Author's response to reviews

Title: Efficacy and safety of Mycophenolate Mofetil treatment on IgA nephropathy: a systematic review

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Author's response to reviews: see over
Reviewer#1's report
Title:Efficacy and safety of Mycophenolate Mofetil treatment on IgA nephropathy: a systematic review
Version:1 Date:30 July 2014
Reviewer:Hong Zhang

Reviewer's report:

General comment:
In this meta-analysis of 273 people with IgA nephropathy included in 7 available trials, Chen and colleagues found that a relatively short term of MMF use might be beneficial in IgAN patients with proteinuria, while no statistical difference was found in the whole therapeutic effect of MMF on reducing proteinuria and protecting renal function, as well as incidence of side effects compared with controls. Moreover, MMF was thought superior to cyclophosphamide in better therapeutic effects and less adverse reactions. On the basis of the above findings, the authors concluded that short term of MMF use may be beneficial in IgAN patients.

The current study has potential interest for the treatment strategy in IgAN, however, my major criticize is the sample size is limited and the studies are highly various, as high quality meta-analysis should benefits from large volume of data in high quality trials.

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Major Compulsory Revisions
Materials and Methods:
1. The authors state that undertook a systematic review of the literature according to the approach recommended by the PRISMA guidelines. However, the manuscript in its current form is missing many elements from the PRISMA checklist (e.g., Protocol, handling of Risk of Bias data, use of PRISMA flowchart). The authors should include a PRISMA checklist in the Supplemental Material: http://www.prisma-statement.org/statement.htm. Please add the study protocol with the detail search strategy as a supplemental material, and update the search results.

   Thanks for the reviewers’ advices. The the detail search strategy (Additional file1), PRISMA checklist (Additional file2.PRISMA checklist) as well as the Protocol(Additional file5.) have been added into the Supplemental Materials.

2. Because the KIDGO guideline suggest not using immunosuppressive therapy in patients with GFR<30 ml/min per 1.73 m2 unless there is crescentic IgAN with rapidly deteriorating kidney function, please clarify how many studies included the patients with GFR<30 ml/min per 1.73 m2?

   Thanks for the reviewers’ advices. How many articals included patients with GFR<30 ml/min per 1.73 m2 is not available because most studies did not
access eGFR, However, mean Scr of all patients is below 3mg/dl, which we reflected in Result/ Characteristics of the included studies (line116-118) and the table1. the basic information of involed articals.

3. The included studies were highly heterogeneous, the authors should also describe how they plan to adjust for differences in those studies and patients characteristics across studies.
   Thanks for the reviewers’ advices. We have improved our Method with a description of how we dealt with the highly heterogeneous across the studies(Line 125-133), We also mentioned it in the Discussion(Line224-240).

Results
1. The authors should consider using the PRISMA template for Figure 1: http://www.prisma-statement.org/statement.htm. Please put the Additional file 1 “characteristics of the included studies” as table 1, then provide mean GFR, mean proteinuria and mean SBP (if available) in Table 1. The risk of bias results and funnel plots should be presented in the Supplemental appendix.
   Thanks for the reviewers’ advices. Changes has been made in the flow diagram(Figure1), ‘characteristics of the included studies’(Table1.) as well as ‘The risk of bias results and funnel plots’ (Additional file3, Additional file4) as required.

2. Outcome (paragraph 1): does the therapeutic effect means the composite endpoint of complete remission significant remission and partial remission? If so, please give a clear definition, if not, please specify the endpoint event for RR separately.
   Thanks for the reviewers’ advices. We have made a clear definition of ‘the therapeutic effect’ in both Method(Line84-85).

3. Figure 2: it is a subgroup analysis of study duration, the between-group heterogeneity is not applicable, and the authors should give a meta-analysis of all included RCTs to assess the heterogeneity.
   Thanks for the reviewers’ advices. a meta-analysis of all included studies has been added as Fiuger2.

4. As the limited number of RCTs available, it would be more informative if the authors could add the observational studies and conduct a subgroup analysis of observational studies.
   Thanks for the reviewers’ advices. Results of some observational studies have been added into our Discussion(Line219-223), however, high quality observational studies is limited, subgroup analysis of observational studies can not be done.

