

RESPONSE TO REVIEWERS

Reviewer's code: 00503191

Dear Authors, thank you for submitting your Review. The baseline data of immunosuppression are very superficial and although the figures provide some clearance, the studies you mention do not provide a very accurate Image of the current Status. A meta-Analysis of the use of immunosuppression has already been made and you could improve your manuscript by providing some statistical data.

Answer: We thank the reviewer for the comments. Due to our review is focused in the analysis of the immunosuppressor potency, specially that from mTOR inhibitors, we do not consider the necessity to carry out any meta analysis about the current efficacy of the immunosuppression, which has been perfectly analyzed before as you indicate. Our work aim to study in a comparative way the different methods to measure the immunosuppressor potency, which are not standardized in the clinical practice so far.

Reviewer's code: 00504828

This short review manuscript summarizes immune suppressive effect of mTOR inhibitors in regard to transplantation. The review particularly focuses on inhibition of T/B-cell proliferation and immunoprotection. Useful illustrations and tables are provided to help understand the topic.

Answer: We thank the reviewer for the comments.

Minor comments1. Figure 1. I think it is visually better to use different sign for inhibitors and activators/stimulators. In this figure, zigzag arrows are used for stimulus (OKT3) and inhibitors. It may be confusing for readers. I would use zigzag arrows for stimulators and dead-end arrows2. Very minor formatting issue: There is no space after periods in many sentences.

Answer: We agree with the reviewer and we have changed the arrows in Figure 1 to differentiate between activators and stimulators.

Reviewer's code: 00503243

This is a good review concerning the main ways of studying the immunopotency evaluation of mTORi.

Answer: We thank the reviewer for the comments.

I have several concerns principally on the introduction section: a) Bottom page 5. The limitation of long term survival is also due to disease recurrence and to death with functioning graft: this must be added.

Answer: We have added new text in page 5 mentioning this issue.

b) page 6 line 4: nothing is said about the mTORi side effects; please add and comment.

Answer: As suggested by the reviewer we have added a comment about the principal side effects described for rapamycin and derivatives.

c) page 6 line 11 : minimimizing, eliminating avoiding. Many trials failed becasure of the high incidence of ABMR (Salvadori et al World Journal of Transplantation). This point such be treated and commented by the authors.

Answer: We have commented now this point as indicated by the reviewer, and we have added a new reference to the bibliography section (Salvadori M and Berton E. Is it time to give up with calcineurin inhibitors in kidney transplantation? 2013. World J Tranplant. 3: 7-25).

d) The explanation of the mTORi is not clear and the figures are not enough explained in the text. mTORC2 is mentioned without explaining the molecule and its role.

Answer: We have added new text in the section "Role of mTORi in the immune response and effects of mTORi in the immune system" explaining extensively the mTOR pathway and how mTORi carry out its inhibition.