Author’s response to reviews

Title: Sustained serological and complete responses in HBeAg-Positive Patients treated with Peginterferon alfa-2b: a 6-Year Long-Term Follow-Up of a Multicenter, Randomized, Controlled Trial in China

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Dear Prof. Reiberger,

Thank you for reviewing our manuscript entitled “Sustained serological and complete responses in HBeAg-Positive Patients treated with Peginterferon alpha-2b: a 6-Year Long-Term Follow-Up of a Multicenter, Randomized, Controlled Trial in China.” We greatly appreciate the reviewers’ detailed comments and advice aiming at emphasizing the study’s scientific findings and improving the quality of our manuscript. We have revised our manuscript based on the additional comments and suggestions and tried to provide as much detail as possible in our information and corrections. We have the manuscript edited by an English-fluent medical writer.
Below you will find our point-by-point responses to the comments, including descriptions of how we integrated the revised material into our manuscript and revised data presentation in the Tables and text.

We are most grateful for this opportunity to revise our report and to resubmit it for reconsideration of publication by BMC Gastroenterology.

Sincerely,

Prof Hou Jinlin on behalf of the study team

Editor Comments:

Abstract:

1) Definition of the population: All HBeAg(+) at the beginning?

Response: The wording is rephrased to “Pegylated interferon alfa-2b (PEG-IFN alfa-2b) is recommended for chronic hepatitis B (CHB) patients” to avoid the misunderstanding. The study population, however, was HBeAg-positive patients with CHB, as shown in the published P05170 study.

2) Presentation of results: the authors start with the significant finding of higher rates of ALT normalization at the end of the study; however, first this analysis has not been introduced in the methods section and second (even more importantly) this analysis is part of the “initial “study and is not related to the “long-term “effects, which should be the primary focus of this study.

Response: In the revised manuscript, the results section of the abstract has been rephrased according to the editor’s suggestion. Thank you very much for the correction of writing mistakes.
3) Typo: „he group” instead of „the group “
Response: The typo has been corrected. Very sorry for the error.

4) Some statements/the presentation is not intuitive: First there is the statement that “no significant difference in the rate of sustainability ….” Which suggested that there are significant differences in long-term “serological” (SR, i.e. HBeAg seroconversion) and “combined” (CR HBeAg seroconversion, and HBV-DNA suppression to <2000 IU/mL) response. However, then the next statement indicates that a significantly higher rate of SR and CR was found in the 48W-high-dose 1.5µg/kg/wk dose than in the other groups (i.e. either 1.5µg/kg/wk for 24W or 1.0µg/kg/wk for 24W). please clarify! Are you first referring to the long-term ALT normalization rates?
Response: Many thanks for the suggestion. We rephrased the results section of the abstract as suggested. New result presentation has been organized in the text. Very sorry for the confusion.

5) Wording: please delete “initial” from PEG IFN therapy… what is “initial?” either just leave it out, or state “48W therapy with … “or similar.
Response: The wording has been rephrased.

6) In the abstract conclusion you suddenly refer to “sustained clinical response”, in the methods you defined “sustained combined response”. Honestly, since the authors also use “CR”. I would use “complete response” throughout the manuscript, since this is usually what is understand by HBeAg seroconversion and HBV-DNA suppression (to at least <2000 IU/mL).
Response: Many thanks for the suggestion. We changed the term “sustained combined response” to “sustained completed response” throughout the manuscript.

Results:

1) What do the authors mean by “… and the levels of HBV-DNA and antibodies to HBs and HBe were low-to-moderate overall.” Are you referring to the HBV-DNA levels at end of treatment= end of study, what would you consider low-to-moderate HBV-DNA levels? I would either indicate the median level, or indicate the number of patients (proportions) with HBV-DNA<2000 IU, or similar. But antibodies to HBs?? Anti-HBe?? Titers what do you mean? I would suggest to delete the latter two statements.
Response: Thanks for the comments. We have revised the corresponding text in the results section and organize to reflect the important results in the tables.
Table-1:

1) It seems that the proportion of patients achieving HBeAg-Seroconversion AFTER the end of treatment (=end of initial study) was very high across all treatment groups, e.g. from n=21 (18.4%) to n=39 (34.2%) in the 1.0µg/24W group and from n=20 (20.6%) to n=36 (37.1%) in the 1.5µg/24W group – but only from 19 (17.1%) to 39 (35.1%) in the 1.5µg/48W. This should be highlighted in the results/abstract. Also, how many of the patients achieving post-treatment HBeAg seroconversion also had ALT normalization and how many had also HBV-DNA suppression <2000IU/mL.

Response: Thanks very much for your comments. This is really an important finding that we did not fully put the focus. We have added relevant descriptions in the abstract, result section, and discussion section to emphasize these data results.

