

## ANSWERING REVIEWERS

January 6, 2014

Dr. Jin-lei Wang  
Director, Editorial Office  
Baishideng Publishing Group Co., Limited



Dear Dr. Jin-Le Wang:

Thank you for your careful review and thoughtful criticisms of our manuscript #7510 entitled "Therapy for alcoholic liver disease" submitted to World Journal of Gastroenterology. We have thoroughly revised the manuscript in accord with the reviewers' criticisms as follows:

Reviewer 00001263

1. *In corticosteroids section the authors discussed the controversial reports on steroid therapy for AH. However, the mechanisms underlying corticosteroid for AH remain largely unknown. A recent study published in Hepatology has carefully examined the effects of prednisolone in liver injury and regeneration in several models including alcohol liver injury (Kwon et al. Opposing effects....in mice. Hepatology 2013 Oct 1 doi: 10.1002/hep26748). This study may give some new insight on the prednisolone treatment for AH.*

Page, 14, Bottom.

As suggested, we have added the following about this study:

Clinical application of corticosteroid therapy for AH is currently limited by insufficient data on its molecular therapeutic mechanisms. However, in a recent study of mice heavily exposed to alcohol for 10 days, administration of prednisolone, a corticosteroid, enhanced ethanol-induced liver injury and fibrosis compared to untreated controls<sup>[105]</sup>. This study further investigated potential mechanisms for the deleterious effects of prednisolone after hepatotoxic injury. In carbon tetrachloride-induced liver injury in mice models, prednisolone led to attenuation of macrophage and neutrophil functions that normally help clear apoptotic cells and resolve hepatic inflammation, and caused delayed hepatocyte regeneration by inhibiting expression of genes involved in hepatocyte proliferation and repair, such as pSTAT3<sup>[105]</sup>. These data may help modify and improve clinical management of corticosteroid therapy for AH.

Correspondingly, Kwon, et al. is added as reference 105.

2A. *In future directions, the authors should mention the recent NIAAA-supported alcoholic hepatitis consortia (there are four consortia), which will explain translational studies and clinical trials for AH. The consortia are discussed in the article: Singal et al. Alcoholic hepatitis: current challenges and future directions. Clin Gastroenterol Hepatol 2013 June 28, doi:pii: S1542-3563(13) 00872-0. 10.1016/j.cgh.2013.06.013.*

Future Directions, Pages 24-25.

As suggested, we have added the following paragraphs on promising therapies discussed by Singal et al.:

Increased intestinal permeability to gut-derived microorganisms appears to increase morbidity and mortality in AH<sup>[149]</sup>. Several multi-institutional consortia are developing therapies for AH based on preventing or neutralizing these effects of increased intestinal permeability. For example, lipopolysaccharide (LPS) antibody may help neutralize injury from lipopolysaccharide

from exposure to gut-derived microorganisms. One study will compare the effects of lipopolysaccharide (LPS) antibody in combination with corticosteroids versus corticosteroid monotherapy in patients with severe AH<sup>[149]</sup>. Other studies will examine the efficacy of probiotics versus placebo for moderately severe AH, or the effect of adding zinc, a mineral that improves gut barrier function, to other therapies for severe AH.

Another promising approach to AH therapy is targeting macrophage/Kupfer cell activation in AH which leads to increased interleukin (IL) 1 beta activation. A clinical trial is examining a combination of Anakinra, an interleukin 1 receptor antagonist, and traditional therapy versus traditional therapy alone for severe AH<sup>[150]</sup>. Another attractive approach is to inhibit caspases which are death induction molecules downstream to TNF-alpha activation during hepatotoxic injury. Emricasan, a pancaspase inhibitor, is proposed to be tested to block hepatocyte injury induced by TNF-beta, without blocking the beneficial hepatic effects of TNF-beta on liver regeneration and immune cell function<sup>[150]</sup>. Other novel potential therapies are in the process of development or undergoing preliminary clinical trials<sup>[14]</sup>.

2B. *In addition interleukin-22 is a promising drug under consideration for the treatment of AH, which should be discussed (Kong et al. Hepatoprotective and anti-fibrotic function of interleukin-22: therapeutic potential for the treatment of alcoholic liver disease. J Gastroenterol Hepatol. 2013 Aug;28 Suppl. 1:56-60. Doi: 10.1111/jgh 12032).*

Future Directions, Page 24, Middle.

As suggested, we have added the following paragraph regarding interleukin-22 therapy for alcoholic liver disease:

Interleukin-22 (IL-22) is a potential therapy for ALD<sup>[14]</sup>. IL-22 ameliorates hepatic steatosis and liver injury in animal models after acute or chronic-binge ethanol feeding<sup>[147]</sup>. It may promote hepatocyte proliferation or hepatic regeneration and inhibit hepatic fibrosis in response to alcohol-induced liver injury<sup>[147]</sup>. IL-22 theoretically appears to be relatively safe because only hepatocytes, epithelial cells, and a few other cell types have IL-22 receptors. IL-22, however, promotes proliferation of preexisting hepatomas, even though it does not initiate hepatoma formation<sup>[148]</sup>. It is therefore likely contraindicated in patients with ALD complicated by hepatoma and may have limited use in patients with alcoholic cirrhosis.

Correspondingly, two references have also been added to correspond with this added text: 146 & 147.

3. *In the introduction, the authors briefly discussed the pathogenesis of alcoholic liver disease. The authors should cite a recent review article (Gao and Bataller. Alcoholic liver disease: pathogenesis and new therapeutic targets. Gastroenterology. 2011 Nov; 141(5):1572-85).*

The article by Gao & Bataller is cited four times (as reference # 14) in the revised version as follows:

- A. Page 3, Bottom: Many alcoholic patients, however, do not develop clinically significant ALD<sup>[14]</sup>.
- B. Page 3, Bottom: Genetic and environmental factors are important, but the specific genes or environmental factors that predispose to ALD are poorly understood<sup>[14]</sup>.
- C. Page 24, Middle: Interleukin-22 (IL-22) is a potential therapy for ALD<sup>[14]</sup>.
- D. Page 25, Middle: Other novel potential therapies are in the process of development or undergoing preliminary clinical trials<sup>[14]</sup>.

Reviewer 02441679

*A high quality review article. But the portion of the SPECTRUM OF ALCOHOLIC LIVER DISEASE seems account for the relatively larger proportion. It would be better if it was shortened properly.*

As suggested, we have made numerous minor changes throughout the review article to improve the quality of the manuscript.

#### Editorial changes

1. Page 1, Title Page.

*Add statement regarding authors contributions.*

As required, we have added the following regarding author contributions:

**Author contributions:** Jaurigue MM performed the review of the literature and wrote about half of the manuscript. Cappell MS wrote about half of the manuscript and edited the manuscript.

2. *Please write a summary of less than 100 words to outline the most innovative and important arguments and core contents in your paper to attract readers.*

3. *Please reformat all the reference numbers like this (as illustrated).*

As required all the references have been reformatted in the requested standard format for the journal.

4. *Please provide the decomposable form of figures, whose parts are movable and can be edited. So please put the original picture as word or ppt or excel format so that I can edit them easily.*

As suggested, all the figures have been changed to a format in which the parts are movable and can be easily edited.

Thank you for your interest in this manuscript. Please note that we will gladly perform further revisions as necessary for publication in this prestigious journal.

Warm regards,

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