Author's response to reviews

Title: Impact of viral replication inhibition by Entecavir on peripheral T lymphocyte subpopulations in chronic hepatitis B patients

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Author's response to reviews: see over
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Author’s response to reviews: see over
Clarifications to reviewers’ comments: manuscript 1378375013171503

Title: Impact of viral replication inhibition by Entecavir on peripheral T lymphocyte subpopulations in chronic hepatitis B patients

Thank you very much for giving us the opportunity to revise and resubmit the above paper. We have gone carefully through the very constructive and pertinent comments from the reviewers and have revised the manuscript accordingly.

We hope that our revision of the paper will make it acceptable for publication, and we are of course willing to revise the paper further if necessary.

Yours sincerely,

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Below, please find our comments to the reviewers:

Reviewer: Karine Lacombe

1. There is a major problem with this paper: 55 patients have been included between January 2006 and August 2007, and the duration of follow-up was 48 weeks. The authors stated that no patient dropped out. How were the authors able to get data ready for publication in February 2008, only 24 weeks after the end of the inclusion period? Is there a mistake in the notification of the inclusion period?

Clarification 1: Sorry about the dating. The correct period of recruitment was Jan 2006 to Feb 2007 as corrected in the revised manual page 5, line 3.

2. Abstract: a sentence on the statistical methods used for evaluating dynamic fluctuations and correlations should be added in the methods section. The results section should start with a brief description of the included patients. The main results should be reported with numbers and the sentence has to be rewritten, as its meaning is unclear (there is a lack of a verb). The conclusion section should also be rewritten: does the term “this antiviral treatment” refers to Entecavir? It is probably the case, but it should be clearly mentioned this way.

Clarification 2: We have added a sentence on the statistical methods used for evaluating dynamic fluctuations and correlations in the last sentence of the methods section. The results section has started with a brief description of the included patients. The results and conclusion sections have been rewritten. Please see “Abstract” section.

2. Background: no study has to date compared the efficacy of adefovir and entecavir. It is therefore not true to say that entecavir is superior to adefovir. The sentence should be rewritten and the references should be shortened (19-32) as many of them are redundant.

Clarification 2: The relevant sentence has been rewritten. Comparison between entecavir and adefovir was deleted.

3. Methods: The exhaustive list of inclusion criteria must be detailed (the notion of clinical diagnosis following international criteria is too vague). The inclusion period must be corrected if August 2007 is a wrong date.

Clarification 3: There is a mistake in the notification of the inclusion period. The data collection period was between January 2006 and August 2007. The inclusion
period was between January 2006 and February 2007. The exhaustive list of inclusion criteria have been detailed. Please see page 4 “Methods section”, first paragraph.

4. Results: Patients were all biopsied. It might of interest to report the results of fibrosis and activity in the description section, as well as the number of patients presenting with cirrhosis and previous hepatic decompensation, in order to have a better clinical picture of the patients included. The results of the multilevel regression must be more clearly stated and interpreted. What is the main finding of the study? Is it that there is an increase of CD4 T cells while HBD-DNA is decreasing due to the antiviral effect of Entecavir? If yes, the last paragraph should report it more clearly. Why are the CD4 and CD8 cells not expressed in absolute values?

Clarification 4: The histopathological results have been inserted in the description section and Table 1. The results of the multilevel regression have been clearly stated and interpreted. Please see page 7 “Results section” and page 9 lines 4-7 and 15-17.

We followed most previous studies that expressed the results of T cells as percentages as this reflects the balance between subpopulation of T lymphocytes.

5. Discussion: See remarks about entecavir superiority in the introduction section. In the last paragraph before the conclusion section, the authors write that intervention strategies should be taken into account to prevent progression and long term consequence. What does that mean in light of their results?

Clarification 5: We have deleted the comparison from the introduction as afore-mentioned and remove the sentence about the consequence that might confuse readers.

Reviewer: Tarik Asselah

1. The authors stated, in the method section, that liver biopsies were taken within 12 months before enrollment showing chronic hepatitis. The authors should give the results of liver biopsies i.e. grade of necroinflammation and stage of fibrosis.

Clarification 1: We have given the results of liver biopsies in results section. Please see page 7 and Table 1.

2. The authors should comment in the discussion the rapid virological decrease during entecavir treatment (in comparison of other treatment).
Clarification 2: We agree and have added review on comparison of HBV clearance as suggested by the reviewers on the middle of page 10, lines 13-19:

3. The authors should make comparison between patients with a good response to entecavir, from those with no response to entecavir. They should make a multivariate analysis to find factors associated with a favourable response.

Clarification 3: There were only 8 complete responders (ALT normal/ HBeAg & HBV DNA-negation) at the end of 48-week therapy. The situation did not allow us the identify predictors for responder This will be reanalyzed a the end of the 2 years treatment.

Reviewer: Antonio Bertoletti

It is my opinion, that the simple analysis of the phenotype without any attempts to analyze the functionality of the cells or the frequency of HBV-specific T cells is meaningless.

It is for example not clear why a change of the ration between CD4 and CD8 should be consider a functional restoration of immunity during HBV infection. Increase number of CD4 does not mean better HBV-specific T cell function and HBV is not infecting and killing directly CD4 cells like HIV.

Clarification 1: We realize the limitation of this study and have provided more literature review on this issue in the discussion.