July 30, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 11393-review.doc).

**Title:** Prophylaxis Against HBV Recurrence After Liver Transplantation: A Database Study Of Registry

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**Name of Journal:** *World Journal of Gastroenterology*

**ESPS Manuscript NO:** 11393

The manuscript has been improved according to the suggestions of reviewers:
1 Format has been updated

2 Revision has been made according to the suggestions of the reviewer

Reviewer 1:

*The paper by Jiang et al. reports on the results of the China Liver Transplant Registry on HBV prophylaxis in patients receiving liver transplantation. They conclude, that a lower dose of HBIG plus Adefovir or Entecavir or Lamivudine results in excellent treatment response, especially the combination HBIG/Entecavir. The paper is well written and of highly clinical implications. Therefore, I recommend publication without any changes.*

Thanks for your appreciation.

Reviewer 2:

*Authors reported that low-dose intramuscular HBIG plus one nucleoside analogue provides an effective prophylaxis against posttransplant HBV recurrence, especially for HBIG plus entecavir. Sample number is enough, and this is national-wide study in China. This paper is well-written, and this report is informative for readers in this field.*

Thanks for your appreciation.

Reviewer 3:

The paper can be accepted without any changes

Thanks for your appreciation.

Reviewer 4:

*(1). In the introduction, the authors mention that the proportion of patients transplanted for hepatitis B is very high (78%). I think the worldwide proportion is lower.*

China is hepatitis B virus infection in high risk areas. We get the data from the article “Hepatitis B

virus infections and risk factors among the general population in Anhui Province, China: an epidemiological study". Maybe it's lower all around the world.

Reference: Li X, Zheng Y, Liau A, Cai B, Ye D, Huang F, Sheng X, Ge F, Xuan L, Li S, Li J. Hepatitis B virus infections and risk factors among the general population in Anhui Province, China: an epidemiological study. BMC Public Health 2012; 12:272 [PMID: 22475135 DOI: 10.1186/1471-2458-12-272]

(2). *It is suprising to find that tenofovir prophylaxis has not been studied.*

The number of patients with low-dose IM HBIG and tenofovir after liver transplant is so small. It's difficult to reach statistical significance for ttenofovir prophylaxis.

*(3). As the results come from a large database, it is not clear is the nucleos(t)ide analogue + intramuscular HBIG have been maintained for the whole period of study.*

China Liver Transplant Registry database [https://www.cltr.org/] provided the relevant data. All the patients were monitored until September 2012 or their death by the website. They are responsible for tracking the drug administration of those patients. These data they provided is reliable.

*(4). Is low-dose intramuscular HBIG as effective as intravenous HBIG (in combination with nucleos(t)ide analogues)*

The answer is positive. Our center has studied in this respect. We obtained the conlusion that combination therapy with LAM and individualized low-dose IM HBIG provides a safe and effective prophylaxis against HBV recurrence after LT at about 5% of the cost of the cost of conventional high-dose IV HBIG regiimens. We have published an article "Prophylaxis Against Hepatitis B Recurrence Posttransplantation Using Lamivudine and Individualized Low-Dose Hepatitis B Immunoglobulin" in American Journal of Transplantation. Furthermore, our results is similar to other published study.

Reference: Jiang L, Yan L, Li B, Wen T, Zhao J, Jiang L, Cheng N, Wei Y, Yang J, Xu M, Wang W. Prophylaxis Against Hepatitis B Recurrence Posttransplantation Using Lamivudine and Individualized Low-Dose Hepatitis B Immunoglobulin. Am J Transplant. 2010 ;10(8):1861-1869 [PMID: 20659092 DOI: 10.1111/j]

(5). *Is any HBIG necessary if adefovir or entecavir are used?*

The optimal protocol is controversial. At present, there are researches about the use of oral antiviral drugs to stop HBIG administration, but the sample is too small, and most of them were limited to the preoperative HBV-DNA negative. So we think it is uncertain to stop HBIG administration. It needs prospective study with large amount of samples.

References:

1. Cholongitas E, Goulis I, Antoniadis N, Fouzas I, Imvrios G, Papanikolaou V,Akriviadis E. New nucleos(t)ide analogue monoprophylaxis after cessation of hepatitis B immunoglobulin is effective againsthepatitis B recurrence. Transpl Int. 2014 6. [ PMID:24909714 DOI: 10.1111/tri.12370]

2. Wesdorp DJ, Knoester M, Braat AE, Coenraad MJ, Vossen AC, Claas EC, van Hoek B. Nucleoside plus nucleotide analogs and cessation of hepatitis B immunoglobulin after liver transplantation in chronic hepatitis B is safe and effective. J Clin Virol. 2013;58(1):67-73 [PMID:23880162 DOI:10.1016/j.jcv.2013.06.035]

(6). *Patients have been recruited between January 2000 and December 2009. In the first part of the database, all the patients should have been treated with lamivudine (because adefovir and entecavir were not available). So, they should be excluded.*

Thanks for the constructive suggestion. According to your request, We have contancted liver transplant registry database to eliminate the first part of the database. Unfortunately, for the study is a multi-center study, it is difficult to eliminate the early data to be compared. We would like to exclude these data in our study in the future.

