Decision Letter (JCQ-2025-0011)

From: [redacted]

To:

CC:

BCC:

Subject: Journal of Clinical Question - Decision on Manuscript ID JCQ-2025-0011

Body: 24-Apr-2025

Dear Professor Elsharkawy,

Manuscript ID JCQ-2025-0011 entitled "Efficacy of Immunosuppression Therapy in Primary IgA Nephropathy in Adults: 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 minor 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.
IMPORTANT: Your original files are available to you when you upload your revised manuscript. Please delete any redundant files before completing the submission.
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.

Once the revised manuscript is prepared, you can upload it and submit it through your Author Center.

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 Isaacs
Editor in Chief, Journal of Clinical Question
jcqeic@gleampub.com

[Editor's Comments]
Associate Editor
Comments to the Author:
Thank you for your submission to JCQ
After reviewing and assessing the credibility of the current submission, the presented evidence is perfect and outstanding for publishing in the JCQ and constitutes clinical efficacy for practical purposes. Although it is well presented, it requires some minor revisions regarding the discussion section, clinical applicability in daily practice, and limitations of the current analysis.
The Discussion section must be improved by adding a paragraph that highlights the comparison of the respective parameters with conventional immunosuppression. Additionally, adverse effects must be clarified by comparing different studies, particularly regarding monoclonal antibodies. The clinical applicability of these drugs was also discussed.
In the limitations sections, all the limitations presented are generalized. The issue of heterogeneity must be discussed in the limitations section in a separate paragraph by mentioning the source of heterogeneity. Despite having high heterogeneity regarding the GFR parameter, meta-regression and sensitivity analyses were not available to provide clear evidence.

[Reviewer(s)' Comments]
Reviewer: 1

Comments to the Author
This study evaluated both conventional immunosuppressive therapies and emerging targeted agents through a network meta-analysis (NMA), the authors tended to provide timely evidence to guide clinical decision-making, particularly for high-risk patients with persistent proteinuria. However, there are still some important issues need to be addressed.
Overview:
1. The search strategy may not appropriate, as some important studies have not been included in the study, such as Telitacicept
2. In the methodology, the SC group and placebo should be combined as one group.
3. PCR and proteinuria were similar or same as effective marker, and they should be converted uniformly and then analyzed as one marker.

Major concerns：
1. Inadequate Handling of Heterogeneity: The random-effects model is mentioned, but sources of heterogeneity (e.g., baseline patient characteristics, dosing variations, follow-up durations) are insufficiently explored. For example, the eGFR analysis shows high heterogeneity (I2=73.7%), yet subgroup analyses (e.g., RAAS inhibitor use across studies) or meta-regression are absent. Sensitivity analyses to address this limitation should be concerned.
2.·Insufficient Risk of Bias Assessment: Risk of bias is only summarized in supplementary materials (Figure S6), with no discussion of its impact on results. For instance, two studies were rated as having "considerable risk of bias," but potential effects on efficacy rankings (e.g., open-label designs overestimating corticosteroid effects) are not addressed. Expand this discussion in the main text.
3. Lack of Transparency in Search Strategy: The full search strategy (mentioned as "S Table 1") is not provided in supplementary materials. Include detailed search terms (how the complement inhibitors were termed).
4. Inconsistent Findings: Atacicept 150 mg ranks highest for UPCR reduction (SUCRA=0.905) but only moderately for proteinuria reduction (SUCRA=0.564). This discrepancy is unexplained and may reflect differences in outcome measurements or study populations.
5. Tacrolimus is associated with the highest AE risk (OR=76.0), but specific AEs (e.g., infections, nephrotoxicity) are not detailed or discussed.
6. Overlapping node labels (e.g., Figure1B "Atacicept 75–150mg). Optimize layout or split.

