Author's response to reviews

Title: Significance of a Reduction in HCV RNA Levels at 4 and 12 Weeks in Patients Infected with HCV Genotype 1b for the Prediction of the Outcome of Combination Therapy with Peginterferon and Ribavirin

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Author's response to reviews: see over
September 26, 2012
The Editor,
BMC Infectious Diseases

Dear the Editor,
Please find the revised version of our manuscript entitled "Significance of a reduction in HCV RNA levels at 4 and 12 weeks in patients infected with HCV genotype 1b for the prediction of the outcome of combination therapy with peginterferon and ribavirin”.

Thank you very much for giving us the opportunity to revise and resubmit our manuscript. We revised the manuscript according to the comments by reviewers and the editor. The points that were added or modified in this revision were underlined. In addition, we attached the point-by-point responses to their comments. We hope that you can be satisfied by this revision. We are looking forward to the final decision.
Sincerely yours,

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Dear reviewers and the editor,
Thank you for your thoughtful comments. Here we describe the responses to them.

Reviewer #1429759057797577
Major Compulsory Revisions
1) Discussion section, third paragraph: In this manuscript, there are some results that should be emphasized more and more by authors. Any on-treatment (viral decline magnitude at 4 and 12 weeks) and baseline variables (host and viral factors) did not predict the likelihood of achieving SVR in slow virologic responders, who were treated with the extended 72-week course. The findings may be original and unique. Prolonged treatment duration may relieve slow virologic responders from unfavorable conditions.
---We fully agree with you. We are well aware that the findings above are the most important point of this article with novelty. We emphasized this point according to your suggestion (page 20, lines 2-5 in the revised version). We added the sentence that you mentioned in your comment in this revision (page 20, lines 10-11 in the revised version).

2) Method section: Where is (iii)?
---(iii) is described at the bottom of page 7 (line 18) as one of the inclusion criteria. We had no additional explanation on (iii) thereafter (page 8).

3) What is reference 33? Authors should confirm reference numbers in the text and references list.
---We are very sorry for this missing. We described reference #33 in the reference list of the revised version.

4) A soft package used for statistical analyses should be described in the revised text.
---We used StatFlex version 6. We described this in the revised version (page 14, lines 5-6 in the revised version).

5) Statistical Analyses section: Were between-group differences analyzed by the chi-squared test alone? Really? How were quantitative variables analyzed to compare groups?

6) Authors should clarify how the best-cutoff values in the ROC curves were yielded.
---We modified this part on the comparisons between groups (page 13, lines 8-10 in the revised version), and added the description on ROC analysis (page 13, lines 10-14 in the
Minor Essential Revisions
1) Paragraph prior to Statistical Analyses section, line 3 from the last line: “the GG genotype...”, instead of “The GG genotype”.
---We are sorry for this mistake. We corrected.

2) Results section, last paragraph, line 2 from the last line: “12 weeks (24 of 42...”
   instead of “4 weeks (24 of 42...”.
---Again we are sorry for this mistake. We corrected.

Discretionary Revisions
Figure 3 had better be removed from the revised text.
---We agree with you in part. However, we prefer Figure 3 to be remained included in the article. We believe that Figure 3 will be useful for better understanding the fact that the decrease in HCV RNA levels 4 and 12 weeks after the start of the therapy did not predict the likelihood of achieving SVR in slow virologic responders, who were treated with the extended 72-week course, because it is visually.

Reviewer #1847660642796455
Thank you very much for your favorable comments.

Minor point
Ref 7 should be changed for Intervirology 2005;48:372-380.
---We are sorry for this. We corrected.

Editor
1) The authors do not indicate their strategy to construct their multiple logistic regression model (strategy used, criteria for selecting the variables to be introduced in the modeling, test of term of interaction...). This should be described.
---We are sorry for this scanty of description. We added the information on this (page, lines, in the revised version). We included for univariate analysis factors that would be potentially associated the response to the therapy. After that, we included for multivariate analysis factors that were associated with SVR by univariate analysis.
2) There are several variables with missing data so that the sample size for the multivariate analysis is 314 and not 516. The authors, therefore, performed a "complete case-analysis" with the implicit hypothesis that this does not create bias. There are different types of missing data (missing completely at random, missing at random and missing non at random) and depending on the type of missing data the complete case analysis may be biased.

--- We agree with you. We described the information on the type of missing data. The data were missing completely at random based on the comparison between cases with and without missing data. We described this in the revised version (page 21, lines 5-8).

In addition, the lost of patients because of missing data in the multivariate analysis reduced substantially the statistical power and alter the value of non-significant results of the multiple regression analysis. Authors should therefore, at least discuss these issues.

--- We agree with you also for this. We described the possible decrease in the significance associated with the decrease in the number of patients analyzed as the limitation of the study in Discussion section (page 21, lines 8-10, in the revised version).

3) The authors have assessed the performing of prognostic criteria on one sample of patients that served also to develop it. A predictive model's performance in the population from which it was developed often over represents its performance in other populations. Internal validation using bootstrap techniques allow to assess the over-optimism of the model and to adjust its predictive accuracy (several references are provided below). This point would need to be at least discussed in the paper.

--- Thank you for your useful and important suggestion. We discussed the importance of internal validation and possible use of bootstrap analysis in Discussion section referring literatures that you kindly suggested (page 21, lines 10-13, and references 34 and 35 in the revised version).