

Format for ANSWERING REVIEWERS



December 19, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 13381-edited.doc).

Title: Natural interferon-beta treatment for patients with chronic hepatitis C in Japan

Author: Sasaki Reina, Tatsuo Kanda, Shingo Nakamoto, Yuki Haga, Masato Nakamura, Shin Yasui, Xia Jiang, Shuang Wu, Makoto Arai, Osamu Yokosuka

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 13381

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

1 Format has been updated

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

(1) The comment from reviewer 02841615

Response to your comment: Thank you for your encouraging comments.

(2) The comment from reviewer 00751081

1. Response to your comment "The authors should include the term "in Japan" in the title of the paper and of Table 1.": Thank you for your valuable comments. We revised title and Table 1 accordingly.

2. Response to your comment "This paper should be carefully edited for proper English grammar.": Thank you for your valuable comments. We asked a native English-speaker to check our manuscript again.

(3) The comment from reviewer 02860712

Response to your comment: Thank you for your valuable suggestions. We agree with you. According to your suggestions, we revised our manuscript as follows.

In page 6, lines 2-3,

.....These studies suggested that natural interferon-beta is a therapeutic option for patients with acute hepatitis C, instead of peginterferon-alpha^[31], although there was a contrary opinion^[32].....

In page 10, lines 5-7,

.....platelet counts. But none of the studies regarding patients with chronic HCV related hepatitis are prospective controlled trials.

In page 6, line 5 from the bottom-page 7, line 1,

.....group but not in the peginterferon-plus-ribavirin group (Table 1). Among the 11 with HCV G1, 7 were re-treated patients, and in 4 of 7 a transient virological response had been observed during the first cycle^[37]. By the end of the second cycle of therapy, a sustained virological response was observed in 3 cases. The study of Arase et al.^[38] is retrospective, and the 40 patients treated with natural interferon-beta were recruited over a period ranging from December 2004 to May 2008. They^[38] reported that treatment.....

In page 9, lines 1-9,

.....ribavirin (Table 1), although this recent study is also a retrospective, non-randomized trial. Among 66 recruited to treatment with natural interferon-beta and ribavirin, 15 were side effect-related treatment discontinuation, 36 patients were available for final analysis according to these figures, and 15 additional patients were lost during the study^[48]. However, they observed in the group of patients treated with peginterferon-alpha plus ribavirin, the rates of patients who discontinued the treatment for adverse effects is 66% (42/66). Thus, this study in elderly patients exceeds the corresponding rate of withdrawals reported in previous studies^[14].....

(4) The comment from reviewer 02860871

Response to your comment 1 "The author would better discuss more about recent chronic hepatitis C treatment and interferon therapy to have a broader insight of what is happening there.": Thank you for your valuable suggestions. We agree with you. According to your suggestions, we revised our manuscript as follows.

In page 11, lines 2-7,

During the preparation of this manuscript, in Japan, since September 2014, interferon-free regimen with daclatasvir plus asunaprevir for 24 weeks has been available for treatment of HCV genotype 1 patients who were ineligible, intolerant, or had not responded to prior interferon-based therapy^[63]. In the near future, we might be using all-oral DAAs and interferon-free regimens for the treatment of all HCV-infected patients^[15].

Response to your comment 2 "Author should discuss the difference between the natural interferon beta and the artificial one.": Thank you for your valuable suggestions. We agree with you. According to your suggestions, we revised our manuscript as follows.

In page 10, line 9 from the bottom-line 1 from the bottom,

RECOMBINANT INTERFERON-BETA

Natural human interferon-beta is produced by human fibroblasts, and is currently available in Japan. Recombinant human interferon-beta-1a and interferon-beta-1b are produced in mammalian cells or *E. coli*, respectively^[57]. It was reported that recombinant human interferon-beta-1a with or without ribavirin has an excellent safety profile, and after 24-week-treatment of recombinant human interferon-beta-1a with or without ribavirin, SVR was 21.6% and 27.4% in HCV genotype 1 and genotype 2 patients, respectively^[57-60]. Peginterferon-beta-1a may be beneficial for patients infected with HCV^[61,62].

Response to your comment 3 "Since chronic HCV might causes HCC and it is still controversy whether beta interferon therapy can improve the prognosis for HCC (Am J Clin Oncol. 1995 Aug;18(4):287-92), author should also provide discussion in separate sub titles about the natural interferon beta and its risk for HCC": Thank you for your valuable suggestions. We agree with you. We revised our manuscript accordingly.

Response to your comment 4 “Response to your comment 3 “Since chronic HCV might causes HCC and it is still controversy whether beta interferon therapy can improve the prognosis for HCC (Am J Clin Oncol. 1995 Aug;18(4):287-92), author should also provide discussion in separate sub titles about the natural interferon beta and its risk for HCC”: Thank you for your valuable suggestions. We agree with you. We revised our manuscript accordingly.

Response to your minor comment a) “When mentioning natural interferon beta, authors often mentioned only interferon beta. It should be clearly stated whether the interferon beta is natural or not, for instance by mentioning its abbreviation (N-IFN- β or natural IFN- β).”: Thank you for your valuable suggestions. We agree with you. We revised our manuscript accordingly.

Response to your minor comment b) “The arrangement for subtitles is a bit messy. The author might use sub titles or sub sub-titles if needed”: Thank you for your valuable suggestions. We agree with you. We revised our manuscript accordingly.

Response to your minor comment c) “In page 5, some sentences are written in different font. Rephrase sentences from other literature and not just copy and paste.”: Thank you for your valuable suggestions. We agree with you. We revised our manuscript accordingly.

Response to your minor comment d) “In page 9, author should first mention the reasonable of the study and not jump to the figure explanation”: Thank you for your valuable suggestions. We agree with you. We revised our manuscript accordingly.

(5) The comment from reviewer 02942455

Response to your specific comment 1 “In abstract and throughout the article, interferon is followed by a symbol and it is not clear what this is! I presume it is interferon beta?”: Thank you for your valuable suggestions. We agree with you. We revised our manuscript accordingly.

Response to your specific comment 2 “We should always have additional treatments for HCV” (page 4, 2nd paragraph- change this sentence, perhaps outlining why alternatives are required.”: Thank you for your valuable suggestions. We agree with you. We revised our manuscript accordingly.

Response to your specific comment 3 “Age of diagnosis of HCC would not necessarily be increasing just because the age of the population is increasing- this needs refining and explanation as to why the age of HCC diagnosis is increasing.”: Thank you for your valuable suggestions. We agree with you. We revised our manuscript accordingly.

Response to your specific comment 4 “Page 5- change "becoming chronic" to "developing chronic infection"”: Thank you for your valuable suggestions. We agree with you. We revised our manuscript accordingly.

Response to your specific comment 5 “Under the "Natural interferon for difficult to treat patients"- perhaps elaborate on the findings of the Montalto et al paper. have there been any direct comparisons between peg IFN and natural interferon? highlight perhaps the differences in side effects more clearly.”: Thank you for your valuable suggestions. We agree with you. We revised our manuscript accordingly.

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

Sincerely yours,

A handwritten signature in black ink that reads "Tatsuo Kanda". The signature is written in a cursive, slightly slanted style.

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