Reviewer: 2

Comments to the Author
The IgA studies included in this article vary in design, follow-up duration, and outcome reporting criteria, which may affect the accuracy of the effect estimation. For example, the follow-up durations in different studies range from 16 weeks to 10 years, and the treatment durations and dosages also differ, which may lead to an increase in heterogeneity. It is necessary to point out the impact of this heterogeneity on the results and the need for unified standards in future studies. The document mentions using a random effects model to deal with heterogeneity, but the baseline differences remain a problem.
There are difficulties in combining the safety data because the definitions and reports of adverse events are inconsistent across different studies, resulting in limitations in the safety analysis.
Overall, the article provides important evidence for the immunosuppressive treatment of IgAN through network meta-analysis

Date Sent: 24-Apr-2025

Author's Response to Decision Letter for (JCQ-2025-0011)

Efficacy of Immunosuppression Therapy in Primary IgA Nephropathy in Adults: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials

Dear Editor and Reviewers,

We sincerely thank the Editor and Reviewers for their thoughtful and constructive comments on our manuscript. We appreciate the recognition of the clinical relevance and methodological rigor of our work, and we have carefully addressed all suggestions to enhance the clarity, applicability, and scientific value of the study. Below, we provide a detailed point-by-point response to each comment, with corresponding revisions incorporated into the manuscript as appropriate.

Editor Comment
Comment 1: After reviewing and assessing the credibility of the current submission, the presented evidence is perfect and outstanding for publishing in the JCQ and constitutes clinical efficacy for practical purposes. Although it is well presented, it requires some minor revisions regarding the discussion section, clinical applicability in daily practice, and limitations of the current analysis. The Discussion section must be improved by adding a paragraph highlighting the comparison of the respective parameters with conventional immunosuppression.
Response: Thank you for your positive assessment and valuable feedback. In response, we have revised the Discussion section to include a paragraph comparing the efficacy outcomes of the evaluated treatments with conventional immunosuppressive therapies, such as corticosteroids and calcineurin inhibitors. We have also addressed their clinical applicability and updated the limitations accordingly on page 16, lines 297-301.

Comment 2 Additionally, adverse effects must be clarified by comparing different studies, particularly regarding monoclonal antibodies. The clinical applicability of these drugs was also discussed.
Response: Thank you for the comment. We have expanded the Discussion to clarify adverse effects, particularly for monoclonal antibodies, highlighting key issues such as infections, infusion reactions, and hematologic toxicity. We also discussed their clinical applicability, especially in refractory cases, and added relevant references to support these points on page 16, lines 297-300.

Comment 3: All the limitations presented are generalized in the limitations sections. The issue of heterogeneity must be discussed in the limitations section in a separate paragraph by mentioning the source of heterogeneity. Despite having high heterogeneity regarding the GFR parameter,
Response: We appreciate the editor's important observation. In the revised manuscript, we have added a separate paragraph in the Limitations section specifically addressing the issue of heterogeneity. Substantial heterogeneity was observed in outcomes such as eGFR, which may be attributed to variations in study populations, treatment durations, baseline kidney function, and differences in intervention protocols. To address this, we conducted a sensitivity analysis including only studies with a follow-up duration of at least one year, as shorter follow-up periods were considered a potential source of variability. This analysis resulted in reduced heterogeneity and reinforced the robustness of the findings (page 13-14, line 246- 255).

Reviewer: 1
Comment 1. The search strategy may not appropriate, as some important studies have not been included in the study, such as Telitacicept
Response: Thank you for this valuable comment. We agree that the inclusion of all relevant studies is essential for a comprehensive and balanced network meta-analysis. Upon rechecking the results of our original search across the four databases, we confirmed that the Telitacicept study was not retrieved. However, we have now identified this study through a manual (hand) search and incorporated it into the revised analysis. Corresponding updates have been made to the Results, Discussion, and Supplementary Tables. We sincerely appreciate the reviewer's insight, which has enhanced the rigor and completeness of our study.

Comment 2. In the methodology, the SC and placebo groups should be combined.
Response: Thank you for this valuable comment. We agree that, conceptually, both supportive care (SC) and placebo groups serve as non-immunosuppressive control arms, and combining them can be methodologically justifiable. However, the two approaches differ significantly in study design—placebo arms are typically implemented in double-blind trials, whereas SC arms are often used in open-label studies. This introduces potential performance and detection biases in the SC groups due to the lack of blinding. To explore and account for these methodological differences, we analyzed SC and placebo groups separately. This approach allowed us to assess whether study design features might influence treatment effects.

