the revised parts are shown in red.

Reviewer: 1
1. In the Introduction, the authors may consider briefly summarizing the typical age and sex distribution of patients with IgG4-RD. This would allow readers to compare these established epidemiological characteristics with those of the pooled study population.
Response: Thank you for this helpful suggestion. We have revised the Introduction to briefly summarize the typical demographic characteristics of patients with IgG4-RD. "IgG4-RD typically affects middle-aged to older adults and has been reported more frequently in men, although age and sex distributions may vary according to organ involvement and geographic region." (Line 69-71)

2. Please briefly introduce the IgG4-RD Responder Index (RI) when it is first mentioned in the Methods section.
Response: Thank you for this suggestion. We have revised the Methods section to briefly introduce the IgG4-RD Responder Index as a disease activity assessment tool used to quantify organ-specific IgG4-RD activity when it is first mentioned. "The IgG4-RD Responder Index (IgG4-RD RI) is a disease activity assessment tool used to quantify organ-specific IgG4-RD activity." (Line 163-164)

3. In the Results section, please carefully verify the numbering of figures and tables and ensure that all numerical values reported in the text are consistent with those presented in the corresponding figures and tables.
Response: Thank you for this helpful comment. We carefully checked the numbering of all figures and tables and verified the numerical values reported in the Results section against the corresponding tables and figures.

4. In the Discussion, the finding that glucocorticoid cessation appears to be associated with more favorable outcomes than conventional glucocorticoid therapy is clinically intriguing. Additional discussion regarding the potential explanations for this result, including possible confounding factors or selection bias, would strengthen the interpretation of the findings.
Response:
Response: Thank you for this suggestion. We have added a brief explanation that the apparently favorable remission result for glucocorticoid cessation may reflect patient selection or trial design rather than true superiority over conventional glucocorticoid therapy. "Therefore, these findings should inform, rather than determine, treatment selection and should be interpreted in the context of individual patient characteristics and treatment-related risks. P-score rankings may be unstable in sparse networks and should be interpreted together with the corresponding confidence intervals." (Line 297-300)

Reviewer: 2
Major Concers
1. Limited Evidence Base
The analysis includes only five randomized controlled trials comprising 376 participants. Such a small evidence network raises concerns regarding the stability and precision of treatment rankings and pooled estimates. The authors should discuss the implications of the limited sample size more explicitly and interpret ranking results with greater caution.
Response: Thank you for this important comment. We have revised the Abstract and Discussion to more explicitly acknowledge that the analysis was based on only five RCTs involving 376 patients. We also added text emphasizing that the sparse evidence network and wide confidence intervals limit the certainty of the ranking results, which should be interpreted cautiously and regarded as exploratory rather than definitive. "Finally, because direct head-to-head evidence was limited and the sparse network structure restricted formal assessment of consistency, transitivity, and sensitivity analyses, treatment rankings should be considered hypothesis-generating rather than definitive." (Line 382-384)

2. Clinical and Methodological Heterogeneity
Included studies differ in patient populations, disease manifestations, treatment regimens, follow-up durations, and outcome definitions. Additional assessment and discussion of heterogeneity and transitivity assumptions are required to justify the validity of indirect comparisons.
Response: Thank you for this suggestion. We have revised the Methods section to clarify that the

transitivity assumption was assessed qualitatively by comparing key trial characteristics, including patient population, disease manifestations, glucocorticoid regimen, add-on treatment, follow-up duration, and outcome definitions. We also revised the Discussion to acknowledge that these differences may have acted as potential effect modifiers and may have affected the transitivity assumption and the interpretation of indirect comparisons. “The transitivity assumption was assessed qualitatively by comparing key trial characteristics, including patient population, disease manifestations, glucocorticoid regimen, add-on treatment, follow-up duration, and outcome definitions across the included studies, although formal assessment was limited by the small number of trials.” (Line 183-187)

