Author’s response to reviews

Title: Peginterferon alpha-based therapy for chronic hepatitis B focusing on HBsAg clearance or seroconversion: a meta-analysis of controlled clinical trials

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Author’s response to reviews:

May 23, 2011

Miss Chantal Botha and Dr. Vincent Lo Re
Editor in Chief, BMC infectious diseases.

Re: MS: 2986655345032012

“Peginterferon alpha based therapy for chronic hepatitis B focusing on HBsAg clearance or seroconversion: a meta-analysis of controlled clinical trials”

We are very grateful for your letter of May 8, 2011 concerning this manuscript, and the offer to allow us to revise it in accordance with the further comments of the reviewers. We are pleased to submit a substantially revised manuscript with changes highlighted in RED, together with a point-by-point response to reviewers’ comments.

We appreciate this opportunity to submit a revised manuscript and trust that you and your reviewers will find it sufficiently improved to justify publication in BMC infectious diseases.

Yours Sincerely

Yuemin Nan (on behalf of the authors).

Response to the comments of the referees in relation to the manuscript:

2986655345032012, “Peginterferon alpha based therapy for chronic hepatitis B focusing on HBsAg clearance or seroconversion: a meta-analysis of controlled
The manuscript entitled “Peginterferon alpha based therapy for chronic hepatitis B focusing on HBsAg clearance or seroconversion: a meta-analysis of controlled clinical trials” is a revised systematic review and meta-analysis of controlled trials evaluating pegylated interferon alpha for the treatment of chronic hepatitis B. The results of 14 eligible trials suggest that this therapy was more effective than lamivudine or conventional interferon alpha in HBsAg clearance and seroconversion. In this revision, the authors have satisfactorily addressed reviewer concerns raised in the first submission. A few minor revisions are still necessary.

Major Revisions

None

Minor Revisions

1. To assess for the potential for publication bias, a common problem in meta-analysis, the authors undertook funnel plots of all relevant outcomes. The funnel plots with the exception of figure 7 were fairly symmetrical, but these can be difficult to determine visually with few studies. I don’t think figure 9 was asymmetrical. I would recommend that they drop all funnel plots except figure 7, add a title to figure 7, and discuss it rather than figure 9 as potentially demonstrating publication bias. They will also need to add to the method section that they used funnel plots to assess for publication bias.

RESPONSE: We appreciate the comments. The manuscript has been re-written accordingly, including below:

(Method section, page 6, line 20): Publication bias was assessed by funnel plots.

(Result section, page 9, line 3): An assessment of publication bias was conducted using funnel plots. Evidences of publication bias based on the funnel plots were found in comparison of combination therapy with PEG-IFN# monotherapy on HBsAg clearance and HBsAg seroconversion only among high-quality studies [Fig.7]. There was no apparent publication bias in the other comparison groups.

2. The authors conducted a sensitivity analysis for the first outcome combination therapy vs. monotherapy with Peg by examining the outcome only among high
quality studies. They should also conduct this sensitivity analysis for all the remaining outcomes and then add to the methods section information on how they conducted sensitivity analyses of quality.

RESPONSE: We appreciate this point. The studies in each of the remaining comparison groups were of same quality. For this reason, we didn’t conduct this sensitivity analysis for all the outcomes except the first outcome of combination therapy vs. monotherapy with PEG-IFN alpha. The information has been added to the Methods section:

(Method section, page 6, line 6): We performed a sensitivity analysis of quality by considering all studies to be of high-quality.

3. Table 1 is in reality a figure. They should relabel it as Figure 1 and then subsequently relabel the remaining tables and figures accordingly.

RESPONSE: Table 1 has been relabeled as Figure 1 and the remaining tables and figures have been subsequently relabeled.

4. The authors did not state what they did with events with “zero” cells. They should state whether they added a “0.5” value to these cells so that the computer program could correctly compute an odds ratio for those studies.

RESPONSE: Adding a “0.5” value was designed to resolve the problem of “zero” cells by RevMan 5.0.24.0. This has been included in the Method section as below:

(Method section, page 6, line 13): If a clinical trial has no subject (0%) developing the outcome of concern in either of the two comparison groups, we just input the “zero” to the computer, then it will add 0.5 to each of the four cells in the 2×2 table by RevMan 5.0.24.0 automatically.

Reviewer: Melissa Osborn

Reviewer’s report:

The authors have done a commendable job addressing the issues raised in the initial review. They have addressed both a sensitivity analysis including only high-quality studies, and have included funnel plots to address publication bias, an issue also raised by the other reviewer. (However, in the discussion, they still raise the possibility of publication bias as a limitation of their analysis, which should be reworded or taken out, as this was addressed to the best of their ability). While they did not address my third point much in their discussion (what the meta-analysis adds to the literature), this does not detract from the paper and should not keep it from moving forward with publication.

RESPONSE: We appreciate the comments. The limitation of publication bias has
been taken out. We have addressed what the meta-analysis adds to the literature in the discussion section.

(Discussion section, page 10, line 15): Compared with any single study, meta-analysis has increased power for statistical tests, and increased precision for confidence intervals, because the conclusions often reflect a broad spectrum of patients and study characteristics, and the results are more generalizable than a single study.

(Discussion section, page 12, line 20): Our study contains several limitations. Firstly, although no difference was found between the high-quality studies and the overall trials in the comparison of the combination therapy group and PEG-IFN# monotherapy group, the low-quality studies in our analysis, especially those in Chinese publications, which lacked randomization, may weaken our conclusions. Secondly, while this study focused on PEG-IFN# and LAM combination therapy, combinations of PEG-IFN# with other potent antiviral agents need to be further explored, which was limited by deficient data currently available. Finally, the absence of adequate controlled trials precluded our analysis on the subsets of PEG-IFN#-2a or 2b, as well as HBeAg positive or negative CHB patients.