Comment 3. PCR and proteinuria were similar or the same as effective markers, and they should be converted uniformly and then analyzed as one marker.
Response: Thank you for this important observation. We agree that both protein–creatinine ratio (PCR) and 24-hour proteinuria are commonly used and closely related markers for assessing protein excretion, and combining them could potentially enhance consistency in the analysis. However, in our dataset, several studies reported both PCR and 24-hour proteinuria, and we observed that the results were not consistently aligned between these two measures. Given that our analysis is based on absolute values, such discrepancies could introduce variability and reduce the reliability of the network meta-analysis. Therefore, it was not feasible to uniformly standardize and combine these outcomes across all studies. We analyzed them separately to maintain data integrity and avoid potential conversion-related bias.

Comment 4. Inadequate Handling of Heterogeneity: The random-effects model is mentioned, but sources of heterogeneity (e.g., baseline patient characteristics, dosing variations, follow-up durations) are insufficiently explored. For example, the eGFR analysis shows high heterogeneity (I2=73.7%), yet subgroup analyses (e.g., RAAS inhibitor use across studies) or meta-regression are absent. Sensitivity analyses to address this limitation should be concerned.
Response: Thank you for this important observation. To address the high heterogeneity observed in the eGFR analysis (I^2 = 73.7%), we conducted a sensitivity analysis by including only studies with a follow-up duration of at least one year, as shorter follow-up times were considered a potential source of variability. This analysis, presented in Figures S6 and S7 and Table S4, demonstrated consistent findings with significantly reduced heterogeneity (I^2 = 0%) and reinforced the robustness of the primary results. In this subgroup, PSL showed the highest efficacy with statistically significant differences compared to Sibeprenlimab (at all doses), mPSL-PSL, and Rituximab. The SUCRA rankings also supported this conclusion (page 13-14, line 246-255). While meta-regression and subgroup analyses based on RAAS inhibitor use were not feasible due to limited reporting across studies, we agree that future trials should report such variables more consistently to enable more granular analyses.

Comment 5. Insufficient Risk of Bias Assessment: Risk of bias is only summarized in supplementary materials (Figure S6), with no discussion of its impact on results. For instance, two studies were rated as having "considerable risk of bias," but potential effects on efficacy rankings (e.g., open-label designs overestimating corticosteroid effects) are not addressed. Expand this discussion in the main text.
Thank you for this important comment. We agree that the potential impact of risk of bias should be more thoroughly discussed in the main text. To minimize the influence of high-risk studies, we implemented several strategies. First, we separated studies with placebo or supportive care as the control arm, helping to reduce confounding effects. Second, for the analysis of UPCR, which served as our primary outcome, we included only studies without open-label designs, thereby minimizing the risk of performance and detection bias. In contrast, the broader proteinuria outcome included more studies, some of which were open-label, which may explain greater variability.

Comment 6. Lack of Transparency in Search Strategy: The full search strategy (mentioned as "S Table 1") is not provided in the supplementary materials. Include detailed search terms (how the complement inhibitors were termed).
Response: Thank you for pointing this out. We apologize for the oversight. The complete search strategy, including all detailed searches used for keywords such as "IgA nephropathy," "immunosuppressive," and "randomized" or "controlled" trials, has now been included in Supplementary Table S1. No language restrictions were applied. In addition, we have revised the main text to reference this supplementary table. These updates aim to improve the transparency and reproducibility of our methodology.

Comment 7. Inconsistent Findings: Atacicept 150 mg ranks highest for UPCR reduction (SUCRA=0.905) but only moderately for proteinuria reduction (SUCRA=0.564). This discrepancy is unexplained and may reflect differences in outcome measurements or study populations.
Response: Thank you for this insightful observation. The apparent discrepancy in SUCRA rankings for Atacicept 150 mg—ranking highest for UPCR reduction (0.905) but only moderately for overall proteinuria reduction (0.564)—can be attributed to two main factors. First, the difference in outcome definitions: UPCR is a standardized, quantitative marker based on spot urine samples, while overall proteinuria reduction includes a mix of 24-hour urine collection and semi-quantitative measurements, which introduces heterogeneity. Second, the sets of studies contributing to each outcome differ; the studies assessing UPCR and those assessing proteinuria involved different patient populations and baseline characteristics, which likely influenced the comparative results. A clarification has been added to the Discussion to address this point and underscore the need for standardized outcome reporting in future research (page 15, lines 270-272).

