Reviewer's report

**Title:** Addition of nucleoside analogues to Peg-IFNα-2a enhances virological response in chronic hepatitis B patients without early response to Peg-IFNα-2a: A randomized controlled trial

**Version:** 0  **Date:** 05 Feb 2017

**Reviewer:** Mar Riveiro-Barciela

**Reviewer's report:**

This clinical trial focus on a new treatment strategy with pegIFN plus NAs in patients with CHB who presented a poor virological response to 12-weeks therapy with pegIFN. The therapeutic protocol is correct, though sometimes it is doubtful that it is actually a prospective controlled trial since in some parts of the text the number and percentage of patients with poor response change. Another limitation of the protocol is the use of ADV in a brand of treatment, since in Europe it is no longer a first-line NAs. Other important limitations of the study are the definitions of efficacy. According to the current EASL guidelines, early virological response during pegIFN therapy, in both HBeAg positive and negative patients, is defined as HBV DNA <20.000 IU/mL. Moreover, off-treatment virological response is defined as HBV DNA < 2000 IU/mL plus normal ALT levels. Therefore, results should be reviewed in order to be in agreement with the EASL´s endpoint definitions.

Another issue that needs further revision is the characteristics of patients. According to the inclusion criteria, patients with cirrhosis can be recruited. However, there is no data regarding the number of patients with liver cirrhosis neither in the text nor in table 1.

Overall there are numerous typos and grammatical errors throughout the manuscript. A fraction of which is listed under "minor points" below. It definitely needs to be carefully edited.

**Minor comments**

**Abstract**

Characteristics of patients, especially HBeAg positivity should be added.

Definitions used to guide response to PegIFN (poor virological response) and SVR may be added to the abstract in order to improve its understanding.
Background.

By the time being, clearance of cccDNA is not a goal of CHB treatment so this sentence may be removed.

Material and methods

Line 4, page 7: there is an extra sentence.

Paired liver biopsies were performed in 38 patients, which brand of therapy were these patients?

Results

Mean HBV DNA differences between PegIFN vs PegIFN plus a NAs may be specified over time and add to figure 1.

Results should be reanalysis in order to be in line with the EASL guidelines.

It is a bit surprising that the combination that achieved the greatest change on HBsAg levels was pegIFN plus ADV. Could this fact be linked to lower baseline HBsAg levels? To the greater proportion of genotype B patients on this group?

If none patient achieve HBsAg loss during or after therapy, this should be pointed out.

Discussion

In the present study, 138 study patients were treated Peg-IFNa-2a for 12 weeks, and only 95 patients who had a poor virological response at the end of this period received combination therapy of Peg-IFNa-2a with either ETV or ADV for 48 weeks. The number patients initially treated with pegIFN was 178 and those with poor response and therefore randomized to the three brands of study 138??

Achievement of HBeAg seroconversion did not differ from TDF or ETV monotherapy rates. According to the authors, what are the benefits of pegIFN combination in comparison with NA monotherapy?
Tables

Table 1. "Type" should be removed from genotype. There is no need for explaining the statistical analysis since it has been previously exposed in the text.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**Does the work include the necessary controls?**
If not, please specify which controls are required in your comments to the authors.

Yes

**Are the conclusions drawn adequately supported by the data shown?**
If not, please explain in your comments to the authors.

No

**Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?**
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

I am able to assess the statistics

**Quality of written English**
Please indicate the quality of language in the manuscript:

Needs some language corrections before being published
**Declaration of competing interests**

Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?

6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license ([http://creativecommons.org/licenses/by/4.0/](http://creativecommons.org/licenses/by/4.0/)). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal.