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:

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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: 5 March 2008

Reviewer: Claudio Tiribelli

Reviewer’s report:

1. Is the question posed by the authors well defined? YES

2. Are the methods appropriate and well described? YES

3. Are the data sound? YES

4. Does the manuscript adhere to the relevant standards for reporting and data deposition? YES

5. Are the discussion and conclusions well balanced and adequately supported by the data? YES

6. Are limitations of the work clearly stated? YES

7. Do the authors clearly acknowledge any work upon which they are building, both published and unpublished? YES

8. Do the title and abstract accurately convey what has been found? YES

9. Is the writing acceptable? YES

Although this a well written, interesting study addressing the response to IFN and RIBA in Pakistan (which is new), the real only but major limitation is that the study is fully confirmatory or previous data reported in the literature and
established in the guidelines of almost all liver societies. The fact that the early viral clearance, the better is the outcome has been reported. Actually in Europe and the US the measurement of HCV-RNA serum level after 4 weeks is suggested and recommended as an early and reliable marker of successful or unsuccessful treatment. The same consideration applies to the effect of age, gender, viral load, genotype and fibrosis in the overall response rate.

**Specific Critiques**

1. How larger was the number of biopsy proved diagnosis? This is never indicated as it should.

   On total 57 patients the liver biopsies were performed rest were not willing for biopsies. This is information is mentioned on page-6 as suggested by reviewer.

2. Why RIBA was given according to the body weight in genotypes 2 and 3 while a fixed dose was given in genotype 1 and 4? This discrepancy needs to be discussed.

   The current standard of care for the treatment of chronic hepatitis C is a combination of interferon plus ribavirin. When the interferon/ribavirin combination was first approved, the usual ribavirin dose was a fixed 800 mg/day. But research suggested this wasn't sufficient, especially for overweight patients, and a standard weight-based dose was approved. Patients who weighed less than 75 kg (about 165 lb) received 1000 mg/day, while heavier patients received 1200 mg/day.

   In the present study all the patients that had HCV genotypes 2 & 3 received ribavirin (10 mg/day/kg body weight) along with 3 MU IFN-α 3 times weekly for a total of 24 weeks. Patients with HCV genotypes 1 & 4 that are hard-to-treat were given ribavirin orally (1,000 mg/d in patients with 75 kg body weight or 1,200 mg/d in patients above 75 kg body weight that is from 13.34 to 15.38 mg/day/kg body weight (3-5 mg more) along with 3 MU IFN-α 3 times weekly to obtained high sustained response rates. In our study no patient was with body weight above 96 kg.

   So in both cases standard weight-based dose (1000 or 1200 mg/d) of ribavirin were given.

3. The reasons for the exclusion of 331 candidates need to be fully reported to avoid selection biases.

   The reasons for the exclusion of total 331 patients were fully reported in method section as the reviewer indicated. These were excluded from the study either they were unwilling to participate in the study (n=119) or failed to meet inclusion criteria of the study (n=212) such as had low haemoglobin level (below 13g/dL in men and 12 g/dL in women), and/or low platelet counts (below 50,000) and/or had
white blood cell count less than 3.0/mm3, abnormal serum bilirubin, albumin, creatinine and thyroxine levels. Six patients were also positive for hepatitis B surface antigen, four were with decompensated liver disease, and five were with autoimmune disorders and 23 had history of depression and cardiac diseases so were excluded from the study. Pregnant women, patients <18 years or above 70 years and had persistently normal ALT/AST levels were also excluded from the study.

4. I realize that this is a retrospective study and the author should be congratulated for the large effort. This explains the use of 3 MU of IFMN 3 times a week rather than the now customary Peg IFN. The comparable response rate obtained in the whole population with this scheme as compared to PeG IFN needs to be highlighted.

Thanks to reviewer for realizing the importance of the study. Regarding comparison with peg interferon, we have not enough peg interferon data as the treatment is very expensive and majority of Pakistanis are very poor and can not afford the treatment. Furthermore it has already been reported worldwide that there is significant difference in the response rates for HCV genotypes 3 (most prevalent genotype in Pakistan).

5. The difference between the 2 ethnic groups (Pashtoons and Punjabi) is of interest and needs to be stressed. It I am not wrong the Punjabi race is frequent in India also. Where the results obtained in your Punjabi series comparable to those obtained in similar Indian studies (if available).

Suggestion well taken and incorporated as indicated by reviewer. The reviewer is absolutely right that the Punjabi race is frequent in Indian Punjab. One study on the response rates of Punjabi race is available from Indian Punjab where the sustained virologic response rate was seen 53% (Sood et al. 2006) that are 7% greater than Pakistani Punjabi race. However, in the Indian study pegylated (peg) interferon and ribavirin were used for treatment in these patients and seems to be the reason for higher response rates.

