MAYO CLINIC

Re: Manuscript
"Rituximab or Plasmapheresis for Prevention of Recurrent Focal Segmental Glomerulosclerosis after Kidney Transplantation: A Meta-Analysis"

Dear Editors,

Thank you for the thoughtful input and review of our manuscript. The reviewers' inputs are extremely helpful. We believe as a result of this review; our study would have more value for your readers. We revised the manuscript based on the reviewer's suggestions. We have attached our point-by-point response.

Thank you for your time and consideration. We look forward to hearing from you.

Sincerely yours,

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Response to Reviewer

Reviewer: 1

Comment to the author

Title: The title is adequate and descriptive of the manuscript

Abstract:

- Inclusion criteria were: original, published, randomized controlled cohort (either prospective or retrospective),

o I think this is a small mistake and it should be: randomized controlled trials OR cohort studies (either prospective or retrospective).

- Methods section: from the abstract, it seems that rituximab is compared to rituximab with plasmapheresis. In the methods section of the article, I read that both are combined in one group and compared to the standard treatment group. I think you should add that in your methods section in the abstract as well.

Response: Thank you for your input. We have edited the text as you suggested.

Introduction: no comments

Methods:

- The authors describe that studies were included if they mentioned odds ratio's, relative risks, hazard ratios and standardized incidence ratios. Even though ratios and relative risks can be easily transformed in one another, this is not the case for hazard ratio's as they take time-to-event into account. I am not sure whether you could pool hazard ratio's with, for example, odds ratios. Could you comment on how you took this into consideration when pooling the data?

- Recurrence is sometimes stated with risk ratio's instead of hazard ratio's. Do you have any idea within which time frame this was assessed? This is important because it is expected that it affects the size of the risk ratio/odds ratio.
- How did you account for censored patients when you did not use hazard ratio's (i.e., if there's more graft loss in one group unrelated to FSGS recurrence).

Response: We thank you for reviewing our manuscript. We really appreciated your input. We have deleted the hazard ratio from the method section since we worked with raw event data in this meta-analysis and did not have to combine odds ratio, relative risks or hazard ratio. We did not calculate the pooled risk ratio for graft loss since it would be difficult to combine hazard ratio with risk ratio as well as account for censored patients, as you suggested.

Results:

- What was the reason for excluding studies published after 2016 in the sensitivity analysis?
- ''Since these four studies were all published after 2016, we hypothesized that rituximab does not provide additional benefits in the context of better immunosuppression in modern transplant practice.''
  - Is this statement supported by any changes in immunosuppression protocol?
- What treatment was given to the comparator cohort, i.e., the 'standard treatment group'?
- Which studies noted hazard ratios and which odds/risk ratios?

Response: We really appreciated your input. We noticed that most studies published before 2016 reported positive association while later studies reported no association so we decided to do sensitivity analysis to test this observation. There was no evidence of any dramatic changes in immunosuppression protocol during this period.

However, during revision of this manuscript, we reran our literature search and included a new study by Mukku et al presented as a poster at the NKF in April 2021, which reported no recurrence in the group that received pre-emptive rituximab/plasmapheresis compared to 3/10 recurrence in the standard treatment group. In light of this new finding, we decided to leave out this sensitivity analysis based on whether the study is published before or after 2016 in the revised manuscript.

Discussion:

- Patients who received rituximab alone and patients who received rituximab with plasmapheresis were combined in the same treatment group. Could you elaborate on how this may have affected your results?

Response. Thank you for your helpful comment. The following has been added to the discussion: "to increase power, we combined the patients who received rituximab alone and those who received both rituximab and plasmapheresis into the same group, which might have overestimated the effect of rituximab. However, sensitivity analyses in the subgroup that received rituximab alone or rituximab with plasmapheresis did not change the association so this is unlikely to be significant".

Figures:

- Figure 1: numbers are incorrect at records screened step

Response: This has been revised. We appreciate your helpful comments.

General comments:

- There's some incorrect use of the semicolon where there should have been a . .Example:

o FSGS has been shown to negatively affect overall graft survival[9-12]; although the exact pathogenesis of this disease is unknown, it is believed that circulating factors, affecting podocytes and glomerular permeability, may play an important role. FSGS recurrence occurs early after kidney transplantation; thus, supporting the pathophysiological role of circulating factors.

Response: We thank you for reviewing our manuscript. We really appreciated your input. The semi colon use has been revised and edited.

Reviewer: 2

Comment to the author

The aim of this study is whether the preventive treatment of rituximab based therapy and plasmapheresis alone strategy for focal segmental glomerulosclerosis (FSGS) before kidney transplantation (KT) can reduce the incidence of recurrent FSGS or delay the timing of recurrence after KT. Research on whether a preventive strategy before KT is effective for recurrent FSGS is scarce. This study is expected to give a significant message on the prevention of recurrent FSGS through rituximab and plasmapheresis. However, this study requires several revisions.

1) The timing of post-transplant recurrence of FSGS, which is written as a result, should be included in methodology of abstract and manuscript.

2) The result of abstract needs to mention the recurrent timing of FSGS.

3) In Core tip, “FSG” needs to be modified to “FSGS”.

4) The discussion of the manuscript has a particularly low correlation between title and result. Therefore, a general revision of the discussion is required. As the authors describe, the pathogenesis of FSGS is not fully understood. Therefore, the detailed explanation of FSGS circulating factor in the discussion seems to confirm that the main pathogenesis of FSGS is circulating factor. Also, considering the title and results of this paper, the discussion needs more detailed description including an association of rituximab and plasmapheresis on the incidence and recurrence timing of recurrent FSGS after KT. When referring to the purpose of this study, which the authors wrote, "Generally, the diagnosis of primary FSGS requires ~ that were not included in our analysis." appears to be an unnecessary paragraph.

5) In conclusion, since this study cannot determine the high risk of recurrent FSGS, a revision or deletion of the sentence "However, the effectiveness of preventive therapy ~ and further research is required" seems to help to express a clearer meaning.

Response: We thank you for reviewing our manuscript. We really appreciated your input.

Comment #1 and #2: Timing of recurrence has been added to both the method and the result section of the abstract.

Comment #3: This has been edited to 'FSGS' as suggested.

Comment #4: We highly appreciate your input. The discussion part has been revised to give a uniform message.

Comment #5: The conclusion has been edited as suggested.

Reviewer: 3

Comment to the author

I reviewed a very good meta-analysis manuscript dealing with preemptive strategies in order to prevent FSGS recurrence after kidney transplantation. It shows that nor rituximab nor plasmapheresis are able to prevent recurrence. It would be nice to address whether preemptive strategies have any impact upon allograft survival and kidney allograft function.

Response: We thank you for reviewing our manuscript. We really appreciated your input. We have added a narrative review paragraph discussing the allograft function in the result section of the manuscript. Although some studies did report worse allograft function in the recurrent FSGS group, it appears that response to recurrent FSGS treatment is the main determinant of allograft function.

Thank you for your time and consideration.