Author's response to reviews

Title: Studies on best positive predictors for sustained virologic response to interferon alpha plus ribavirin therapy in Naive Chronic Hepatitis C Patients

Authors:

Muhammad Idrees (idreeskhan96@yahoo.com)
Sheikh Riazuddin (riaz@ihr.comsat.edu.pk)

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Author's response to reviews: see over
The Biomed Central Editorial Team

Object: MS: MS: 2037671906198646- “Studies on best positive predictors for sustained virologic response to interferon alpha plus ribavirin therapy in Naive Chronic Hepatitis C Patients”. Dr. Muhammad Idrees and Dr. Sheikh Riazuddin.

Thank you for consideration of our manuscript for publication in your esteemed journal.

We have reviewed the above manuscript according to your reviewer’s comments. Our revisions and responses appear below:

First Reviewer's report
Title: Studies on best positive predictors for sustained virologic response to interferon alpha plus ribavirin therapy in Naive Chronic Hepatitis C Patients
Version: 2 Date: 10 June 2008
Reviewer: Claudio Tiribelli

Reviewer's report:
The author addressed my critiques in a acceptable way although the main reservations I had still holds i.e. the nature of retrospective studies, the poor selection of the patients and the largely confirmatory results. I understand that the ethnicity is different from what previously reported in other larger and prospective studies, but this is not enough to have this paper published as full Ms. I suggest to shorten the text and submit as short report.

→Twice checked and edited by a Native English man. Thanks to reviewer for accepting the responses to critiques submitted against the first version review. As the reviewer acknowledges that the ethnicity is different from other studies on the subject reported from other countries regarding patient selection and confirmatory results. The manuscript had a lot of information on the subject and the reviewer had already acknowledged that this is retrospective study with a lot of information and congratulated the authors for the large effort in the first reviewer report. We have shortened the text as suggested by the reviewer and request to publish it as a full manuscript instead of short report.

Level of interest: An article of limited interest
Quality of written English: Needs some language corrections before being published

→Twice checked and edited by a Native English man. Suggestion well taken and the text of the manuscript were improved and revision was done by a friend of mine whose mother tongue is English.

Statistical review: Yes, but I do not feel adequately qualified to assess the statistics.
Declaration of competing interests:
I have no competing interests.
2nd Reviewer's report

Title: Studies on best positive predictors for sustained virologic response to interferon alpha plus ribavirin therapy in Naive Chronic Hepatitis C Patients

Version: 2 Date: 12 July 2008

Reviewer: Gloria Taliani

Reviewer's report:
Major comments:
In the present study a really good rate of SVR (51.56%) is reported in HCV patients treated with non-pegylated IFN and ribavirin. Although this result may depend on racial and/or virological characteristics of the study population, it is quite different from the results reported in other populations treated with the same schedule and IFN type. To this high response rate could, at least in part, contribute the exclusion of some patients from the analysis. In fact, on page 9 we find the following sentence: “Out of these 400 patients, 280 were males and 120 females. Six patients (four males and two females) discontinued treatment due to severe side effect of treatment at month 2 and were excluded from data analysis”. This is not correct because these patients have received the treatment for 2 months and should be computed as non-responders on intention to treat analysis. Thus, SVR rate should be recalculated after inclusion of these patients and the result should be correctly reported in all the sections of the manuscript, including the abstract.

→Suggestion well taken and recalculated the SVR rate after the inclusion of all the six patients (four males and two females) who discontinued treatment due to severe side effect of treatment at month 2. Furthermore we have also changed the new rates of NR, ETR and SVR rates accordingly in all sections of manuscript including abstract, results and discussion as suggested.

In addition, although the PCR method employed in the present study has a quite low sensitivity (100copies/ml of HCV-RNA) which may contribute to misclassify partial responders with low residual HCV-RNA titer as end treatment responders, the relapse rate after therapy withdrawal is surprisingly low (16%), and this is an unexpected result which deserves some comments and some clarification from the authors.

→As suggested we have included comments on the relapse rate in the discussion section of the manuscript and compared it to other studies reported from this country and reported in other populations treated with the same schedule and IFN type. It can be seen from the discussion that this relapsed rate is very high as compared to that reported by Khokhar and Co-workers in Pakistani patients where only 4% relapse rate was reported but is very low as reported by Sarrazin and colleagues that was 43%. So it is obvious that this is not surprisingly low for our country due to difference in racial and virological characteristics that is why it is
quite different from the results reported in other populations treated with the same schedule and IFN type.