Comment 8. Tacrolimus is associated with the highest AE risk (OR=76.0), but specific AEs (e.g., infections, nephrotoxicity) are not detailed or discussed.
Response: Thank you for this critical comment. We agree that a more detailed description of adverse events (AEs) is essential for clinical interpretation. Tacrolimus showed the highest overall AE risk (OR = 76.0); however, the included studies provided limited data on specific. We have now expanded the Discussion to acknowledge this limitation and highlight the need for future trials to systematically report and categorize AEs by type and severity (page16, line 297-301).

Comment 9. Overlapping node labels (e.g., Figure 1 B "Atacicept 75–150mg). Optimize the layout or split.
Response: Thank you for pointing this out. The overlapping node label in Figure 1B corresponds to data reported as a combined dosage range of Atacicept 75–150 mg in the original study, without stratification by individual dose. As such, it is not feasible to split this node without introducing unsupported assumptions. However, to improve clarity, we have optimized the figure layout and adjusted the node positioning to reduce overlap and enhance readability.

Reviewer: 2
Comment 1 The IgA studies included in this article vary in design, follow-up duration, and outcome reporting criteria, which may affect the accuracy of the effect estimation. For example, the follow-up durations in different studies range from 16 weeks to 10 years, and the treatment durations and dosages also differ, which may lead to an increase in heterogeneity. It is necessary to point out the impact of this heterogeneity on the results and the need for unified standards in future studies. The document mentions using a random effects model to deal with heterogeneity, but the baseline differences remain a problem.
Response: Thank you for this valuable comment. We agree that variability in study design, follow-up duration, treatment protocols, and outcome definitions contributes to heterogeneity and may affect effect estimates. Although we used a random-effects model to address between-study variability, residual heterogeneity remains due to baseline differences, including treatment durations (16 weeks to 10 years) and dosing. To mitigate this, we conducted sensitivity analyses on studies with ≥1 year follow-up, which improved result consistency(page 15, lines 270-272).. We have updated the Discussion to reflect these limitations and stress the need for standardized methodologies in future IgAN trials.

Comment 2 There are difficulties in combining the safety data because the definitions and reports of adverse events are inconsistent across different studies, resulting in limitations in the safety analysis.
Response: Thank you for highlighting this important limitation. We agree that the inconsistency in definitions, grading, and reporting of adverse events across the included studies presents significant challenges in synthesizing safety data. This variability limits the ability to perform a comprehensive and reliable safety analysis. In response, we have revised the Discussion section to more clearly acknowledge this issue and to stress the need for future clinical trials to adopt standardized safety outcome definitions and reporting frameworks. Such uniformity is essential to enable meaningful comparisons and ensure the robustness of safety evaluations in future meta-analyses (page 16, lines 304-306).

Overall, the article provides important evidence for the immunosuppressive treatment of IgAN through network meta-analysis
Response: We sincerely appreciate the reviewer's positive evaluation. We are pleased that the findings of our network meta-analysis are recognized as contributing meaningful evidence to the field of immunosuppressive treatment for IgA nephropathy. Our goal was to provide a comprehensive and methodologically robust synthesis to inform clinical decision-making, and we are encouraged by your supportive feedback.

We are grateful to the Editor and Reviewers for their insightful feedback, which has significantly improved the quality of our manuscript. All suggested revisions have been carefully implemented, including enhancements to the Discussion and Limitations sections, clarification of adverse event profiles, and expanded discussion on heterogeneity and risk of bias. We hope the revised version meets the standards of the Journal of Clinical Question, and we look forward to your further evaluation.

Sincerely,
Magdy Elsharkawy, MD (on behalf of all authors)
Department of Nephrology Ain-Shams University
Email: magdi35@hotmail.com
Tel: (+20) 26831231

1. Response letter.pdf PDF

Print Close Window