

RESPONSE LETTER

Responses to reviewer n° 2462024

Comments to author: Thank you for an interesting and useful study. It is not clear to me whether the patients were consented and how they were randomized (if indeed they had been randomised.) Some areas of language need tidying up as some sentences are not easy to follow.

Response: All patients provided a written informed consent. The study protocol was approved by the Institutional Review Board of Azienda Ospedaliera-Universitaria, Modena (N°:23/2009) and was conducted in accordance with provisions of the Declaration of Helsinki and Good Clinical Practice guidelines. The patients underwent to liver transplant were not randomized. Between December 2009 and December 2010, 16 consecutive not randomized adult patients received a liver graft with thymoglobulin infusion. We decided to begin a retrospective case control study in a later period comparing those patients with a controls.

I have inserted these explanations in the text.

As regards the language, we have made the text to be corrected by a native English.

Responses to reviewer n° 3015790

Comments to author: Overall, it's a well performed and thought out study with many relevant findings.

- 1) However, the extremely small sample size makes it difficult to draw any strong conclusions
- 2) Power calculations were not performed making it hard to define primary and secondary endpoints. Please provide a sample size calculation to improve validity of the results.

1-2) Thank you for your observations. The side effects described in the study suggested stopping the intraoperative administration of thymoglobuline, and this is why the sample size could not increase.

Regarding the calculation of sample size, we decided not to perform it, because of the retrospective nature of the study. Power analysis (a priori or prospective power analysis) is usually performed before planning a study but, as you suggested, it can be done either after data collection (post hoc or retrospective power analysis). While the utility of prospective power analysis in experimental design is universally accepted, the usefulness of retrospective techniques is controversial[1]. The use of the statistical analysis of the already collected data to estimate the power, may result in uninformative and misleading values. In particular, it has been shown [2] that post-hoc power in its simplest form is a one-to-one function of the obtained p-value. This has been extended[2] to show that all post-hoc power analyses suffer from what is called the "power approach paradox" (PAP), which is presented in the paper cited.

For all these reasons and for the complex calculation of several sample sizes related to every variable examined, we considered unwise to perform a post hoc analysis.

Furthermore we are confident that a statistically significant p value still can offer a reliable and useful information even if the power analysis has not been performed.

3) It's unclear why some patients received Everolimus in one group and others did not.

Response:

3) Thanks for pointing out this difference. The different postoperative management it's due to the surgeon approach to immunosuppression. The ATG protocol gave the surgeon full freedom to choose the postoperative treatment and this is the reason why a few patients received everolimus puls advagraf while others got only advagraf. The patients of the control group received only advagraf according to the protocol in use at that time.

We considered this treatment choice a possible bias in the interpretation of the postoperative results of the study, as you pointed out, and we thought necessary to underline this topic in the discussion.

Comments to author:

Minor revisions -

Title Page: Author contributions - Instead of "conceived, designed and performed the paper", change it to "Conceived and designed the research study; wrote and revised the manuscript".

Response: we did the correction

Conflict of interest statement has a "12" which may not belong there.

Response: you are right, we deleted it

Abstract – TEG has not been defined yet in the abstract.

Response: you are right, we better specify that Thromboelastography states for TEG

Introduction – “The potential for adverse events after ATG administration has been evaluated so far mainly in the long period” needs to be rephrased.

Response: we submitted the paper to a native English for language correction. He rephrased the sentence:

From the available literature we know that the incidence of adverse effects after ATG administration has not been evaluated in the intra and immediate postoperative period, and this is the reason why our understanding of the role of Thymoglobulin as an induction therapy in liver transplantation (LT) is still evolving.

Methods – Please provide a sample size calculation to improve the validity of results.

Response: because of the above-mentioned motivations, we did not provide a sample size calculation.

Results – Need major language polishing and simplification to make it easily understandable.

Response: we submitted the paper to a native English for language correction and we simplified this session

Conclusion – Given the small sample size and lack of power calculation, it's hard to generalize the findings and conclude that thymoglobulin should not be used as an induction agent. The conclusion should report the study's major limitations.

Response: you're right, our conclusions could not lead to a similar generalization. We modified the text and added the identified limitations of the study in the conclusions

References

- 1) Thomas, L. (1997) Retrospective power analysis. *Conservation Biology* 11(1):276–280
- 2) Jump up to:a b Hoenig and Heisey (2001)The Abuse of PowerThe American Statistician 55(1):19-24