Discussion
1. Please discuss the potential for this bias and its effect on your conclusions
that a relatively short term of MMF use may be beneficial, and explain why short term of MMF use may be beneficial.

Thanks for the reviewers’ advices. Explanation for ‘why short term of MMF use may be beneficial’ refer to Discussion(Line198-200). Potentials for this bias have been discussed in both Result (Line 124-132) and Discussion(Line224-240).

2. The authors should consider the analysis of heterogeneity source from other respects, for example race, baseline renal function, drug doses or others in the discussion?

Thanks for the reviewers’ advices. Potentials for this bias have been discussed in both Result(Line 125-133) and Discussion(Line224-240).

Minor Essential Revisions
1. Make sure to give the abbreviation and complete description the first time it appears, not the second time, see ESRD (Introduction first paragraph).

Thanks for the reviewers’ advices. Changes have been made in Abbreviation as required.

2. Materials and Methods: in the first paragraph Cochrane Library was spelled repeatedly.

Thanks for the reviewers’ advices. Changes have done as required.

3. Add the databases starting data separately in the text (material and methods first paragraph), for example MEDLINE (1946- October 2013) and update your research results.

Thanks for the reviewers’ advices. We have updated the searching results in the revision.

4. Please add the number of literature search form each database in Figure 1, also the duplicate number in Figure 1 if available.

Thanks for the reviewers’ advices. Number of literature search form each database and the duplicate number have been added into Figure 1.

5. Please consider revising the description from “with placebo (steroid)”, what it means? Does it mean “with placebo or steroid”???

Thanks for the reviewers’ advices. ‘placebo (steroid)’ has changed into ‘placebo or steroid’ in the revision.

6. Suggest the authors consult a native English speaker to polish the manuscript.

Done.

Discretionary Revisions
1. Outcome measures should be in front of the Statistical analysis.

Thanks for the reviewers’ advices. Changes have been made.

2. For your revisions, please carefully follow the PRISMA Checklist.

Done.

Level of interest: An article of importance in its field

Quality of written English: Needs some language corrections before being
Reviewer#2’s report

Title: Efficacy and safety of Mycophenolate Mofetil treatment on IgA nephropathy: a systematic review

Version: 1 Date: 4 August 2014
Reviewer: Nan Chen

Reviewer’s report:
The system review about Efficacy and safety of Mycophenolate Mofetil treatment on IgA nephropathy had provided us some useful information. These results are interesting and give the nephrologists some constructive view. Also, there are some limitations about the review as follows.

- Major Compulsory Revisions
1. Were the patients in the MMF groups, CTX group or LEF group treated with steroid meantime? Are the patients in the placebo group not given with steroid? What are the treatment regimen in the placebo group?
   Thanks for the reviewers’ advices. A more clear description of the therapeutic regimen of ‘the control group’ has been added into Result (Line 109-112) and Table1.

- Minor Essential Revisions
1. This review included 7 studies involved 273 patients, 148 of which were in the MMF groups and 125 in the control groups (48 in the placebo group, 31 in the steroid group, 26 in the CTX group, and 20 in the LEF group). The quality are quite different among these 7 studies. The race is different. The selected control groups are different.
   Thanks for the reviewers’ advices. We have improved our Method with a description of how we dealt with the highly heterogeneous across the studies (Line 125-133), we also mentioned it in the Discussion(Line224-240).

2. In the sub-group analysis in comparing MMF with CTX or LEF, the number of the studies is too few, just about 1-2 studies. Same as in the sub-group analysis in the short period or long period.
   Thanks for the reviewers’ advices. We have updated our search results in our new manuscript. There we have a new study comparing MMF with CTX, we also added some information of observational studies into our
Discussion (Line 219-223). However, the fact is, number of high quality trials of MMF treatment in IgA nephropathy is limited.

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Acceptable

**Statistical review:** No, the manuscript does not need to be seen by a statistician.

**Declaration of competing interests:**
No