

Dear Professor Shui Qiu,

Thank you for your interest in our Review and for considering our manuscript: "Influence of tacrolimus metabolism rate on renal function after solid organ transplantation" which had been submitted to *World Journal of Transplantation*. We have carefully revised our paper according to your suggestions and we herein would like to answer by a point-to-point reply. We have implemented or discussed all requested changes.

We also would like to thank the referees for their helpful and constructive comments, which have enabled us to improve the manuscript.

We are looking forward to your kind reply and would appreciate to find our paper to be published in *World Journal of Transplantation*.

Sincerely,

Gerold Thölking, for the authors

### **Responses to the Editor:**

Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.

#### Audio Core Tip

Please offer the audio core tip, the requirement are as follows:

In order to attract readers to read your full-text article, we request that the first author make an audio file describing your final core tip. This audio file will be published online, along with your article. Please submit audio files according to the following specifications:

Acceptable file formats: **.mp3**

Maximum file size: 10 MB

To achieve the best quality, when saving audio files as an mp3, use a setting of 256 kbps or higher for stereo or 128 kbps or higher for mono. Sampling rate should be either 44.1 kHz or 48 kHz. Bit rate should be either 16 or 24 bit. To avoid audible clipping noise, please make sure that audio levels do not exceed 0 dBFS.

- The core tip file was reduced to less than 100 words and an audio file was uploaded as requested.

Table.

NOT BE THE VERSION OF FIGURE!

- The table was added as requested by the Guidelines and Requirements for Manuscript Revision: Review.

#### **Responses to Reviewer 00503286:**

The paper should be published after minor correction with the editor.

- We thank this reviewer for his / her friendly comment. We will follow the queries stated by the editor.

#### **Responses to Reviewer 00503339:**

Worried Transplant Teams concerned with how to optimize and preserve the action of Tacrolimus in Kidney and Liver Transplant recipients will find current concerns and possible solutions well stated. But, when they return to their Operating Rooms the next morning, they have not been armed with a proven empiric regimen that is likely to preserve Tacrolimus effectiveness without generating new possible problems. Your suggestion that larger Clinical Trials of Drug combination A versus B would prove helpful does not answer the question of how to manage the patient about to be transplanted immediately. One way of resolving the lack of a proven

effective means of optimal Tacrolimus management might be to include a brief "Work Protocol" as a component of your Manuscript to assist Transplant Teams in determining just how they might wish to participate in generating an answer to the overriding question of "How might the best strategy for Tacrolimus usage be determined?". Recognizing that the "Approach to Tacrolimus Usage" must be empirically clarified, the most helpful communication might be a concise statement of how this question can be answered in the shortest time.

- We thank this reviewer for his / her careful evaluation of our manuscript and constructive comments which helped us to improve it. The question for a "Work Protocol" would represent a desirable aspect in the context of our Review. To date, we are not able to present a "one fits all" Tac C/D ratio-protocol from analysis of our mainly retrospective data. Currently we are working on a prospective study to confirm the predictive value of the C/D ratio in a renal transplant cohort. Results of this study might offer data to present a clear "Work Protocol". At the moment, we think it would be presumptuous to give a clear instruction how to handle the Tac C/D ratio or tacrolimus usage.

#### **Responses to Reviewer 00503176:**

This is a well-written and useful review on the topic. I have no comments - the manuscript is ready for publication.

- We thank this reviewer for his / her friendly comment.

#### **Responses to Reviewer 00504828:**

- We thank this reviewer for his / her careful evaluation of our manuscript and constructive comments which helped us to improve it.

This review manuscript seeks clinically useful parameters to personalize the best daily dose of one of the clinically used calcineurin inhibitors, tacrolimus (TAC), during organ transplantation. The core of the manuscript includes a line of research by the author's group and is credible. The introduction clearly states the current

challenge of using TAC as an immunosuppressant in organ transplantation - very narrow therapeutic window makes physicians very difficult to determine the best daily dose of TAC. The topic is absolutely well aligned to the aim and scope of the journal and I have no doubt that the topic is important in this area.

Major comment 1. Page 7, from line 26~. CYP3A5\*1-expressors are characterized as fast TAC metabolizers meaning that TAC will be quickly metabolized, correct? In the following sentence "...TAC metabolism is only present in CYP3A5\*3/\*3 patients while the decline is absent in CYP3A5\*1 allele carriers.". I am confused here. If "decline=rapid TAC metabolism", then the description in this paragraph sounds controversial. It may require clearer re-writing.

- The reviewer is absolutely right. CYP3A5\*1-expressors are mainly characterized as fast TAC metabolizers. In this context our statements were a little confusing. CYP3A5\*3 carriers are mainly characterized as slow metabolizers but seem to show a great decline of Tac exposure during the early months after transplantation. This decline may be contributed by high steroid doses during the early weeks after transplantation that induce activity of CYP3A5\*3 and CYP3A4 (de Jonge, et al. BJCP 2015). The gradual rise in hematocrit might also influence the activity of these enzymes.

Minor comments 1. Pages 4~5 "In pancreas, heart, lung, or combined organ transplantation,...Notably, none of these CNI-free...immunosuppressive efficacy that equals those of CNIs". I think literature(s) may need to be cited. Please confirm.

- The author is right. References are added in these contexts now.

2. Page 6, line 9. "...leads to an immediate increase in GFR". I guess GFR appears first time here in the text. Maybe better to spell out abbreviations in their first appearance (Sorry if I missed in previous page(s)).

- GFR was changed to eGFR in all cases and was spelt out when mentioned for the first time in the text.

Also, mTOR is shown as mTor in many cases. I think TOR should be all capital letters. Just a little thing but better to correct.

➤ mTor was changed to mTOR in all cases mentioned.