ROUND 1

26 December 2020

Re: **Manucript 58278**

Early tacrolimus exposure does not impact long-term outcomes after liver transplantation

Dear Editor,

Thank you for the opportunity to submit a revised version of our manuscript. We thank all the reviewers and the editorial board for their comments, which have improved our manuscript.

Following your suggestions, we provide a point-by-point reply to the queries raised by reviewers

1.- This manuscript is potentially publishable if the authors address a number of the limitations noting the numbers of recipients in each cohort and hence the limited numbers who experienced the adverse outcomes of interest (ie impairment of renal function as well as HCC recurrence).

Indeed, the number of patients included in the study groups are limited and we have recognized it. According to the reviewer´s comment we have modified the text addressing the limitation of experiencing a low rate of adverse events.

2.- First the abstract is too wordy. The methods section in the abstract can be compressed down.

We have reduced the background and methods sections

3.- Plus one of the significant findings from the data analysis is not mentioned either in the abstract nor addressed in the discussion section of the manuscript. That is that the mean donor age was significantly higher for the recipients in the Tacro level > 10ng/ml versus for the recipients in the other group. It is known that the age of the donor liver can be a factor that needs to be considered with respect to the dosing of Tacrolimus in the post transplant phase but this has not been mentioned.

It is true that it has been suggested that donor age might influence drug pharmacokinetics; however, this has not been demonstrated.
According to the reviewer´s concern we have included the difference of mean donor age in the abstract and a comment in the discission.

4.- The decision to place the recipients into either of the two Tacrolimus level subgroups seems extremely arbitrary in that it is based on the median level of a minimum of 5 recorded Tacrolimus levels recorded in the first 30 days. This is problematic as it could have led to confounding of the results (and hence constrained the potential results that could instead have been obtained from a more focused type of data analysis). Would it not have been better to have obtained a median of all of the Tacrolimus levels that were obtained for each of these recipients for the first 30 days and then place the recipients into the low or high Tacro level subgroups? This would more accurately reflect the Tacrolimus exposure. What would perhaps even more accurately reflect the impact of prolonged Tacrolimus exposure of > 10 ng/ml would be the actual number of days that the Tacro level was greater than this for the recipients in the > 10 ng/ml subgroup. This would facilitate further subgroup analysis for the end points that were selected.

This is really our fault as our explanation was not adequate.
We used all samples of TTL during the first month to obtain the mean level in every patient. Finally, median samples per patient was 7 with a range of 5 to 12. This is the reason why we wrote that the minimum samples used to obtain the mean level was 5.
We have modified the description in the Methods section and include a comment in the Results section.

5.- Did the presence of T-tubes impact the Tacrolimus levels at all noting that these were utilised during the time period this study encompasses? There is some limited published data that biliary diversion can impact on Tacrolimus levels. For example was the bile fed back to the recipients or were the T-tubes all able to be clamped at the same stage post transplant? It may also be useful to mention how this was managed (and refer to the relevant literature).

Although we commonly use T-tube in our transplants, we close the tube in postoperative day 3 when the patient progressed well. By doing so, we do not diverse biliary output avoiding the potential effects on the tacrolimus levels.
We have included this explanation in the Methods section

We hope that this improved version is considered satisfactory for publication and look forward to your decision. We will gladly address further changes if necessary.

Sincerely,

Mikel Gastaca on behalf of all authors

ROUND 2

Specific Comments To Authors:I believe that the reviewers questions have been adequately addressed. The authors need to make one final check of the spelling particularly of terminology etc through the manuscript including for Mycophenolate-mofetil and choledochocholedochostomy

I send the manuscript with the changes highlighted. I have not included the figures as they are the problem because of their quality and you already have them from my previous submissions. Hope this is ok for you.