

Format for ANSWERING REVIEWERS

January 21, 2014

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 6961-Review.doc).

Title: Meta-analysis of interferon-associated retinopathy risk in diabetic and hypertensive hepatitis C patients

Author: Jihua Xue, Haihong Zhu, Jing Wang, Zhi Chen

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 6961

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

Reviewer #1:

1) Authors did not mention in the methodology section if they needed to contact other authors for queries regarding insufficient data.

Response:

Whenever possible, we contacted the authors to inquire about insufficient data. And this information has been mentioned in the methodology section in the revised manuscript (Page 5, Line 140-141).

2) L176-178: Three [11, 18, 19], one [22], two [20, 21], one [25] and one [18] studies (study) were conducted in Japan, Egypt, USA, Canada and France, respectively. According to table 1: study [18] is a Korean one.

Response:

We realized the problem mentioned by the reviewer, and it has been corrected in the revised manuscript (Page 6, Line 176-178).

3) L180-182: Patients in one [19] study were followed for 24 weeks, while the patients of other studies [11, 18, 20-22, 24, 25] had a longer follow-up. Authors must mention how they calculated the duration of follow up either from start of IFN therapy or that of retinopathy.

Response:

We understand the reviewer's concern, and the duration of follow up was calculated from the start of IFN therapy (Page 5, Line 139-140).

4) L193, L216: Can the authors add the total number of cases in all studies used regarding HTN and

IAR and DM and IAR?

Response:

As suggested by the reviewer, the total number of cases in all studies used regarding HTN and IAR and DM and IAR has been added in the revised manuscript (Page 6-7, Line 199-201; Page 7, Line 224-226).

5) L332: Remove the initials in: Takase B et al [34] and Nagaoka T et al [26] reported that flow-mediated vasodilation.

Response:

In the revised manuscript, we re-wrote the section about the mechanisms of interferon-associated retinopathy (Page 10-11, Line 334-350) and the problem mentioned by the reviewer has been corrected throughout the manuscript.

6) Tables L: 570 the No. of cases/ controls. Mention if they are HCV or retinopathy cases and if HCV negative or retinopathy negative controls.

Response:

It has been mentioned in the revised manuscript according to the reviewer's suggestion (Page 23, Table 1).

Reviewer #2:

1) Numerous English language mistakes are included throughout the manuscript. This point impacts on the clarity and quality of the manuscript. In order to make the manuscript intelligible, it should be revised extensively.

Response:

We revised the manuscript extensively according to the suggestions of the reviewer.

2) The abbreviations used throughout the text need to be clarified previous to be used, otherwise it is confussed.

Response:

We realized the problem mentioned by the reviewer and it has been clarified in the revised manuscript.

3) In all cases, the authors referred as "incidence" of retinopathy. They should explain whether they discarded preexisting retinopathy at baseline.

Response:

We discarded preexisting retinopathy at baseline (Page 5, Line 140).

4) Please explain the rationale to analyze differences between different interferon-alpha as well as against peg-interferon.

Response:

Because a study of d'Alteroche et al. reported that peg-interferon was a risk factor for interferon-associated retinopathy. And we also want to exclude the influence of different types of IFN used in each study on the incidence of IAR in patients concurrent with HTN or DM.

5) The authors should check the number of references because there are several numbers that did not

correlate with the citation on text.

Response:

We realized the problem mentioned by the reviewer. And following the reviewer's suggestion, we checked the number of references throughout the text in the revised manuscript.

6) The authors should clarify the methodology to estimate the time of follow-up: have they considered the retinopathy diagnosis or, alternatively the HCV-therapy commencement?

Response:

We agree with the reviewer. Based on the reviewer's suggestion, the methodology has been clarified in the revised manuscript. The time of follow-up was calculated from the commencement of HCV-therapy (Page 5, Line 139-140).

7) The authors mentioned that "...Patients in one study were followed for 24 weeks, while the patients of other studies had a longer follow-up (line 180)". Please define the mean time (\pm SD) among these cited studies.

Response:

According to the reviewer's suggestion, the mean time (\pm SD) has been defined in the revised manuscript. The mean follow-up time is 46.50 ± 13.51 wk (Page 6, Line 181-182).

8) During the study design the authors should include the controls considered among different studies. Were included HCV chronic infected patients without retinopathy included? What about patients with retinopathy without HCV infection?

Response:

In our meta-analysis, we included studies with controls who were chronic hepatitis C patients without diabetes mellitus and/or hypertension. And chronic hepatitis C patients without retinopathy were used to calculate the incidence of retinopathy.

Patients with chronic hepatitis C who were not having interferon therapy were also mentioned for the purpose of clarifying the effect of IFN on the development of retinopathy in the revised manuscript (Page 9, Line 270-272). The results of three studies showed that no retinal lesion was detected in any sample from the IFN-untreated controls. Therefore, it is more acceptable that IFN treatment does induce retinopathy in patients with chronic hepatitis C.

However, all the studies included in our meta-analysis had not include patients with retinopathy without HCV infection as control.

