

Format for ANSWERING REVIEWERS

July 12, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format (ESPS Manuscript NO: 19950).

Title: Alcoholic hepatitis: The pivotal role of Kupffer cells

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Name of Journal: *World Journal of Gastrointestinal Pathophysiology*

ESPS Manuscript NO: 19950

Reviewer 1:

This is a nice review about the role of Kupffer cells in the pathogenesis of alcoholic hepatitis. However some points need to correct

1. Repetitions in the paper

Reorganized mechanism/future research sections to minimize repetition

2. Pathogenesis may be defined more comprehensively

Expanded the sections "Activation of Immune Response in Alcoholic Hepatitis" and "Importance of Kupffer Cells in Alcoholic Hepatitis" to include a more detailed discussion of pathogenesis and Kupffer cell function

3. Treatment may be defined more clearly

Included more detail in the "Current Treatment of Alcoholic Hepatitis" section, including current guidelines, and a discussion on liver transplant

4. Grammatical/typographic errors

Corrected

Reviewer 2:

Authors review the role of Kupffer cells in the pathogenesis of alcoholic hepatitis. This topic has been thoroughly and repeatedly addressed in the past and therefore the ultimate reason to write such review is to provide a comprehensive update with recent advances. This goal is only partially met by this work. To be fair, there has been disappointingly little progress in this field.

1. Old references

Included several recent papers, see following replies to the comments.

2. Alcohol effects on gut microbiota are mentioned only in a cursory manner

We provided a detail discussion on gut microbiota in the “Activation of Immune Response in Alcoholic Hepatitis” section

3. There is no mention of the role of recruited macrophages in the process —

Discussed at the end of the “Importance of Kupffer Cells in Alcoholic Hepatitis” section

4. Little if any is written about how Kupffer cells may play a role if co-morbidities (hepC and NAFLD) are present, which is often the case

Discussed at the end of “Importance of Kupffer Cells in Alcoholic Hepatitis” section

5. Genetic/epigenetic factors

Included in the “Future Areas of Research” section

6. The results of STOPAH trial described with more detail

Further detail about the STOPAH trial was included in the “Current Treatment of Alcoholic Hepatitis” section

- 7. It is clear that anti-TNF therapy for AH has miserably failed - one would not perhaps discuss this issue under 'Future Areas of Research'**

Reworded this portion to clearly convey that anti-TNF therapy is a failure and that perhaps it is time to move forward with a new direction on augmenting the anti-inflammatory pathway

- 8. Mention the current debate about transplantation in AH in the chapter on therapy**

Included in the “Current Treatment of Alcoholic Hepatitis” section

- 9. Leukocytapheresis as an experimental treatment option (Kamamura Dig Dis Sci 2004;59:482)**

Included in the “Future Areas of Research” section

- 10. Grammatical/typographic errors**

Corrected

- 11. The Theodossi (1982) study - which table does this belong to?**

Belongs to table 1. There is only one table. Formatting error on print

Reviewer 3:

This is a good review on the role of Kupffer cells in the pathogenesis of alcoholic hepatitis that could be improved in the following aspects.

- 1. The pathogenesis should be better reported.**

Expanded the sections “Activation of Immune Response in Alcoholic Hepatitis” and “Importance of Kupffer Cells in Alcoholic Hepatitis” to include a more detailed discussion of pathogenesis and the Kupffer cell function as well as that of recruited macrophages

- 2. The influence of altered gut microbiota on the liver could be more extensively explain.**

Further detail on gut microbiota was extensively discussed in the section of
“Activation of Immune Response in Alcoholic Hepatitis”

- 3. In the same way, concomitant metabolic factors should at least be mentioned.**

Discussed the role of Kupffer cells in NASH in the section of “Importance of
Kupffer Cells in Alcoholic Hepatitis”

- 4. The paragraph “Future areas of Researches” is rather confused: it should be written more clearly avoiding repetitions.**

Reorganized to make it clearer

- 5. Abbreviations need to be explained when used for the first time (see ALD in the last page). There are some grammar errors and typos.**

All addressed and corrected

Editor:

See below for list of comments addressed

1. Changes to manuscript are highlighted
2. Conflict of interest statement signed
3. Audio core tip provided
4. Running title provided
5. Reformatted author names and affiliations
6. Author contributions added
7. Conflict of interest statement included
8. Correspondence author information added
9. Key words added
10. Core tip added
11. Headings formatted

12. In-text citations formatted
13. Table formatted
14. Image formatted in PowerPoint
15. Added PMDI and DOI to citations