Author’s response to reviews

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

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Replies to recommendations on revision

1. 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.
The study was designed with the patients grouped according to the early virologic response, some for extension of the treatment and some for combination with nucleotide analogues, to investigate whether the extension and combination could improve the efficacy. International guidelines on definition of virological response is not exactly the same, The study is mainly based on China's guidelines are defined.

The patients on combination with nucleotide analogues were based on the following considerations: a) The adverse effect from interferon combined with telbivudine; b) The high resistance to lamivudine and the limited effect on improving the efficacy from interferon combined with lamivudine as shown in the previous clinical studies; and c) TDF is on the market in China in 2014. Therefore the study was a randomized investigation on the efficacy of treatment with another 2 drugs, i.e. entecavir and adefovir dipivoxil, combined with interferon and whether any adverse effect existed.

2. 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.

In this study, 178 patients with chronic hepatitis B (n=131) and compensated (n=47) HBV-induced cirrhosis were enrolled. No decompensated cirrhosis patients were included, as indicated in the inclusion criteria. Because the study was to investigate whether the extension and combination could improve the efficacy, and number of patients with liver cirrhosis is small, so do not compared in patients with hepatitis and liver cirrhosis.

3. 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.

The data has been added.
4. Background.

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

The sentence has been removed.

5. 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?

Line 4, page 7:

The original: CHB diagnosis was based on the “Guideline for the Prevention and Therapy of Chronic Hepatitis B in China” issued by the Infectious Diseases Branch of the Chinese Medical Association, Hepatological Diseases Branch of the Chinese Medical Association, and the Chinese Foundation for Hepatitis Prevention and Control [17].

The guide is constituted by three association.

Line 13, page 13:

Thirty eight patients (11 in Peg-IFNα-2a group, 14 in Peg-IFNα-2a+ETV group, and 13 in Peg-IFNα-2a+ADV group) received liver histological examinations before therapy and after the 48 week follow-up period.

6. Results

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

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

International guidelines on definition of virological response is not exactly the same, The study is mainly based on China's guidelines are defined. All the patients are Chinese people, I think it doesn't have to according to the European guidelines for evaluation. There are a lot of the definition of effective evaluation, I think the results are meaningful.

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?

The mean HBsAg levels of this group (peg IFN plus ADV) is really the lowest, and the proportion of genotype B patients are the most. May be associated with these two factors.

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

The description has been added to the above results

7. Discussion

In the present study, 138 study patients were treated Peg-IFNα-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-IFNα-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??

A total of 178 patients diagnosed with CHB were recruited, All study patients received a subcutaneous injection of Peg-IFNα-2a (180 μg) once weekly for 12 weeks. A total of 138 patients had a poor virological response after 12 weeks of anti-viral therapy with Peg-IFNα-2a. After fully communication with patients, According to patients' willingness, Study patients were divided into 3 groups: Continue to treat with interferon, Plus ETV and ADV group.
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?

The quantitative assay of S antigen has been widely applied for patients treated with the interferon anti-virus therapy, helpful for treatment. Reduction in HBsAg levels has been shown to be closely related to seroconversion of HBeAg. The study began with the comparison on the correlation between the decrease in S antigen of the group with early response and the group without early response, presenting the significant difference. Changes were seen at Week 12 during treatment, but as it was a cohort comparison based on the patients without the early response, and there was no significant change in S antigen previously; and the decrease in S antigen after the conventional treatment, the prolonged treatment and the combined treatment was compared in the study, showing no significant difference, but the more significant decrease after the extension and combination.

8. 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.

Has been modified