27 August 2016

To whom it may concern:

It is a privilege to submit our manuscript entitled **Tacrolimus confers lower acute rejection rates and better renal allograft survival compared to Cyclosporine** (ID: 26863). In this retrospective study, we compared the impact of the tacrolimus and cyclosporine on acute rejection and renal allograft survival. We also investigated the predominant causes of graft loss among the patients who received these calcineurin inhibitors.

This manuscript is a product of the collaborative effort among transplant physicians and pharmacist, working closely in the clinical care of kidney transplant recipients at the Medical University of South Carolina. The authors intend to share the insights we have gained in our study not only to transplant providers but to the whole medical community.

We thank the editors and reviewers for their constructive comments about our manuscript and would like to address their points below:

1. Under abbreviations used in manuscript, we defined FK as tacrolimus and CYA as cyclosporine. The above abbreviations were used in manuscript in the authors' attempt to improve readability of the article.
2. The kidney donor risk index (KDRI) encompasses the donor characteristics. It was used to provide a universal language for kidney donor characteristics since KDRI is now widely used among transplant centers in the United States.
3. The panel reactive antibody (PRA) encompasses the kidney transplant recipients' immunological characteristics. Given very low prevalence of antibody-mediated rejection among the subjects, we do not have enough data on donor specific antibodies (DSA) and concurrent mean fluorescence index (MFI).
4. The etiology of kidney disease of the subjects was added in the tables, including diabetes, hypertension, FSGS, and IgA nephropathy, which were the prevailing causes of kidney disease in our cohort of patients.
5. Non-adherence was defined as documentation in the medical record by a provider that a patient was not taking their immunosuppressive regimen as prescribed. Underimmunosuppression was defined as evidence of kidney transplant injury related to rejection that led or contributed to graft loss.

6. The Banff '97 criteria were used to define the different types and grades of acute rejection. Based on our center's protocol, Banff 1A and 1B rejection are treated with Methylprednisolone IV. Banff 2A rejection and higher are treated with anti-thymocyte globulin. Individual response to therapy was difficult to document given the retrospective nature of the study.

7. Histopathological changes of acute rejection were the focus of the study. Since renal histological changes of calcineurin inhibitor toxicity may be non-specific and overlap with other disease entities (i.e hypertension, diabetes), it was difficult to account for calcineurin inhibitor toxicity.

8. We have clarified in the methods section that we looked into the subgroup of subjects who experienced graft loss. We then retrospectively investigated the factors leading to graft loss. For patients who died, we presented the causes of death as overall prevalence of infections (encompassing sepsis, bacterial, fungal, CMV, and other viral infections), malignancies (encompassing solid organ tumors, hematologic malignancies, and post-transplant lymphoproliferative disorder), and cardiovascular diseases (encompassing acute myocardial infarction and cerebrovascular accident). Cause of death classified under "Other" includes accidents, unknown, or undocumented.

9. There was a trend towards a slightly higher prevalence of cardiovascular disease as a cause of death in the tacrolimus group, although this was not statistically significant.

10. Using multivariate analyses (regression), adjusting for recipient, donor and transplant characteristics known to influence the outcome, we demonstrated that tacrolimus was an independent predictor for lower acute rejection rates (logistic) and better renal allograft survival (Cox), as compared to cyclosporine.

11. The discussion was revised to interpret the results much more comprehensibly.

Respectfully,

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