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests: NONE
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: 31 March 2008

Reviewer: Gloria Taliani

Reviewer’s report:

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

This is a retrospective study on predictors of sustained response to antiviral interferon and ribavirin therapy in chronic hepatitis C patients from Pakistan. The study could be of great interest for the scientific community since it brings an interesting piece of knowledge about patients of different ethnicity compared to the most widely studied American or European patients. Nevertheless, it presents some important flaws.

In particular:

Major comments
1) A clear definition of the methods of data collection and patient's recruitment should be provided. Also, the reasons why 400 patients out of 731 screened (as indicated in the Discussion section) should be clarified. In fact, selection of patients is a relevant way to introduce biases in the rate of response to antiviral therapy. Although selection is perfectly admitted before treatment if the treatment is not recommended or contraindicated, the reasons for exclusion from the treatment should be accurately reported in the Methods section.

Suggestion well taken and incorporated. Method for data collection and patients recruitment are provided in Materials & Method section supported by Figure-1.

2) The statistic methods are not appropriately described. In particular, no information are given concerning the comparisons between categories (i.e. dichotomous variables), although in the text some comparisons of different categories are reported as significant. In particular, page 9, Virologic Response section: a significantly higher end treatment response (ETR) among females compared to males is reported, but methods of calculation, numbers and significance level are not indicated neither in this neither in any other manuscript section, nor in the tables). Moreover, the two patients who dropped out from the study after two months of therapy administration should be retained in the final intention to treat (ITT) analysis and considered as non responders, while in the
present paper they have been incorrectly excluded from the analysis (page 9, results section).

The statistic methods are now appropriately described in materials & method. Information concerning the comparisons between categories are given as suggested by reviewer.

3) Overall, data are poorly presented. There are some calculation mistakes (i.e. in the section Patients studied, page 6 (Patients originated from the provinces of Punjab (Panjabi; 294), North West Frontier Province (Pashtoons; 77), Sindh (Sindhi; 11) and Balochistan (Balochi;12) the sum of different groups is 394 while the population studied consists of 400 subjects). There are some divergences in the presentation of results: for example, at the end of page 9 it is stated: “Similarly sustained virological response was also significantly higher in females as compared to males (P<0.001) (table-2)”. On the opposite, at the end of page 10 it is reported: “However, no significant difference was seen in male and female patients for SVR”. Which of the two contrasting sentences is true? The data presented in the Tables are not fully representative of what the manuscript describes. In addition, a more accurate and better readable presentation of data in the table should be given.

The mentioned sentences were re-written and now the ambiguity has been removed. Now it can be read as “Over all sustained virological response was also significantly higher in females as compared to males (P<0.001) (table-2). However, no significant difference was seen in male and female patients with HCV genotype 1 for SVR”.

4) The discussion and conclusions are really not well balanced and adequately supported by the data. For example, the Authors indicate either in the abstract as in some section of the text that early virological response (corresponding to HCV-RNA negativization or at least 2-logs titer reduction compared to pretreatment) predicts sustained virological response. This is a really sound result which has been widely reported in other treated population worldwide. However, data regarding HCV-RNA detection at week 12 among the patients are not reported in any section of the manuscript.

Data regarding HCV-RNA detection at week 12 among the patients are reported in results section of the manuscript.

5) The writing in generally notl accurate and deceive a throughly revision by an English speaking person.

Suggestion well taken and the text of the manuscript were improved and revision was done by English man as reviewer indicated.
Minor comments

1) In the abstract it is stated: “Four hundred consecutive patients were prospectively evacuate”, however, from the text it appears that the study is retrospective. The discrepancy should be clarified.

   Clarified the discrepancy and clearly given in abstract (line 4) and materials & method section (Lines 3-4) that this is a retrospective analysis of data collected prospectively of patients with chronic HCV infection at multiple hospitals/clinics given antiviral therapy. Now we believe that the reviewer will have no confusion.

2) Some calculations should be corrected. For example page 9: 268 out of 394 is 68.02% (reported as 68.08). In Table 1, the number of males and females with genotype-1 infection are to be corrected (in the table are reported 66 males and 23 females while the sum should be 69 patients with genotype-1 infection), and the corresponding percentages should be amended.

   Amended and corrected all calculation as indicated by reviewer. Replaced 68.08 with 68.02. Replaced 66 with 46 that was a typing mistake, the corresponding percentages are correct.

3) Table 2 should be re-disegned with the Response in row and the gender in coulumn. The p-value should be presented at the end of each row.

   Suggestion well taken and incorporated by redesigning table 2 with the response in rows and gender in column as indicated by reviewer.

Level of interest: An article of limited interest

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

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

Declaration of competing interests:
I declare that I have no competing interests