Format for ANSWERING REVIEWERS

May 7 , 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 9511- revised review.doc).

Title: VERTICAL HEPATITIS C VIRUS TRANSMISSION: MAIN QUESTIONS AND ANSWERS

Author: Grazia Tosone, Alberto Enrico Maraolo, Silvia Mascolo, Giulia Palmiero, Orsola Tambaro, and Raffaele Orlando

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 9511

As requested, the manuscript has been revised and edited by a professional author's editor who is a member of the European Association of Science Editors and of the Council of Science Editors, and whose first language is English . Enclosed is the Editor'certificate.

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

Reply to reviewer 02539433 :

Thanks for your criticisms. The language has been seriously revised by an professional English language editing company and also the grammar mistakes have been corrected.

Item-by-item reply

I believe that you could go in more depth into the immune responses involved in the process. Given the crucial role of NK cells in acute HCV infection..... it is important to describe their role in maternal HCV infection

We agree with your suggestion and we added text (Section HCV infection and pregnancy: reciprocal effects) the following sentence :

"Also the innate immune system, through natural killer (NK) cells, plays a role in modulating immune response to the virus. This process involves the interaction between the inhibitory NK cell receptor KIR2DL3, which belongs to the family of cell immunoglobulin-like receptors (KIR), and its human leukocyte antigen C group1 (HLA-C1), which is an inhibitory receptor for self-MHC class I ligand. The effector functions of NK cells occur only when activating signals overcome inhibitory signals. Therefore, individuals with two copies of HLA-C1 alleles (HLA-C1C1) and homozygous for KIR2DL3 (which binds HLA-C1 with less affinity than do other inhibitory receptors) tend to resolve HCV infection. In these subjects the weaker inhibitory receptor-ligand interaction, is easily overridden by activating signals and results in a stronger activity of NK cells. This effect was demonstrated in Caucasians and African Americans with expected low

infectious doses of HCV but not in those with high-dose exposure, in whom the innate immune response is likely overwhelmed[24]. "

It would help if you give a brief description of the course of acute and chronic hepatitis outside pregnancy in the introduction.

We have in the introduction the following sentences:

"Acute HCV infection, which is asymptomatic in 50% to 90% of cases, can progress to chronic hepatitis in more than half the patients and can be associated with variable rates of fibrosis progression [1,3]. About 10% to 20% of patients with chronic C hepatitis develop cirrhosis 20–30 years after contracting the infection. Patients with liver cirrhosis have a risk of about 1% to 5% of developing HCC[1,3]."

I think it would be clearer for the reader if question 1 and 2 was addressed separately

We now discuss the 2 questions separately.

Answering question 1, can also include the association with maternal ALT levels and HCV specific immune response.

We agree and added in the text (Section: Question 1) the following sentence:

" *Indeed, expansion of CD4+ CD25+ Treg cells begins early in gestation and reaches a peak in the second trimester. CD4+CD25+ T regulatory cells may affect the clinical presentations of chronic HCV infection by suppressing CD4+ T cell responses. Le Campion et al. [22] and Bolacchi et al. [30] reported that the HCV-specific TGF-β response induced by CD4+ CD25+(high) T cells was significantly greater in patients with a normal ALT level than in patients with abnormal ALT levels.*""

In page 9, the footnote regarding.....The same applies for the other footnotes.

Given the length of the review, we would prefer to retain these data as footnotes (as in other papers published in the WJH). However, should you and the editor prefer, we will discuss these data in the text.

For your consideration you can take a look in the following papers...

Done

Reply to reviewer 00051373:

Thanks for your comments

Reply to reviewer 00012386:

Thanks for your helpful comments

Item-by-item reply

1 The abstract has been added to the text
2 Introduction section page 2 , line 8 **done**
3 Introduction section page 2 , line 24: **done**
4 "HCV-RNA" should read "HCV RNA" troughout the text : **done**
5 Page 4, line 29: " **done**
6 Page 6, line 8: **done**
7 Page 6, lines 16-17: **done**
8 We have uniformed "interleukin 28B polymorphism , polymorphism of IL28B" into "**IL28B genotype"**
9 Page 9, line 7: **done**
10 We now discuss the paper by Tsunoda and have added the reference:

"*PEG IFN-a-2a has an inhibitory effect*[1] *on children's growth. A study of 31 Japanese children showed that the Z-scores of height and body weight decreased during treatment and, although they improved after withdrawal, they were significantly lower than pre-treatment scores. This growth inhibitory effect was smaller in children aged 10 years and older*[116] ."

11 We have added in the text the following sentences:
In fact a cohort study of 1,787 mother-child pairs showed that the rate of vertical HCV transmission was 6.2% and was not influenced by caesarean section [66]. *The failed protective effects of cesarean delivery was confirmed in a meta-analysis study*[72].

Reply to reviewer 01221188:

Thanks for your helpful comments

Item-by-item reply

Page 6, "UI/ml" read **"IU/ml"**

Reply to reviewer 00058438

Thanks for your criticisms.

The language has been revised and edited by an experienced professional author's editor who is a longstanding member of the European Council of Science Editors (EASE) whose first language is English

Item-by-item reply

Major concern

We are aware that the issue of HCV vertical has been widely reviewed in several SCI journals, also including the excellent review by Floreani et al (that has been widely cited in the present manuscript). However, to our knowledge, none has provided an all-round view of the topic , namely the main clinical and prognostic aspects of HCV infection in pregnant women, the impact on delivery outcome, the clinical and prognostic aspects of intrauterine/perinatal HCV infection in the offspring, and an overview of available antiviral drugs, including data on animal model, and side effects and contraindications that limit their use in this setting.

Minor concern

1. We have scanned the text for redundant non-essential statements and have deleted or edited these out.
2. We do not think that additional tables could be useful for the readers
3. All the grammar mistakes have been corrected.

[1] The mechanism remains still poorly understood.; it could be due to the changes of cytokines or hormone production caused by PEG IFN and/or to the loss of caloric intake caused by gastrointestinal adverse events due to PEG IFN. Both these hypothesis lack clinical supports [116]

3 References and typesetting were corrected

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

Sincerely yours,

Grazia Tosone, MD,

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