

December 11, 2015

Dear editor

Thank you for considering our previous manuscript entitled **"High-dose hepatitis B immunoglobulin therapy in HCC with HBV-DNA/HBeAg-positive patients after living donor liver transplantation (WJG-2015-23329)"**

We are happy to hear the news that the manuscript is available for publication with a pending satisfactory revision. We accepted all suggestions elaborated by two reviewers, and tried to answer to all questions to the best of our abilities. In our annotated version, we revised our previous manuscript by using Track Change function with marginal notes indicating changes (*e.g.*, R00503228-#1). Our specific responses to indications and suggestions are as follows:

TO THE COMMENTS OF Reviewer 00503228

Comments to the Author

1. Interesting article. Please make clarification about how the 168 patients have been entered the survey. If they were consecutively included or what? - Please make a subsection in your METHODS section entitled "Inclusion & exclusion criteria" and give any criteria you have used for this.

Patients who are HBV-DNA/HBeAg-positive and received living donor liver transplantation (LDLT) during the period from January 2008 through December 2013 are consecutively included in this research. Those who have extrahepatic metastasis or obvious cases of major vascular incidents, such as portal vein or hepatic veins, have been excluded from the research. Patients with any other types of cancers in addition to HCC, severe cardiopulmonary comorbidity, active drug or alcohol abuse or active septic infections have also been excluded. Your comments have been incorporated in the section titled "MATERIALS AND METHODS - Patients." (page 6, line 7-11)

2. Please Give setting of your study: If it was retrospective or prospective? If the patients randomly got assigned to the treatment dosage groups or there were any criteria for this

purpose? - If authors and data analyzers were blind to the study groups or not? - Please make a subsection and give ethical concerns about your study.

Our research is a retrospective study. If you see the section titled "MATERIALS AND METHODS - HBV prophylaxis," patients prior to May 2011 received low-dose HBIG and those thereafter received high-dose HBIG. At that time, while no solid worldwide consensus existed as to HBIG dose for HBV prophylaxis following liver transplantation for patients with HBV high infectivity, our center determined that high-dose HBIG can be beneficial for HBV prophylaxis after liver transplantation for patients with HBV high infectivity, and as such changed the protocol. Again, this research is not a randomized controlled trial, but is a retrospective study through medical records review, and so indicated in the title page. Also, this research was approved by the Institutional Review Board (IRB) within our center, and such has been indicated in the title page and the section titled "MATERIALS AND METHODS - Patients." (page 6, line 15)

3. Since you have found "a significant difference in the Child-Pugh score" between the groups at the baseline, you may make multivariate analyses for your findings regarding this.

As you mentioned, before propensity matching between the two groups, in case the Milan criteria was met (n=109), there was a disparity in the Child-Pugh score ($P=0.002$), and in case the Milan was not met (n=59), there was a disparity in the AFP ($P=0.049$). However, what we wanted to understand through this research was if there is any difference in the HCC, HBV recurrence and overall survival depending on the HBIG dose where all the other variables than HBIG dose are controlled. In order to rule out such variables in the two groups, we conducted propensity matching. As a result, as shown in Table 2, we were able to confirm that there was no meaningful difference between the two HBIG dose groups, regardless of Milan status.

4. Your article needs some revisions regarding scientific writing of the article. For example instead of saying "95.6%, 95.6%, and 95.6%, respectively" you can simply say "95.6% for all".

Thank you for the thoughtful comment. I have revised lines 24 and 26 of page 10

accordingly.

5. The subsection "HCC recurrence, HBV recurrence, and overall survival before propensity matching" can be simply entered into a table, and only significant or important analyses to be given. Most figures are excessive. Please consult with someone who is experienced in the scientific writing. Only give figures which represented significant disparity between the two groups. And give titles for each figure separately just above or below it.

I understand your point. However, please note that we had a relatively small size of patients group and a substantial number of them dropped out during the propensity matching. As we were conscious that the research result or the adequacy of the matching might be questioned if the research is based on the few patients who went through the matching, please understand that we had to disclose all of the results prior to the matching and go by figures to enhance the transparency of the research. If deemed necessary, the figures prior to the matching can be deleted. Please also note that, according to the author guideline of your journal, the title of each figure has been noted as figure legend in separate pages from the figure itself. (page 21)

6. In the limitations of the study you specify that it was not randomized. It puts a fatal limitation on the credibility of your findings. Since it wasn't randomized, so undoubtedly the physicians were putting patients on the high dose if they had worse conditions!! This limitation, unfortunately, puts a thorough shadow on your study findings.

I believe it is a good comment. However, as previously mentioned, our research is a retrospective study and the limitations coming from such have been described in the discussion section. Although our study is not a prospective randomized controlled trial, any other confounding variables than hepatitis B immunoglobulin dose have been controlled through propensity score matching, and we came up with a result based on that. We would be very pleased if an opportunity to conduct a randomized controlled trial was given that would support this research.

TO THE COMMENTS OF Reviewer 00504150

Comments to the Author

1. The manuscript entitled, “High-dose hepatitis B immunoglobulin therapy in HCC with HBV-DNA/HBeAg-positive patients after living donor liver transplantation” is well written, and easy to read. The overall topic and study questions are relevant and of potential interest to the readers of World Journal of Gastroenterology. Retrospective nature of the study is weakness but the authors state its limitation.

We are very thankful for the positive evaluation of you, and we are expecting very to do a prospective nature study to overcome the limitation of ours like you.

Thank you again for reconsidering our manuscript. We think we did our best to revise our previous manuscript. We hope the revised version would meet with deputy editor's and two reviewers' approval and be finally accepted.

Eung Chang Lee, MD

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Clean and annotated copy of revision