

Response to Reviewers' Comments

Jan 7, 2014



Prof. Ferruccio Bonino

Editor-in-Chief

World Journal of Gastroenterology

Dear Sir,

On behalf of my co-authors, I am submitting the revised version of the manuscript authored by El Naghi *et al.* "6485". All the authors have revised the manuscript and approved its contents. Response to reviewers' comments was addressed carefully point-by-point in the following pages and changes in the manuscript are highlighted yellow.

Please find enclosed the edited manuscript in Word format (file name: 6485-review.doc).

Title: Safety and Efficacy of Hansenula-Derived Pegylated-Interferon Alpha-2a and Ribavirin Combination in Chronic Hepatitis C Egyptian Children

Author: Suzan El Naghi, Tawhida Y Abdel-Ghaffar, Hanaa El-Karakasy, Elham F Abdel-Aty, Mona S El-Raziky, Aleef A Allam, Heba Helmy, Hanaa A El-Araby, Behairy E Behairy, Mohamed A El Guindi, Hatem El-Sebaie, Aisha Y Abdel-Ghaffar, Nermin A Ehsan, Ahmed M El-Hennawy, Mostafa M Sira

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6485

The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

2 The manuscript has been revised for proper English language by a specialized office for scientific writing services.

3 Revision has been made according to the suggestions of the reviewer

Reviewer # 02520511

Comments To Authors

Well done study, presented in a detailed fashion. Though it is already known that extending treatment beyond 48 weeks achieves little extra benefit, your paper convincingly proves the case for Genotype 4 children (including prior non-responders) which is a not so widely studied sub-group.

Specific comments:

Comment 1

Under "Study Population" - 5th line: Replace "Pepatology" with "Hepatology"

Answer 1

Corrected as indicated

Comment 2

Under "Laboratory Investigations" - Consider avoiding the term "LFT". Please consider using the term "liver enzymes" or whatever is the lab that you are trying to indicate (?INR, albumin)

Answer 2

The term was replaced by "Alanine transaminase, aspartate transaminase, gamma-glutamyl transpeptidase, alkaline phosphatase, and prothrombin time"

Comment 3

Please pay attention to column sizes in the tables. Some words had missing alphabets in Table 2 presumably due to discrepancy in column widths.

Answer 3

All tables were carefully revised and corrected accordingly.

Comment 4

In discussion section, would add 2-3 lines about role of direct acting antivirals in this population in future because it appears that a majority of patients in this cohort are now non-responders to interferon based therapy.

Answer 4

A few sentences about direct acting antivirals were added to discussion section, page 15, paragraph 4, last 9 lines

Reviewer # 00031627

Comments to Authors

The aim of the study was to investigate the safety and efficacy of Hansenula-derived pegylated (PEG) interferon (IFN)-alpha-2a (Reiferon Retard) plus ribavirin customized regimen in 46 chronic hepatitis C genotype 4 infected Egyptian children. Only 11 out of 46 (23.9%) patients showed sustained virological response (SVR). Breakthrough was seen in 18 (39.1%) patients, one patient (2.17%) showed relapse and 14 (30.4%) were non-responders. Male gender, short duration of infection, low viral load, mild activity, and mild fibrosis were the factors related to better response. 5-day schedule did not affect response rate (1/17 had SVR). Treatment duration (whether 48 weeks or extended course to 72 weeks) gave similar response rates. Only mild reversible adverse effects were observed and children tolerated the treatment well.

The Authors conclude that Reiferon Retard plus ribavirin combined therapy was safe.

The study is interesting; however some major points could be addressed.

Comment 1

The Authors suggest: "The lower SVR in genotype 4 infected children in this trial compared to other trials in adults using the same IFN type and in children using other IFN types might be partially explained by the high percentage of previous non-responders included in the study (12/46). Of those 12 previous non-responders, only 2 showed SVR." To avoid this bias the results should be shown separately in patients with previous treatment with respect to those without. The type of previous treatments should be shown, and the interval time between previous and actual treatment could be shown and evaluated as a parameter that might influence SVR.