Reviewer #3:

1) This is a systematic review with meta-analysis dealing with interferon-associated retinopathy (IAR). The authors studied with firm methodology, and the results are reliable. However, the most primitive matter is that IAR is basically benign and its clinical significance is not so big.

Response:

Although IAR is basically benign, in some case reports cotton-wool spots (indicating a precapillary arteriolar occlusion) were symptomatic or associated with other symptomatic ischemic signs of retinopathy such as papilledema, retinal artery occlusion and retinal vein thrombosis, and were sometimes responsible for a definitive decrease in visual acuity. Moreover, Dropping out of IFN treatment was reported in patients with retinopathy in all the included studies (Page 9, Line 276-280).

2) The authors emphasize roles of hypertension (HT) and diabetes mellitus (DM) in the development of IAR. HT and DM themselves can be etiologies of retinopathy. I wonder whether interferon is truly harmful (whether interferon is an additional etiology of retinopathy) in HT or DM patients. To clarify a contribution of interferon to the development of retinopathy, a comparison with HT/DM patients who have not received interferon therapy is necessary.

Response:

We understand the reviewer's concern. But a meta-analysis can not be done due to the fact that only one study included patients with DM and/or HT without chronic hepatitis C as a comparison group. The study demonstrated that no retinal lesion was detected in patients with DM and/or HT without chronic hepatitis C. Moreover, Three studies reported that no retinal lesion was detected in any sample from patients with chronic hepatitis C who were not having interferon therapy and only patients receiving interferon suffered from retinal lesions. All these results demonstrated the effect of interferon on the development of retinopathy (Page 9, Line 270-272).

Reviewer #4:

1) Though a very good study, inclusion of some more sample papers on the subject would improve the data.

Response:

We understand the reviewer's concern. However, of the 568 references identified, only 8 studies finally met our inclusion criteria.

2) Please be consistent in defining the abbreviations and the expanded form. Define them at first place, and then use the abbreviations later.

Response:

We realized the problem mentioned by the reviewer. The abbreviations has been clearly defined in the revised manuscript.

3) Please rephrase the long sentences in to small ones to avoid ambiguity.

Response:

According to the reviewer's suggestion, the long sentences has been rephrased into small ones to avoid ambiguity in the revised manuscript.

4) Please mind the mixing of past and present tenses in a sentence.

Response:

Based on the reviewer's suggestion, we carefully conducted editing of the manuscript and corrected the improper use of English in the revised manuscript.

5) Be consistent in citing authors (references) in the text. For example 'Xue et. al.' not 'Xue J et al'.

Response:

Based on the reviewer's suggestion, it was changed accordingly in the revised manuscript.

6) There should be spaces between paragraphs of the 'Discussion' section.

Response:

Spaces between paragraphs of the 'Discussion' section has been kept in the revised manuscript.

Reviewer #5:

1) The prevalent HCV genotype are different in different countries. In addition, patients with different HCV genotype may receive different duration of antiviral therapy. The authors should do the meta-analysis by stratifying various HCV genotypes. Following this issue, it will be interesting to assess whether HCV genotype may have impacts on the IFN-associated retinopathy.

Response:

According to the reviewer's suggestion, the effects of HCV genotypes on the IAR have been assessed in the revised manuscript (Page 8, Line 234-240).

2) The diabetes and hypertension are chronic diseases. Patients with these diseases should take medicines regularly to control for their blood sugar and blood pressures. Thus the compliance of taking DM or hypertensive medicines was a major concern for assessing the risk of retinopathy. Although it was a meta-analysis, the information might not be available in all the papers the authors selected, it should be discussed.

Response:

Based on the reviewer's suggestion, the effect of compliance of taking DM or HTN medicines on IAR was discussed in the revised manuscript (Page 12, Line 370-374).

3) In table one, the time of follow-up in the eight studies were different. Did it reflect the treatment regimen was various in different studies? Will the various treatment duration be associated with the incident of retinopathy?

Response:

Based on the reviewer's comment, the effects of treatment duration on the incidence of retinopathy have been assessed in the revised manuscript (Page 7, Line 217-220).

Reviewer #6:

1) The title is Meta-analysis of risk of interferon-associated retinopathy in diabetic and hypertensive hepatitis C patients. The authors should discuss more details to the mechanisms between HTN and IAR, although the authors provided some data with the impaired vascular function in the retinal microcirculation.

Response:

The mechanisms between HTN and IAR have been discussed in depth in the revised manuscript (Page 11, Line 352-361).

2) Do you have discussions for different antihypertensive drugs between HTN and IAR?

Response:

We have discussed different antihypertensive drugs between HTN and IAR (Page 12, Line 370-374).

3) There is minor language polishing.

Response:

The language has been polished in the revised manuscript.

3 References and typesetting were corrected

Thank you again for publishing our manuscript 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 black ink, reading "Chen Zhi". The signature is written in a cursive, flowing style. The first name "Chen" is written with a large, sweeping 'C' that loops around the 'h'. The second name "Zhi" is written with a 'Z' that has a long horizontal stroke extending to the right, followed by a 'h' and a 'i'.

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