Author’s response to reviews

Title: Validity and Reliability of a Novel Immunosuppressive Adverse Effects Scoring System in Renal Transplant Recipients

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Author’s response to reviews: see over
April 11th, 2014

Hayley Henderson
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Dear Dr. Hayley Henderson:

Thank you for the thorough and thoughtful review of our manuscript entitled: *Validity and Reliability of Novel Immunosuppressive Adverse Effects Scoring System in Renal Transplant Recipients* for consideration in *BMC Nephrology*. We also appreciate the efforts and suggestions of the reviewers and statistical referee.

Enclosed with this letter are the following:

1. A detailed response to reviewer’s comments found in bold italics with page and line reference to placement of these edits in the revised manuscript.

2. The revised manuscript using tracked changes in Microsoft Word.

We look forward to receiving feedback from the reviewers on this revised manuscript. Thank you for your consideration.

Best Regards,

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**Editorial Review**

Editorial Comments:

As you will see from the referees' reports, several major concerns have been raised that we would like you to address in a revised manuscript. Please ensure that you respond to each of their concerns as thoroughly as possible, as your revised manuscript will be returned to the referees for further consideration.

-- In addition to the Referees' comments, could you please also address the following editorial points --

1. **Cover Letter**
   We would be grateful if a cover letter accompanied your revised manuscript submission. This should provide a detailed point-by-point response to each of the referees' concerns, describing exactly how you responded to each point and where you can find the amendment in your revised manuscript (e.g. document line and/or page numbers). Please also highlight (with 'tracked changes'/coloured/underlines/highlighted text) all changes made to the revised manuscript to make it easier for the Editors to give you a prompt decision on your manuscript.
   
   • **Author's Response:** Thank you for the opportunity to revise this manuscript. We have included a cover letter (above) with a detailed description of our revisions and response to reviewer comments (below). All changes to the manuscript file are denoted with underlined text.

2. **Line Numbers**
   Please can you include line numbers in your revised manuscript. Please refer to these in your cover letter when describing to referees where specific changes have been made to the text in response to their concerns. This will allow both the editorial team and the referees to assess all revisions more efficiently.
   
   • **Author’s Response:** We have included line numbers in the revised manuscript which are referred to below as we respond to the reviewer’s comments.
Responses to Reviewers

Reviewer 1
Reviewer's report:
No revisions needed. Overall sounding methodology and good clinical relevance.

Author’s Response:
Thank you for the review of this manuscript. We appreciate your time and efforts.

Reviewer 2
Reviewer's report:
• Author’s Response: Thank you for the thorough and thoughtful evaluation of our manuscript.

1. Abstract - language regarding administration of AE tool seems paternalistic – administered – would change – sounds like a survey as opposed to “employed a standardized evaluation” or something like that.
• Author’s Response: This wording has been modified to reflect the thorough evaluation completed.
• Changes to Manuscript: Abstract section; Page 3, Line 16: “Nephrologists employed this standardized adverse effect evaluation process in each stable renal transplant patient…”

2. Methods - the methods section is not easy to follow. It would be easier to follow if the authors first explained the development of the tool followed by the implementation of the tool/process.
• Author’s Response: The manuscript has been revised to reflect this comment.
• Changes to Manuscript: Methods Section; Page 9 Lines 4-23 has been moved from earlier in the methods section and includes a new header on Page 9, line 4: “Implementation of Adverse Effects Scoring System”.

3. Why was baseline established as pre-transplant as opposed to at enrollment.
• Author’s Response: In this reliability/validity study, patients were assessed at a single point in time. Therefore, we used the pre-transplant baseline to determine if the adverse effects that were identified by the scoring system were associated with the immunosuppressive drugs prescribed post-transplant.
• Changes to Manuscript: Methods section; Page 9, Lines 10-11: “Adverse effects were assessed as a change from pre-transplant status in an effort to identify the post-transplant development of immunosuppressive adverse effects.”
  Additional modifications based on the comment below will also clarify this point.

4. Was the assessment performed at a standard time? Was it administered only once or multiple visits after the enrollment period? This should be clear from the methods section. If administered more than once were AEs counted multiple times? i.e. if GI sx persisted were they counted in each assessment.
• Author’s Response: This was a cross-sectional study. Stable transplant patients were evaluated for adverse effects at one time point during a clinic visit. The patient assessment was completed at a clinically stable period at least 12 months post-transplant. There was no longitudinal evaluation of adverse effects.
• Changes to Manuscript: Methods section; Page 9, Lines 8-9: “Evaluation of the immunosuppressive adverse effects using the standardized scoring system was completed once during a clinic visit for each patient in this cross-sectional study.”
5. **If AEs could be attributed to multiple medications, was this captured? How was it handled clinically?**

   **Author’s Response:** We agree that specific adverse drug effects may be due to multiple medications. This objective adverse effect evaluation was designed to quantify a composite score associated with immunosuppressive drugs and not distinguish direct causation. This issue has been included as a limitation.

