

ANSWERING REVIEWERS



April 25, 2015

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 17785-edited.doc).

Title: Cross talk of the immune system in adipose tissue and the liver in Non-Alcoholic Steatohepatitis: pathology and beyond

Author: Luisa Vonghia, Sven Francque

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 17785

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

1 Format has been updated.

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

Reviewer n 2861012

1. Page 3: Here we report the results of Henning *et al.* (Hepatology 2013), who found no difference in the total number of T lymphocytes (CD3+ leucocytes) but could demonstrate an alteration of the T lymphocytes subtypes (CD4+ and CD8+ cells among the CD3+ cells) in the NASH group. In the NASH group there was indeed an increase of the CD8+ cells, therefore the balance between these subsets of cells was altered. Further on in the text we report other data that describe NASH-induced variations within the other T lymphocytes subsets. In conclusion, although the total number of the lymphocytes does not appear to change in NASH, the differentiation of the subsets of T cells is altered in NASH. The text in the paper was modified.
2. Page 4: the sentence "although immunohistochemical evaluation...NASH patient with a more advanced disease" was rewritten, including a better explanation of the different stages of the disease. Furthermore, a further explanation of the data regarding dendritic cells (DC) and Tregs was added.
3. Page 5: the sentence "to mediate an allogenic T cell and antigen-restricted CD4+ T cell stimulation and a Treg down-regulation" was substituted with the sentence: "to mediate an allogenic T cell proliferation, an antigen-restricted CD4+ T cell stimulation and a Treg down-regulation".
4. Page 5: The sentence "Opposite to this findings...development of obesity" has been changed according to the reviewer's suggestions. The protective role of IL17 described in some experiments has been better explained.
5. Page 6: the sentence "Considering the B lymphocytes, they rapidly increase in serum and adipose tissue of mice fed a HFD and seem to be implicated in insulin resistance" has been adapted, resulting in the sentence "Considering the B lymphocytes, they rapidly increase in serum and

adipose tissue of mice fed a HFD and favour insulin resistance". This concept is further explicated in the following sentence.

6. VAP-1: a paragraph on VAP-1 (Weston *et al.*, J Clin Invest 2015) was added in the treatment perspectives section on page 10.

Reviewer n 2860814

1. This editorial article is not intended to review all the aspects of the pathogenesis of NASH. It was indeed focused on the immune system, and particularly on the role of the immune cells in NASH (we slightly changed the title to make this more clear). We agree, however, with the reviewer that adipokines play a key role in the onset of NASH and therefore we added a section on this topic. The drugs that are emerging in this field have been added in the treatment section.
2. A summarizing table has been added.
3. Page 3: Pioglitazone and Vitamin E are indeed considered as potential treatment options mentioned in the AASLD guidelines (Chalasani *et al.*, Hepatology 2012) as they have shown beneficial effects on NASH histology in RCT. These drugs, initially not developed for treatment of NASH, are not FDA or EMA approved for the treatment of NASH, so they are not licensed for the treatment of NASH and don't have treatment of NASH in their label. Therefore we stated that there is no approved treatment for NASH. Furthermore, there are some safety issues with these drugs, so they must be used with caution. We agree, however, with the reviewer that it is worthwhile mentioning them as potential pharmacological treatments for NASH. The text has been changed according to the reviewer suggestion

3 References and typesetting were corrected.

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

Sincerely yours,

Luisa Vonghia

A handwritten signature in black ink, appearing to be 'Luisa Vonghia', written over the printed name.