

Format for ANSWERING REVIEWERS

June 1, 2015

Dear Editor,



Please find enclosed the edited manuscript in Word format (file name: 16265-Review.doc).

Title: Mesenchymal stem cell therapy for cirrhosis: present and future perspectives

Author: Young Woo Eom, Gaeun Kim and Soon Koo Baik

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 16265

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

1 Format has been corrected

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

Reviewer 3259001

MSCs are considered to be a potential therapeutic agent for the treatment of cirrhosis because of their potential to differentiate into hepatocytes, their immune-modulatory properties and their ability to secrete trophic factors. Nevertheless, several issues, including the fibrogenic potential of MSCs and their ability to promote pre-existing tumor cell growth, must be carefully considered. This editorial review deals with these issues. The work is interesting but it has considerable overlap with a paper appeared in WJG in this January. The message of the two papers are practically the same. Therefore the reviewer suggest to rewrite the paper, giving the credit of the previously written review, and emphasizing the additional concepts of the authors. Here is the referred paper: Berardis S, Dwisthi Sattwika P, Najimi M, Sokal EM. Use of mesenchymal stem cells to treat liver fibrosis: current situation and future prospects. World J Gastroenterol. 2015 Jan 21;21(3):742-58. doi: 10.3748/wjg.v21.i3.742. PubMed PMID: 25624709

We greatly appreciate this critical comment from the reviewer. Previously, Berardis et. al, wrote a review paper entitled "Use of mesenchymal stem cells to treat liver fibrosis: current situation and future prospects." This review provided comprehensive information on liver fibrosis, including physiopathology of liver fibrosis and current therapeutic approaches. In a section regarding

cell-based therapy, Berardis et. al summarized experimental data which showed that isolated hepatocytes, stem/progenitor cells, embryonic stem cells, induced pluripotent stem cells, and mesenchymal stem cells could be successfully used to treat liver fibrosis in preclinical and clinical trials. However, in our editorial, we focused on clinical studies using bone marrow-derived cells (i.e., BMCs, HSCs and MSCs) and put it in context of cell-based therapy for treatment of liver fibrosis. This editorial will be helpful in the understanding of the mechanisms of BMCs, HSCs and MSCs and their clinical application for the treatment of liver fibrosis. Therefore, we respectfully suggest that our editorial will supplement and expound upon one aspect of the Berardis review.

Reviewer 2527481

In this manuscript, the authors outlined the results of bone marrow cells (BMCs), hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) in treatments for cirrhosis. This review is in line with other recent published articles that suggested MSCs would be a potential therapeutic agent for the treatment of cirrhosis. Although authors cited some possible mechanism of these stem cells, further information about the therapeutic mechanism of BMCs, HSCs and MSC will be more attractive.

We greatly appreciate this critical comment and agree with the reviewer's comments. However, our manuscript is an Editorial not a comprehensive review paper. In our Editorial, we wanted to provide comments on an important topic in MSC therapy for cirrhosis; regarding its current research status and future directions that will promote development of this discipline. Currently, we are preparing a review paper that will elaborate on the therapeutic mechanisms of MSCs.

Reviewer 2438413

The authors have summarized some clinical studies using stem cells for the liver failure and cirrhosis. All clinical trials showed a beneficial therapeutic effect of Stem cells without adverse effect. This review was clear and well written. Major comments In this review, authors summarized trials and addressed some possible therapeutic mechanisms of BMCs, HSCs and MSCs. Recently, another review have been published concerned the clinical trials on the MSC transplantation in cirrhosis (Ma XR, Tang YL, Xuan M, Chang Z, Wang XY, Liang XH. Transplantation of autologous mesenchymal stem cells for end-stage liver cirrhosis: a meta-analysis based on seven controlled trials. Gastroenterol Res Pract. 2015;2015:908275). These authors have axed the beneficial therapeutic effect on the biochemical markers.

To stand out from this previous study, the authors could develop more the resulting mechanism aspect of these different stem cells transplantations.

We greatly appreciate this critical comment and agree with the reviewer's comments. However, our manuscript is an Editorial not a comprehensive review paper. In our Editorial, we wanted to provide comments on an important topic in MSC therapy for cirrhosis; regarding its current research status and future directions that will promote development of this discipline. Currently, we are preparing a review paper that will elaborate on the therapeutic mechanisms of MSCs.

Reviewer 3011757

In this editorial, the authors give a systematic overview about the current treatment options for patients with liver failure or liver cirrhosis using cell therapy. After a short introduction about studies using unsorted bone marrow cells (BMC) or hematopoietic stem cells (HSC) for treatment of liver disease, the use of mesenchymal stem cells (MSC) in clinical studies is stressed out. In this order, therapeutic mechanisms of BMSs, HSCs and especially MSCs for cirrhosis are discussed. The authors conclude, that MSCs should be considered as a potential therapeutic agent for treatment of liver cirrhosis. In summary, this work presents a very good overview about cell therapy in liver cirrhosis and I therefore do recommend to accept this article.

We greatly appreciate this comment from the reviewer.

Editor

(1) Three reviewers gave a language evaluation score of Grade B. To improve the English component of the manuscript, we outsourced this manuscript to a professional English language editing company (American Journal Experts). A certificate has been uploaded.

(2) As suggested by the reviewer, the conflict-of-interest statement was mentioned in the revised manuscript.

(3) According to reviewer comments, audio file (mp3 format) describing our Core Tip was up-loaded.

(4) According to reviewer comments, we provide the decomposable figure (ppt format) of Figure 1.

3 References and typesetting were corrected

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely yours,

A handwritten signature in black ink, appearing to read 'Soon Koo Baik', with a stylized, flowing script.

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