   **Changes to Manuscript:** Discussion section; Page 15, Lines 6-8: “Potential construct limitations include confounding factors such as concomitant medications with overlapping adverse effects and the inability to distinguish causative relationships to individual medications.”

6. **Why is there only a cumulative score for CNI AEs vs MPA AEs. Was this a decision a priori or after the data was assessed.**

   **Author’s Response:** A cumulative score was developed as a composite quantitation of common immunosuppressive adverse effects associated with calcineurin inhibitors, mycophenolic acid, and steroids. This score is not specific to one pharmacologic category. Therefore, we have removed the notation that the cumulative score is calcineurin inhibitor related. The decision to create a cumulative adverse effect score was made a priori and has been clarified in the Methods and Discussion.

   **Changes to Manuscript:** Methods; Page 9 lines 18-23: “An overall adverse effect total was determined for each patient using the sum of individual adverse effect scores. The cumulative adverse effect ratio was then calculated as the quotient of each patient’s total score divided by the maximum score of all possible manifestations. This cumulative adverse effect ratio represented the number of adverse effects with corresponding severity rating. The gastrointestinal, central nervous system (CNS), and aesthetic ratios were generated a posteriori to further evaluate the organ system specific adverse effects.”

   Discussion section: Page 15, Lines 1-6: “The cumulative adverse effect ratio was created a priori with incorporation of the normalization for interpatient comparison. No differences were noted in the cumulative ratio between regimens. However, gastrointestinal, CNS and aesthetic adverse effect ratios were generated a posteriori to further quantitate system specific adverse effects and interpatient differences of these drug manifestations were successfully demonstrated.”

7. **Explain the utilization of scales than contain different numbers of ratings - 0-2 vs. 0-4. Can these be compared and accumulated for purposes of analyses?**

   **Author’s Response:** The scoring system includes ratings based on different numerical scales and warrants discussion in the manuscript. In order to create an objective rating scale, each level (1+ to 2+) was determined based on the smallest detectable incremental change in specific adverse effect that could be assessed clinically by the physician. During the developmental process, different rating scales (0-2+, 0-4+) for individual adverse effects resulted. The use of different rating scales is then adjusted by the use of the adverse effect ratios incorporating normalization for each total score.

   **Changes to Manuscript:** Methods Section; Page 10, Lines 3-4: “The denominator for each ratio provides normalization for the different severity rating among patients to allow comparison.”

   Discussion section: Page 13, Lines 18-23: “Differences in the rating scales for the individual adverse effects are present (i.e. 0-2+, 0-3+) based on the smallest detectable incremental change in manifestation clinically observed by the physician. This rating is adjusted by using the cumulative and organ system specific adverse effect ratios which incorporates internal normalization in order to compare patients. This approach documents adverse effect frequency and severity which is rarely verified in clinical studies.”
8. Was there a patient assessment of AEs? I would think that for really assessing the impact in particular of aesthetic and GI effects on compliance a patient-centered evaluation of the impact that these adverse effects has would be important to include.

- **Author’s Response:** The study objective was to develop and validate an objective, practitioner administered scoring system. Although the impact of adverse effects on medication compliance is an important endpoint, it is not the goal of this short report. The adverse effect assessment was completed with patient directed questions from the nephrologist regarding clinical responses and possible adverse effects as an integral component of this evaluation. In addition, the transplant pharmacist completed a medication adherence assessment at time of enrollment and during the study period. This has been clarified in the Methods section.

- **Changes to Manuscript:** Methods, Page 9, lines 7-8: “Medication adherence was assessed by the physician and pharmacist through patient interviews.”

9. Why was alopecia not included in aesthetic adverse effect? Why was nausea not included in GI effects?

- **Author’s Response:** We agree that alopecia and nausea are adverse effects associated with maintenance immunosuppressive regimens. Alopecia was not included in the adverse effects rated due to infrequent occurrence and subjective manner of assessment and reporting. Nausea is a non-specific symptom which was difficult to place objective rating with potential overlap with concurrent non-immunosuppressive medications. This has been included as a limitation to the study.

- **Changes to Manuscript:** Discussion section, Page 16, Lines 14-15: “A few infrequent adverse effects (e.g. alopecia) were not included and may be considered a study limitation.”

10. ME - Paragraph 1 - I would change the focus of the background and introduction to put adherence and its impact over the long term on allograft survival. I don't think the stats on the number of people with ESRD is really important for this problem. One might also include the importance of adherence on other disease outcomes which is where this report may extrapolate. Then the logical segue is to tools to routinely assess adherence in the clinical setting. You might include the contrast of systematic routine for efficacy is an important aspect of clinical practice.

- **Author’s Response:** We appreciate this suggested modification. The importance of adherence on disease outcomes is critical and we have revised this section in accordance with study objectives.

- **Changes to Manuscript:** The Background section on page 6, paragraph 1 and 2 have numerous underlined revisions included based on the above comments.

11. Results - would be clear that the Tac group was in fact a tac/myfortic group and CSA group was a CSA/MMF group when explaining AEs.

