

Dear Dr. Ma and Reviewers:

Thank you for your letter and for the reviewers' comments regarding our manuscript entitled **"Inflammation, a novel target for current therapies of hepatic encephalopathy in liver cirrhosis"** (ESPS Manuscript No: 18335). The comments are all valuable and very helpful for revising and improving our manuscript, as well as the important guiding significance to our study. We have read the comments carefully and made several modifications that we hope meet with your approval. The revised portions are marked in red in the manuscript. The responses to the reviewers' comments and the main modifications to the manuscript are listed below:

RESPONSES TO COMMENTS OF REVIEWER #1:

1. Question:

Good review needs minor English editing and removing the repetition (same phrase in abstract, introduction and the body of the review)

Answer:

Thank you for this comment. Based on your valuable suggestion, we have consulted with *American Journal Experts*—a professional English editing company—to modify our manuscript and enhance the language quality. Furthermore, we have revised the repeated portions in the abstract, introduction, and the body of the review.

RESPONSES TO COMMENTS OF REVIEWER #2:

1. Question:

Authors provide very solid review of the inflammation, as potential novel target for current therapies of hepatic encephalopathy in liver cirrhosis. Their application is clear because significant association was found between progressive encephalopathy and infection in literature. It was well known that infected patients with progressive encephalopathy manifested more SIRS components than other infected patients. Although I have some concerns relating to suggestion authors to include few reference of older basic papers in this field of research by Ronaldo et al (Chemother 1992;30:215-220, HEPATOLOGY 1995;22(Supp 1):366A. HEPATOLOGY 1993;17:196-201) and Garcovich et al review paper-Prevention and treatment of hepatic encephalopathy: Focusing on gut microbiota. World J Gastroenterol 2012 December 14; 18(46): 6693-6700.

Answer:

Thank you for this valuable comment.

Studies by Ronaldo *et al* (Chemother 1992;30:215-220, Hepatology 1995;22(Supp 1):366A. Hepatology 1993;17:196-201) have focused on the therapeutic effects of selective parenteral and enteral antimicrobial regimens among patients with HE secondary to fulminant liver failure. However, in the current review, we aimed to discuss the clinical utility of anti-inflammatory agents that target the inflammatory pathogenesis of HE among patients with liver cirrhosis. Therefore, the results of these studies would not be appropriate for citation in this review. According to your valuable suggestion, the review by Garcovich *et al* (Garcovich M, Zocco MA, Roccarina D, Ponziani FR, Gasbarrini A. Prevention and treatment of hepatic encephalopathy: focusing on gut microbiota. *World J Gastroenterol* 2012;**18**:6693-6700) has been cited in the manuscript.

The following texts have been modified:

Cirrhotic patients are commonly found to have substantial disturbances of intestinal flora, with significant small intestinal bacterial overgrowth of potentially pathogenic Gram-negative bacteria including *Enterobacteriaceae*, *Alcaligenaceae* and *Streptococcaceae*^[16].

The following reference has been added to the manuscript:

[16] Garcovich M, Zocco MA, Roccarina D, Ponziani FR, Gasbarrini A. Prevention and treatment of hepatic encephalopathy: focusing on gut microbiota. *World J Gastroenterol* 2012;**18**:6693-6700 [PMID: 23239905 doi: 10.3748/wjg.v18.i46.6693]

RESPONSES TO COMMENTS OF REVIEWER #3:

1.Question:

General comments: *The review article idea is good and the content add new data. The presentation and readability of the review article is good. I think this review article is of good quality and deserve publication.*

Title: *is accurately reflects the major topic and contents of this review article.*

Abstract: *It gives a clear delineation of the content and the goal of this review article. It summarizes the inflammatory mechanisms involved in the pathogenesis of HE and evaluates the evidences of current therapies which target the inflammatory pathogenesis of HE in the clinical practice.*

The review article: *is well written give new idea on the pathogenesis of hepatic encephalopathy and new promising therapeutic approaches for cirrhotic patients with HE.*

Answer:

Thank you for this constructive comment.

We tried our best to improve the manuscript and made some modifications. We greatly appreciate your help and that of the reviewers regarding improvement to our manuscript. We hope that the revised manuscript is acceptable for publication.

With kind regards

Sincerely

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