Answer 1

The details of previous treatment trial were added to table 3, including previous treatment type (short-acting IFN+RBV vs. PEG-IFN+RBV) and previous response type (non-responder vs. relapse). Comment on the new data in table 3 was added in results section, page 12, paragraph 2 "Predictors of response" and in page 15, discussion section, 4th paragraph, line 6. The result was also added to abstract, results section. The interval between previous IFN treatment& the current one had to be ≥ 1 year, (a shorter interval was an exclusion criterion).

Comment 2

In Results Authors affirm: "They were all type 4, 65.2% were 4a and 17.4% were 4b. The genotype could not be determined in 8 patients". Please correct this apparent contradiction.

Answer 2

Corrected to be "HCV genotype was detected in 38 out of 46 patients. All were genotype 4, 30 (65.2%) were 4a and 8 (17.4%) were 4b."

Comment 3

Please correct Tab. 2

Answer 3

Corrected as instructed and all other tables were carefully revised.

Reviewer # 00504455

Comments To Authors

This paper is about the safety and efficacy of treatment for 48 or 72 weeks with a novel pegylated-interferon alpha 2a formula & ribavirin in Egyptian children with hepatitis genotype 4 or unknown genotype, who were treatment naive or previous non-SVR to interferon based therapy. My major issue with your study is that the hepatitis C genotype was not determined in 8 of 46 patients. A lot of the statements in the paper should be

considered invalid as long as the hepatitis C genotype has not been determined for these 8 patients. It is very likely that the hepatitis C genotype will be 4, but I would like to see some proof. The paper needs to be restructured, and several key references are missing.

Comments and suggestions

Comment 1

The title does not reflect the study. There were 2 different treatment groups, this should be mentioned. Hepatitis C genotype was not determined in all patients. Hence the current title is misleading. Some patients were non-SVR to previous IFN based treatment, this should be mentioned.

Answer 1

Genotype 4 was removed from the title and the data of genotyping was described in the manuscript only so as not to generalize the tem for all the study population. Changing the title to include the patients with treatment naïve, previous non-responders and relapsers would make the title too long and far exceeding the word count limit specified by the journal. So we had to leave it as it is and decide the treatment groups elaborately in the manuscript.

Comment 2

Has this study been registered in one of the clinical trial databases such as www.clinicaltrials.gov? Please provide the link to the record. Please register the study if it hasn't been registered.

Answer 2

We registered the study at www.ClinicalTrials.gov (NCT02027493). The information was added to the "METHODS" section of "Abstract" and to the "PATIENTS AND METHODS" section, page 11, line 4.

Comment 3

The abstract is too long, 556 words. Please reduce to about 300 words, or whatever the limit is for this journal.

Answer 3

Abstract word count is 449 words and within the limit instructed by the WJG.

Comment 4

Please restructure the abstract and describe methods and results in a logical sequential order.

Answer 4

Abstract was restructured as indicated

Comment 5

Please describe the aim, the patient group (naive and previous non-SVR), the 2 treatment groups clearly.

Answer 5

Patients groups were described clearly in the aim, both in abstract and in the introduction section, last paragraph, lines 2 and 3

Comment 6

Please provide a word count for the manuscript. I now count 3476 words (good).

Answer 6

Manuscript word count was provided after the abstract. It is 3928 words in the revised manuscript

Comment 7

Manuscript throughout: There is a tendency to refer to too many papers. It would make more sense to refer multiple times to a few standard references. Sometimes it is not obvious why a certain reference was chosen, such as references 1, 9, 11, 17.

Answer 7

We revised references carefully and the following changes has been made accordingly. Reference 1 "Welborn and Pause, 2007" was replaced by the original report of such information "Hoofnagle et al., 1997". The two sentences of references 8 and 9 "Irshad

and Peter, 2002; Fischer 2007" were deleted and replaced by the new information of vertical transmission with new references "Mack et al., 2012; Jara and Hierro, 2010". Reference 11 "Reddy et al., 2009" and its sentence were deleted. A new reference "Yee et al., 2006" was added for the last sentence in paragraph 3 of introduction. Reference 17 "Salmeron et al., 2008" was deleted and the sentence was referenced by Russo and Fried, 2004 which include the same information.

Comment 8

Introduction paragraph 2: Blood transfusion is NOT “the principal route of transmission in children”. The paper you quote describes a highly selected group of children in a resource poor setting. Please refer to a more general review article on hepatitis C infection in children. Table 3 also contradicts your statement. It’s certainly important, but it’s not the principal route.