Results for patients achieving post-treatment HBeAg seroconversion + ALT normalization / +HBV-DNA suppression <2000IU/mL at EOS were added to the table 1.

Table-2:

1) Terminology is VERY confusing. E.g. already in the header: what is “sustained treatment clinical response” … please stick to your definitions of “sustained serological response (SR)” and sustained “combined” or “complete” response (CR). Otherwise this is way too confusing!

2) Please also avoid a sudden introduction of “VR” virological response, this is important but either you analyses long-term “VR” for all analyses or you don’t. but not only in subgroups.

Response: Thanks very much for the instructions. Table 2 has been revised accordingly. The definitions of CR and SR are now included in the footnote of Table 2. Serological response (SR) was defined as HBeAg loss and seroconversion to anti-HBe. Sustained combined clinical response (CR) was defined as HBe seroconversion and HBV-DNA less than 2000 IU/mL. As explained in the previous response, the “combined clinical response” has been changed to “complete response.” Virologic response (VR) was removed from the table.
Table-4

1) The hazard ratio for Additional antivirals of 1.0 with 95%CI of 1.0 to 1.0 re very unlikely…. Similar to the HR of 0.00 with 95%CI of 0.0 to 0.0… this is most likely a statistical error during computing of the analysis. This need to be consulted with an expert statistician!!

Response: Thanks for your comments. We have verified the results of Table 4. The corresponding description of “Not Applicable (NA)” is shown in the footnote. The “additional antivirals” variable included in the model does not have a predictive profile for the dependent variable (outcome); thus, the HR and 95% CI cannot be determined. The duration of follow-up is included in the Cox model as a component of survival/hazard functions and therefore is not applicable for calculating HR in the model. To be consistent with the original output, we have modified the results.

Overall, the presentation of results MUST be streamlined, I would suggest the following table:

Response: We have revised and created a new Table 2 in the revised manuscript to meet the below requirements as much as possible. Many thanks for helping with the table presentation.

<table>
<thead>
<tr>
<th></th>
<th>PEGIFN 1.0/24W</th>
<th>PEGIFN 1.5/24W</th>
<th>PEGIFN 1.5/48W</th>
</tr>
</thead>
<tbody>
<tr>
<td>End-of study results (EOS)</td>
<td>n/% (of all patients)</td>
<td>n/% (of all patients)</td>
<td>n/% (of all patients)</td>
</tr>
</tbody>
</table>
Pat eligible for long-term follow-up (LTFU)

Patients  n/% (of initial study)
SR at EOS  n/% (of LTFE patients)
CR at EOS  n/% (of LTFE patients)

Pat receiving NA between EOS and LTFU
no NA      n/n (of LTFE patients)
NA         n/n (of LTFE patients)
NA for relapse after CR n/n (of patients with CR at EOS)

Patients with sustained response
SR at LTFU  n/n (among patients with SR at EOS)
SR at LTFU with NA n/n
CR at LTFU  n/n (among patients with CR at EOS)
CR at LTFU with NA n/n

Patients with “new response”
New SR at LTFU  n/n (among patients without SR at EOS)
New SR at LTFE with NA  n/n
New CR at LTFU  n/n (among patients without CR at EOS)
New CR at LTFU with NA  n/n
Additional comment by a reviewer:

The numbers in the "LTFU"-Section of table 2 do not fit to the numbers given in table 3. For example, according to table 2 there were 45 patients with HBe Negativity at LTFU in the low dose PEG-group (without additional antiviral treatment) and in table 3 there are 46 patients in the low dose PEG group without NA-therapy! For me the main conclusion of this paper is that there are no clinically relevant differences between the three treatment groups during the long-term follow-up.

Honestly, I do not understand the clinical significance of the term "cumulative response rate" in the context of the paper. From table 3 it can be seen that the overall complete response rate is far below 70% in the high dose 48 weeks group after 6 years - and this is the most significant clinical end point.

Response: Thanks for your comments. After revision, the number of patients with/ and without additional NA in each group now match between Tables 2 and 3 in terms of patients who were with or without additional NA treatment. Actually, Table 3 indicated patients with a clinical outcome only at the LTFU (no any consideration of prior clinical outcome) as grouped by additional antivirals (patients with additional antivirals vs. without additional antivirals).

Moreover, we sincerely appreciate the comments pointing out the low-to-moderate rates of SR and CR for patients at the LTFU. This is helpful in terms of clinical practice. We have added the descriptions in the result and discussion sections to emphasize the findings and interpretation.

BMC Gastroenterology operates a policy of open peer review, which means that you will be able to see the names of the reviewers who provided the reports via the online peer review system. We encourage you to also view the reports there, via the action links on the left-hand side of the page, to see the names of the reviewers.
Reviewer reports:

Michael Gschwantler (Reviewer 3): The authors have well addressed most issues raised by the reviewers.

I have the following comments:

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