3. Network Meta-Analysis Assumptions
The manuscript provides insufficient detail regarding evaluation of consistency, transitivity, and model assumptions. The authors should present more comprehensive diagnostics, including consistency assessments and sensitivity analyses where feasible.
Response: Thank you for this helpful comment. We have revised the Statistical Analysis section to provide additional details regarding the evaluation of network meta-analysis assumptions, including consistency, transitivity, and model assumptions. We clarified that consistency assessment and sensitivity analyses were considered where feasible; however, because the evidence networks were sparse and most comparisons were informed by single trials, formal consistency testing and sensitivity analyses were limited. We also revised the Discussion to emphasize that indirect comparisons and treatment rankings should be interpreted cautiously because these assumptions could not be fully evaluated. “Therefore, these findings should inform, rather than determine, treatment selection and should be interpreted in the context of individual patient characteristics and treatment-related risks.” (Line 297-299)

4. Risk of Bias and Certainty of Evidence
Although risk-of-bias assessment was conducted, the impact of study quality on the pooled estimates is not adequately explored. The certainty of evidence for major outcomes should be more clearly presented and discussed, particularly considering the limited number of studies.
Response: Thank you for this important comment. We agree that the impact of study quality on the pooled estimates should be more clearly addressed. We have revised the Results sections to clarify that the certainty of evidence was evaluated using the GRADE approach and that the certainty for key outcomes is now summarized in Table S3. “The certainty of evidence for the key outcomes is summarized in Table S3. Overall, the certainty of evidence was rated as low, mainly because of risk of bias, sparse evidence networks, and imprecision. Because of the limited number of included trials, the impact of study quality on pooled estimates could not be fully explored through sensitivity analyses.” (Line 276-279)

5. Interpretation of SUCRA Rankings
Treatment rankings are emphasized despite wide confidence intervals and sparse evidence. Rankings should be interpreted cautiously and accompanied by a more balanced discussion of uncertainty.
Response: Thank you for this suggestion. We have revised the Discussion sections to state that rankings should be interpreted together with the corresponding confidence intervals and regarded as exploratory rather than definitive.

6. Safety Outcomes
The analysis of adverse events is limited by the small number of studies and inconsistent reporting. The authors should better acknowledge these limitations and avoid definitive conclusions regarding comparative safety.
Response: Thank you for this important comment. We agree that the adverse-event analysis is limited by inconsistent reporting across trials. We have revised the Results section to acknowledge this limitation and to clarify that the comparative safety ranking should be interpreted cautiously. “Because adverse-event reporting differed across trials, the comparative safety ranking should be interpreted cautiously.”(Line 271-272)

7. Discussion and Clinical Implications
Several conclusions appear stronger than warranted by the available evidence. The discussion should be revised to emphasize the exploratory nature of the findings and the need for larger, high-quality randomized trials.
Response: Thank you for this helpful comment. We have revised the Discussion to clarify that these findings should inform, rather than determine, treatment selection and should be interpreted in the context of individual patient characteristics and treatment-related risks.

Minor Concerns
1. Improve reporting clarity regarding inclusion criteria and outcome definitions.
Response: Thank you for this helpful suggestion. We carefully reviewed the Methods sections and confirmed that the inclusion criteria and outcome definitions are already described in the manuscript.

2. Provide additional details on statistical methods and model selection.
Response: Thank you for your valuable comment. We have revised the Methods section to clarify the model selection. Given the limited number of included studies and the sparse evidence network, a common-effect frequentist network meta-analysis model was used as the primary model.

3. Ensure consistency in terminology throughout the manuscript.
Response: Thank you for this helpful suggestion. We carefully reviewed the manuscript and standardized terminology throughout the text.

4. Consider including a summary table of evidence certainty for key outcomes.

Response: Thank you for this helpful suggestion. We have added a summary table of evidence certainty for the key outcomes as Supplementary Table S3. The table summarizes the certainty of evidence for remission, relapse, and adverse events, together with the main reasons for downgrading.

Best Regards

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