

ANSWERING REVIEWERS

February 20th, 2015.



Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 16713-review.doc). All modifications are highlighted.

Title: Peroxisome proliferator-activated receptors as targets to treat non-alcoholic fatty liver disease

Author: Vanessa Souza-Mello

Name of Journal: *World Journal of Hepatology*

ESPS Manuscript NO: 16713

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) Reviewed by **02860895** - The review article, written by Vanessa Souza-Mello, thoroughly covers the current perspectives of therapeutic implications of PPARs for NASH/NAFLD. I sincerely appreciate this perfect work. Congratulation! I'd like to ask the author to quote the below article to strengthen a crucial role of lipid peroxidation in the development and progression of NASH/NAFLD. Localization of oxidized phosphatidylcholine in nonalcoholic fatty liver disease: impact on disease progression. *Hepatology* 2006; 43: 506-514.

Answer: The reference suggested by the reviewer was added to the manuscript (page 5).

- (2) Reviewed by **02861019** - Dear Editor, I have read with great interest dr. Vanessa Souza-Mello manuscript entitled "Peroxisome proliferator-activated receptors as targets to treat nonalcoholic fatty liver disease". Although it is not completely innovative, I really appreciate the form and the style of this editorial. However, I suggest some minor revision to the author, in order to give more attractiveness to the paper: - I suggest to check the english language and stile; there are some refuses; - on the basis of the editorial title, I suggest to increase the manuscript section on the clinical application (in human) of PPAR-agonist in NAFLD-NASH setting; - I suggest to update the bibliographic references and include the published (and ongoing) clinical trial in this field.

Answer: I am grateful for the comments. English language was carefully revised. In order to

increase the section on the clinical application, some clinical trials that used rosiglitazone were added and discussed accordingly as well as the use of PPAR agonists in NAFLD-NASH was discussed in detail (page 8).

- (3) Reviewed by **02860874** - This article describes clearly the physiological mechanisms involved in NAFLD focusing on PPARs. The authors made a good review. Nowadays searching for potential therapeutic targets for treating NAFLD and NASH is necessary. As the authors described in this review article, PPARs represents attractive targets. However, currently some studies (clinical trials) have been conducted in patients with NAFLD/ NASH. These studies must be discussed by the authors: for example: The PIVENS trial by Sanyal AJ published in N Engl J Med in 2010. The FLIRT trial by Ratzliff V, published in Gastroenterology in 2008. Also the study by Ratzliff V (Long-term efficacy of rosiglitazone in nonalcoholic steatohepatitis: results of the fatty liver improvement by rosiglitazone therapy (FLIRT 2) extension trial. Published in J Hepatol in 2010.

Answer: I completely agree with the reviewer and thank for the opportunity to add these important references. The suggested trials were added to the text on page 8.

- (4) Reviewed by **02860875** - Thank you for asking me to review the manuscript by Souza-Mello, entitled 'Peroxisome proliferator activated receptors as targets to treat non- alcoholic fatty liver disease'. The author has described the epidemiological problem of NAFLD worldwide before describing the disturbances in PPAR protein expression in various disparate mouse models of NAFLD and obesity. There is a limited section towards the end of the article dealing with the therapeutic potential of agents intended to manipulate this pathway. I have the following comments: Major: 1. The written English is not good. The article needs to be re-drafted as there are a large number of grammatical errors. 2. The emphasis should be changed. There are a huge number of review articles, particularly within WJG / WJH (See PMID: 25232450; 24073298; 18176957) about the role that the PPAR receptors play in the pathogenesis of NAFLD. The author needs to decide whether to re-describe the metabolic derangements of NAFLD or concentrate on what drugs that modify these pathways could offer in the future to our patients. 3. The author has taken an entirely 'metabolic-centric' view of NAFLD despite the clear evidence that other pathways such as RAS / MAPK and NF- κ B / inflammation play. These could be drawn in whilst discussing the anti-inflammatory effects of PPAR α and γ agonists. 4. Whereas the title suggests PPAR as a treatment target for NAFLD, there is practically no discussion of the use of drugs to modulate this pathway in humans. There is a limited discussion of therapy in animal models, but nothing of the previous evidence generated for glitazones or fibrates in humans (see PMID: 24799988). This must be addressed.

Answer:

1. English was carefully revised.
2. I am grateful for this comment, which has certainly improved the quality of this editorial. As the invitation was for writing an editorial, I found it should be short. In fact, I opted for focusing on the benefits that PPAR agonists can bring by explaining the main endpoints and pathways related to their actions (pages 7-10).
3. Once again, I agree with the reviewer and added some evidences of the interplay between PPAR activation and RAS/MAPK and NF- κ B pathway to tackle inflammation (pages 9 and 10).
4. Some trials were added to discuss the relevance of PPAR agonist use in humans and more evidences from experimental studies were inserted to treatment section (pages 7-10).

4 I am sending in attach the certificate of proficiency in English from University of Cambridge in my name. It attests that my level of knowledge in English language is comparable to a native speaker.

Thank you once again for the opportunity to improve my manuscript.

Sincerely yours,

Vanessa Souza-Mello, RD, PhD

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