Author’s response to reviews

Title: Effect of CYP3 A4, CYP3 A5 and ABCB1 gene polymorphisms on the clinical efficacy of tacrolimus in the treatment of nephrotic syndrome

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BMC Pharmacology and Toxicology

Dear editors,

Please find revised manuscript entitled “Effect of CYP3 A4, CYP3 A5 and ABCB1 gene polymorphisms on the clinical efficacy of tacrolimus in the treatment of nephrotic syndrome” that we would like you to consider for publication in BMC Pharmacology and Toxicology as original paper.

This manuscript ID was PHAT-D-17-00164. We thank you for your efforts for the paper review, and the reviewers for their positive comments and constructive suggestions, which have substantially improved the manuscript. We have made point-by-point responses to reviewer comments raised in your letter. These changes will not influence the content and framework of
the paper. We earnestly appreciate the editors and reviewers’ hard work, and hope that the correction will meet with approval.

Once again, thank you so much for your comments and suggestions.

Thank you for your consideration.

With best wishes,

Yours sincerely

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Response to Jiraganya Bhongsatiern, PhD (Reviewer 1)

Authors thank the reviewer for these comments and constructive suggestions. We would like to answer the questions you raised one by one below. We have numbered each point as comment 1 (C1), response 1 (R1), and so on.
C1: Background section, line 39-42: Please consider adding references indicating 'the recent years' of using tacrolimus for treating patients with nephrotic syndrome.

R1: We thank you for reminding us very much. We have added the relevant references according to your suggestion (References 22 and 23). The details can be seen in Background section, line 42, page 7.

C2: Background section, line 50-55: Please consider adding references of 'drug genomics studies' or clinical pharmacology study of tacrolimus.

R2: We thank you for reminding us very much. We have added the relevant references according to your suggestion (References 11 and 18). The details can be seen in Background section, line 56, page 7.

C3: Methods section, Evaluation of safety, line 25-26: Misspelling of 'observed'.

R3: We thank you for reminding us very much. We have made a revision. The details can be seen in Methods section, line 28, page 9.

C4: Results, Characteristics of patients, line 34-35: Please correct the sentence 'Among them, one child was 6 years old and the rest were…'

R4: We thank you for reminding us very much. We have made a correction. The details can be seen in Results section, line 29, page 12.

Response to Chun Shing Kwok (Reviewer 2)
C1: Conclusions should be toned down as a non-randomized study of 100 patients which is susceptible to bias related to observational study is unlikely definitively conclude that genotype influences treatment.

R1: We really appreciate the reviewer’s pertinent comments very much. We have made a revision. Conclusions: ABCB1 C1236T, ABCB1 G2677T/A genotype and BMI are probably the factors influencing the clinical efficacy of TAC in treating patients with NS. The details can be seen in Abstract section, line 15, page 7.

C2: Revise first sentence as nephrotic syndrome is not commonly seen in every clinic -
Nephrotic syndrome (NS) is a common condition in renal medicine which has high morbidity in middle aged and elderly people.

R2: We thank you for reminding us very much. We have made the corresponding revisions. The details can be seen in Background section, line 31’, page 7.

C3: Second sentence: The response to treatment (NOT treatment effect) varies greatly,…

R3: We thank you for reminding us very much. We have made the corresponding revisions. The details can be seen in Background section, line 34, page 7.

C4: In the introduction: "The majority of the studies focused on the impact of gene polymorphisms in renal transplant recipients." This sentence needs some lead into the sentence or explanation. The existing literature investigating these gene polymorphisms have been mainly derived from cohorts of renal transplant patients.

R4: We thank you for reminding us very much. We have made a revision. The details can be seen in Background section, line 42, page 8.
C5: Under ethical consideration should state be completely revised. We received approval from the Medical Ethics Committee of the 88th Hospital of PLA (What is PLA?) for undertaking this study. The study was designed to be secure and fair to patients while minimizing risk of harm to participants. The included participants provided written informed voluntary consent and participants under the age of 18 years had written consent obtained from their parents. Participants had the right to withdraw from the study at any time.

R5: We thank the reviewer for this suggestion very much. We are so sorry that we have not explained it clearly. PLA is the Chinese people's Liberation Army. We have made a revision. The details can be seen in Methods section , line 39, page 9.

C6: Discussion first sentence needs to be toned down. We found evidence that X are factors which may influence the clinical therapeutic effects of TAC on NS patients…

R6: We thank the reviewer for pointing out our deficiency very much. We have made the corresponding revisions. The details can be seen in Discussion section , line 11, page 17.

C7: Do not use contractions have not NOT haven't

R7: We thank you for reminding us very much. We have made a revision. The details can be seen in Discussion section , line 17, page 17.

C8: The first paragraph of discussion does not explain why it is important? Should we test patients genotype routinely prior to treatment to tailor treatment?

R8: We thank the reviewer for the question. As a result, we should test genotypes in NS patients routinely prior to treatment to tailor treatment. The details can be seen in Discussion section , line 28, page 17.
C9: Regarding "Previous studies have focused on the effects of gene polymorphisms of CYP3A4 and CYP3A5 and ABCB1 genes on TAC metabolism in other setting and there are few studies on NS." What are the few studies?

R9: We thank you for reminding us very much. We've made a change. Previous studies have focused on the effects of gene polymorphisms of CYP3A4 and CYP3A5 and ABCB1 genes on TAC metabolism in other setting and we have not found the relevant literature on NS. The details can be seen in Discussion section, line 56, page 17.

C10: Regarding "Some studies think that ABCB1 polymorphisms have nothing to do with the clinical efficacy of TAC." Studies do not THINK!

R10: We thank you for reminding us very much. Because of our negligence, we have made such a low error, and we have made some adjustments in the article. Some studies show that ABCB1 polymorphisms have nothing to do with the clinical efficacy of TAC. The details can be seen in Discussion section, line 6, page 18.

C11: In the discussion: "First, the study population is different, and the formula given by the National Health and Family Planning Commission is suitable for kidney transplant patients, but the objects of this study are NS patients." Does not make sense and needs to be explained.

R11: We thank the reviewer for this point very much. Our modifications are as follows. First, there may be other factors affecting the metabolism of CYP3A4 and CYP3A5 enzymes in patients with NS. The details can be seen in Discussion section, line 48, page 19.

C12: In the discussion explain what you mean: "Second, It may be that the sample size is smaller."
R12: We thank the reviewer for the question. We've made a change. Second, It may be that the sample size is smaller, which leads to some deviation from the actual situation. The details can be seen in Discussion section, line 50, page 19.

C13: In the conclusion do not use "to sum up" use In summary.

R13: We really appreciate the reviewer’s point. We've made a change. The details can be seen Conclusion sections, line 6, page 21.

C14: In the conclusions have to be soften as this is an underpowered non-randomized study to provide strong evidence.

R14: We thank the reviewer for this point very much. Our modifications are as follows. In summary, the results of this study reveal that the gene mutations of CYP3A4 and CYP3A5 and CCB may not directly affect the clinical efficacy of TAC. However, ABCB1 C1236T, ABCB1 G2677T/A genotype and BMI are probably the factors influencing the clinical efficacy of TAC in treating patients with NS. The details can be seen Conclusion sections, line 6, page 21.

C15: Last sentence needs to be improved. Therefore, out study provides evidence that there may be a potential role for gene detection in tailoring therapy for patients with NS in order to improve response to treatment.

R15: We thank the reviewer for pointing out our deficiency very much. We have made the corresponding modification according to your opinion. The details can be seen Conclusion sections, line 17, page 21.