Table 2, which reports the results of the analysis of virological response at week 8, end of treatment and end of follow up, is difficult to understand. I made the calculation myself with either Fisher’s exact test and Chi square test and found no significant difference between males and females in any type of virological response. Thus I wonder which test has been applied for the calculation of such a significant difference reported by the Authors. Besides, I did not find any difference between males and females by Chi Square test and Fisher’s exact test based on the data reported in table 5. Thus, a revision of the statistical analysis is strongly advised. The definition of Rapid Virological Response (RVR) given by the Authors in not correct. By definition, the RVR is the negative HCV-RNA by week 4 of therapy and not by week 8 as indicated by the Authors. The wrong definition should be corrected along all the manuscript. The number of patients who had a liver biopsy examination is really low (57 patients) compared to the cohort of treated patients (400 patients) and this makes impossible to infer data about the response rate of different ethnic groups (Pashtoon versus Punjab), of cirrhotic patients or make a multivariate analysis concerning the predictors of response. In addition, no data about the compliance of the patients to the therapy are reported, which introduces a further uncertainty about the reliability of the predictors of response.

We have revised the statistical analysis as mentioned in the materials and method section as suggested. Furthermore, we have deleted Table 2 as had not new and/or important information. As suggested we have also corrected the definition of Rapid Virological Response (RVR) given in the entire manuscript. Data regarding the compliance of the patients to the therapy are included and given in the result and discussion sections of the manuscript.

In Table 3, the groups of patients divided according to the infecting genotype are too many and some groups include less than 5 patients, which is useless: genotypes may be grouped in 1 and non-1. This last group can be sub-divided in genotype 2 and 3. Finally, it could be interesting to examine in deeper detail those patients with mixed genotypes who did not respond to the treatment in order to evaluate which genotype was the resistant one.

Table 3 (Now Table 2 after deletion of table 2) was redrawn and grouped genotypes in 1, 2, 3, others and mixed as suggested by reviewer.

Also Table 4 is too detailed. A ROC of age and response could be done to determine the best age cut-point and age analysis should be done according to it.

Table 4 (Now Table 3 after deletion of table 2) was shortening as suggested by reviewer.
Finally, the discussion is too long. It should be shortened and focused on really relevant points regarding data correctly re-analyzed.

→Discussion section of the manuscript was revised after re-analyzing data and was condensed as suggested by reviewer.

The manuscript should undergo a careful revision by an English mother tongue reviewer.

→As suggested a careful revision of the manuscript was done by an English mother tongue reviewer in USA.

Minor Comments:
In the text it is reported that some examined factors are “…..independent risk factors for low SVR”…. Which is not correct. These factors are independent PREDICTORS OF NON RESPONSE. The concept of “low response” is not applicable to HCV treatment: there is only the possibility of “response” or “non response”.

→The mentioned sentences were re-written and corrected as suggested by reviewer. Now it can be read as “These factors are independent PREDICTORS OF NON RESPONSE.”.

In the abstract, the following sentence should be reworded ” the patients data collected prospectively was at this Centre from 2001 to 2007 was analyzed”.

→Suggestion well taken and the given sentence were reworded as “the patients data collected prospectively was at this Centre from 2001 to 2007 was analyzed.

On page 7, the following sentence should be reworded “Further the patients were required to negative for hepatitis B surface antigen…”

→Reworded the sentence as suggested by reviewer as “Further the patients were required to negative for hepatitis B surface antigen…”

On page 7, the following sentence should be reworded “Patients were excluded from the studies that were <18 years or above 70 years.

→Corrected the sentence by rewording as “Patients were excluded from the studies that were <18 years or above 70 years.

Tables should be carefully revised because of typing errors (e.g. Table 1, the percentage of genotype 3 females is not 18.78) or mistakes (Table 2 P values; Table 5 sex P value).

→Suggestions well taken. Tables were revised carefully and all typing errors were removed.
Many other misspelling, grammar and syntax errors are present in the manuscript and should be corrected.

→ All the spelling, grammatical and syntax errors were correct in the manuscript by an English gentle man.

Level of interest: An article whose findings are important to those with closely related research interests

→ Thanks to reviewer

Quality of written English: Not suitable for publication unless extensively edited

→ Twice checked and edited by a Native English man.

Statistical review: Yes, and I have assessed the statistics in my report.

Declaration of competing interests:
No competing interests exist