*(7). The groups are different between them in some important points such viral load, duration of pre-transplant treatment. It could be of interest to compare the rates of recurrence with each strategy in patients with low viral load and in patients with high viral load.*

Thanks for the constructive suggestion. According to your request, We have contancted liver transplant registry database to provide us these data. Unfortunately, for the study is a multi-center study, it is difficult to rearrange these data. We would like to do some research in the future.

*(8). The information given in figure 2 and table 2 is repetitive.*

The figure 2 shows the differences among the three therapy methods in the form of more imagine, while the table 2 shows the differences in the form of data.

*(9). The information given in figure 3 and table 3 is repetitive.*

The figure 3 shows the differences among the three therapy methods in the form of more imagine, while the table 3 shows the differences in the form of data.

*(10). The comparison between group B and group C does not show significant differences in the recurrence rates between them (the differences between them are only found in the long-term, when a small number of recurrences increases the rate). The authors should temper they discussion for the use of entecavir (ETV plus HBIG may be considered as first-line therapy…)*

According to your suggestion, we have changed the original sentence "ETV plus HBIG may be considered as a first-line therapy in the prevention of HBV recurrence after transplantation…" into the sentence "ETV plus HBIG may be considered as an efficient therapy in the prevention of HBV recurrence after transplantation…" in the fifth paragraph of the part of "Discussion".

(11). *In the discussion, the authors suggest that intramuscular HBIG should be preferred to intravenous HBIG because of its high efficacy and lower price. The study has not been designed to compare them; thus, the discussion*

*about this comparison should be avoided.*

According to your suggestion, In our manuscript we have revised this part of discussion.

*(12). The authors have found that patients transplanted for HCC have a higher HBV recurrence rate. They suggest that occult metastases could be a reservoir of HBV. Have they found if patients with recurrent hepatitis B have a higher risk of recurrent HCC?*

This is a good suggestion for us to find if patients with recurrent hepatitis B have a higher risk of recurrent HCC. Because we don't have relative data to make a conclusion, we might make a perspective study to find the relationship between recurrent hepatitis and recurrent HCC in the future.

Reviewer 2:

*(1). The intramuscular administration of HBIG should be clarified in the abstract, since intramuscular HBIG is not prevalent worldwide.*

According to your suggestion, we have clarified the intramuscular administration of HBIG in the first paragraph in the part of "**Methods**"

(2). *This is the database study of registry. This should be clarified in the title.*

According to your suggestion, this is clarified in the title.

*(3). Adefovir and entecavir were used in recent cases according to the figures. I recommend authors to use the data after the introduction of these drugs, meaning that cases with lamivudine in earlier days had better be excluded from the study. This can minimize the learning curve bias.*

Thanks for the constructive suggestion. According to your request, We have contancted liver transplant registry database to eliminate the cases with lamivudine in earlier days. Unfortunately, for the study is a multi-center study, it is difficult to eliminate the early data to be compared. We would like to exclude these data in our study in the future.

*(4). How was HBs-Ab titer? Was there any lower limit? Anyway, authors should discuss about the HBs-Ab titer monitoring.*

The level of HBs-Ab titer was monitored weekly for the first month, monthly thereafter until stable, and every 3 months. Since the level of HBs-Ab hasn't been provided by China Liver Transplant Registry, it is hard for us to discuss about the HBs-Ab titer monitoring.Whether the HBs-Ab levels achieved by low-dose IM HBIG are adequate to prevent HBV recurrence is controversial. We would like to do some research about HBs-Ab in the future.

*(5). Please refer to Am J Transplant 2013; 13:353. There many other studies of the combination prophylaxis*

*with HBIG and entecavir.*

According to your suggestion ,we have cited the conclusion of their studies in in the first paragraph of the part of "Discussion".

*(6). Please change the scale of the vertical axis of Figure 3 to make the difference very obvious.*

Thanks for the constructive suggestion. According to your request, We have contancted liver transplant registry database to change the scale of the vertical axis of Figure 3 . Unfortunately, for the study is a multi-center study, it is difficult for them to change the scale of the vertical axis.

*(7). The descriptions in "Patient survival" and "HBV recurrence" in Results are redundant.*

"Patient survival" and "HBV recurrence" are to explain the differences among the three therapy methods in two aspects. Thus we can make a more accurate conclusion. Almost all the HBV recurrence after liver transplantation need reporting patient survival and HBV recurrence, because recurrence of HBV patients in the rescue measures are not necessarily die.

*(8). I wonder how the authors checked the adherence to the combination prophylaxis in this cohort. Was it possible to confirm the adherence of each patient based only on the registry database?*

China Liver Transplant Registry database [https://www.cltr.org/] provided the relevant data. All the patients were monitored until September 2012 or their death by the website. They are responsible for tracking the patients use of drug. These data they provided is reliable.

In addition, we want to change the original correspondence author"Li Jiang" into "Jiayin Yang". And Shu Shen and Li Jiang contributed equally to this study and are co-first authors.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

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