- **Author’s Response:** We have included both the calcineurin inhibitor and mycophenolic acid formulation for all instances where the treatment groups are discussed. To improve readability, the mycophenolic acid formulations have been abbreviated.

- **Changes to Manuscript:**
  - Methods section: Page 8 Lines 6 to 9 have the addition of either tacrolimus (Prograf) with enteric coated mycophenolate sodium (EC-MPS; Myfortic) or cyclosporine (Neoral) with mycophenolate mofetil (MMF; CellCept).
  - Results section, Page 11, Lines 3-4 and 14-23: “cyclosporine and MMF” replaces “cyclosporine” and “tacrolimus and EC-MPS” replaces “tacrolimus”.
  - Page 27; Table 2 has been adjusted to reflect the addition of “cyclosporine and MMF” and “tacrolimus and EC-MPS”.
12. GH - did 76.7% of CSA pts experience GH or was it 76.7% of pts total who has GH were on CSA.
   • Author’s Response: We have adjusted the Results section to reflect this clarification.
   • Changes to Manuscript: Results section, Page 11, Lines 21-23: “For individual adverse effects, 76.7% of patients treated with cyclosporine and MMF experienced gingival hyperplasia compared to 21.4% of those treated with tacrolimus and EC-MPS (P<0.0001).”

13. Discussion - I believe the inclusion of a systematic clinician assessment for AEs constitutes a major part of this report and that emphasis in your discussion should be given to the opportunity to identify AEs with systematic assessment.
   • Author’s Response: We appreciate this comment and have inserted these revisions for clarification.
   • Changes to Manuscript: Discussion section, Page 16, Lines 12-15: “The novelty of the scoring system is the utilization of clinician directed evaluation of these adverse effects in transplant recipients using a systematic, objective approach instead a reactive response to these manifestations.”

14. The question that remains is a) what was done when AEs were identified and does doing something improve adherence or graft outcome. These questions remain to be answered and addressed, if even hypothetically. If you have the data about action following AE identification, that would be nice to see.
   • Author’s Response: We agree that the future direction of this adverse effect scoring system has notable clinical utility for modification of routine post-transplant evaluation of immunosuppressive therapy or medication adherence. Since the study objective was to develop and validate the adverse effects scoring system, no data was collected in transplant patients over a longitudinal period to address these issues. We have included this suggestion as future direction in the revised manuscript.
   • Changes to Manuscript: Discussion section, Page 16, Lines 17-21: “Future research using this validated adverse effect rating system may include longitudinal evaluation of immunosuppressive adverse effects during the acute and chronic post-transplant periods and relationships to medication adherence, physician evaluation and allograft outcomes. This preliminary report provides a novel, standardized adverse effect assessment which may benefit other solid organ transplant populations through prospective evaluations.”

15. Discretionary revisions - I would be careful of the use of assessment and assessed. These words appear a lot in the abstract and manuscript and would try to find some alternatives to increase readability.
   • Author’s Response: We acknowledge this repeated use of “assess” and appreciate the suggestion. The manuscript has been edited to reflect this comment.
   • Changes to Manuscript: Throughout the manuscript, revisions have been made to replace the word “assess” or “assessment”.

Statistical Review
Statistical Referee:
Overall the statistical methods are sound for this type of study and I think the methods section does a reasonable job of explaining the utility of each component of the analysis.

I do have a couple of questions for the results section:

1. In the second paragraph, last line: the assessment of 17 adverse effects, I thought there were 18 adverse effects contained in the assessment tool.
• **Author’s Response:** Thank you for pointing out this inconsistency in the Results section. There were 18 adverse effects included in this assessment scale which were graded by content experts.

• **Changes to Manuscript: Results section,** Page 11, Line 10: “...the assessment of the 18 adverse effects in renal transplant recipients.”

2. **In the last paragraph, first line:** The Kappa statistic, I feel that line is a little confusing. I thought from the methods section that the Kappa and ICC were measured on all the adverse events pooled together? That sentence makes it seem otherwise, which if that is that case it should be clearer here or in the methods.

• **Authors Response:** We appreciate the opportunity to clarify these results. The Kappa statistic was measured for each individual adverse effect and presented as the mean with standard deviation for all 18 adverse effects. The ICC was measured as the pooled score for all 18 adverse effects.

• **Changes to Manuscript: Methods section,** Page 8, Lines 19-22: “Intra-class correlation was generated from a pooled adverse effect score including the 18 adverse effects. The Kappa statistic was determined for each adverse effect to document inter-rater reliability and reported as an overall mean with standard deviation.”

• **Results section,** Page 12, Lines 4-5: “The mean Kappa statistic was 0.68 ± 0.25. The intra-class correlation was 0.81 (95% confidence interval [CI]: 0.65-0.90) to represent the reliability of summary scores for the 18 adverse effects.”

3. **In the discussion I thought they did a good job describing the potential limitations of the scoring system and methods. Which is important in this type of study.**

• **Authors Response:** Thank you for your expertise and statistical review. We appreciate your comments and have addressed all of your concerns in this revised manuscript under consideration in *BMC Nephrology.*