Answer 8

We agree with the reviewer. The information in paragraph 2 was modified indicating vertical transmission as the most common route for HCV infection in infants and children. The references for such information were added, "Mack et al., 2012; Jara and Hierro, 2010".

Comment 9

Introduction paragraph 2: Perinatal transmission is important for this paper, can you elaborate? See PMID: 19382251

Answer 9

Perinatal transmission was elaborated in introduction section, paragraph 2 as reported in Shebl et al., 2009 and Mack et al., 2012.

Comment 10

Introduction paragraph 3: The first sentence should be the last sentence of paragraph 2.

Answer 10

The sentence was moved as instructed

Comment 11

Introduction paragraph 3: The rest of the paragraph is difficult to read.

Answer 11

Last sentence of paragraph 3 was deleted. The paragraph reference was changed to be Yee et al., 2006.

Comment 12

Introduction paragraph 3: The last sentence, why choose reference 11 and not a standard paper or a paper that described all definitions, EVR, RVR, SVR, non-SVR, breakthrough, relapse, etc?

Answer 12

The sentence of SVR was deleted as the information was included in methodology section.

Comment 13

Introduction paragraph 5: Can you be more specific and lead us to pediatric hepatitis C?

Answer 13

In this paragraph, we aimed to justify the treatment customization which is one of the major targets in our study. To our knowledge this has not been previously attempted in children.

Comment 14

Introduction paragraph 6: Can you reference the registration trials?

Answer 14

There are three clinical trials (NLM Identifier: NCT01896609, NCT01276756 and NCT01649245) which are still ongoing. We cited only NCT01276756 which showed interim results (reference 22).

Shehab HM. Efficacy of Nitazoxanide in the Treatment of Chronic Hepatitis C Virus (HCV) Sponsors and Collaborators. In: ClinicalTrials.gov [Internet]. Egyptian Railway Hospital; Cairo University (EGY). [cited 2013 Dec 27]. Available from: <http://clinicaltrials.gov/show/NCT01276756> NLM Identifier: NCT01276756.

Comment 15

Introduction paragraph 7: Redundant. Please remove.

Answer 15

Removed as instructed

Comment 16

Materials and Methods: Please remove all numbers of patients from materials and methods. How many patients were enrolled, treated in which arm, and came from which centers should be regarded as results and describe in the results section. Here please describe your materials and methods but no numbers.

Answer 16

Numbers removed as instructed and described later in results section.

Comment 17

Materials and Methods paragraph 5 & 6: Group I and group II. I don't understand how you grouped your patients and treated them. How can you group patients who are HCV-RNA negative at week 12 and patients with a < 1 log decrease in HCV-RNA in 1 group? Please describe this in a logical sequential order.

Answer 17

Our plan was to give the 5-day interval injection only to patients who showed partial response of treatment at week 12 (> 1 log and < 2 log decrease in viremia, and not to those who had an EVR nor who failed to show any response (< 1 log decrease in viremia) assuming that a shorter duration between injections might help partial responders to achieve complete response.

Comment 18

Materials and Methods paragraph 7: The last sentence is redundant. You also describe the laboratory investigations in paragraph 8.

Answer 18

The last sentence was deleted and the information was included in 1st paragraph of laboratory investigations.

Comment 19

Materials and Methods paragraph 9: Please divide into two paragraphs. If you use the definitions from reference 21 you can omit reference 11 and substitute that with 21, see my earlier comment.

Answer 19

Paragraph 9 was divided into two paragraphs. The first titled "Dose modification regimen" and the second titled "Definitions of virological responses". Reference 11 and its sentence were omitted from introduction section, paragraph 3.

4 References and typesetting were corrected

5 Figures are supplied as editable PowerPoint slide (Fig. 1) and excel (Fig. 2)

We appreciate the careful review and would like to thank the reviewers for their comments and suggestions that were helpful in revising the manuscript. We believe that the manuscript has significantly improved with the changes made. We hope that our manuscript is now suitable for publication in the *World Journal of Gastroenterology*.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in blue ink, appearing to read 'Sira', is shown on a light blue background.

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