

September 3, 2014

Dear Editor,

Thank you for granting us the opportunity to revise our manuscript for publication in *World Journal of Gastroenterology*. The reviewer raised many concerns and pointed out many important points related to our study, and we thank them for their helpful comments. We have modified our manuscript as suggested and have attempted to address all of the concerns raised. Here, we submit the revised version with a point-by-point response to the reviewer's comments. Please find enclosed the edited manuscript in Word format (file name: 13237-review.doc).



Title: The negative impact of bone-marrow-derived mesenchymal stem cells on DSS-induced colitis

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Name of Journal: *World Journal of Gastroenterology*

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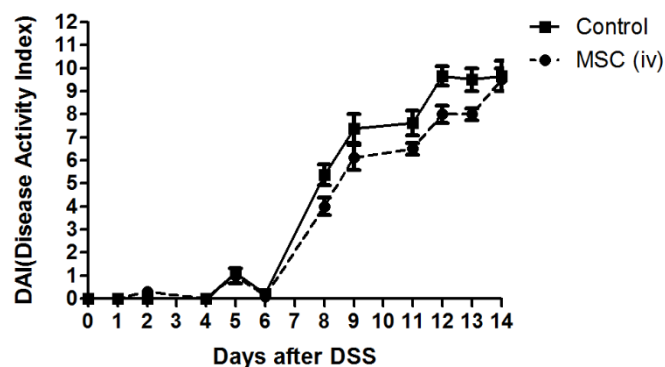
The manuscript has been improved according to the suggestions of reviewers:

1 Format has been updated

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

(1) Methodology is partly appropriate it is not clear why authors only studied ip administration but not intravenous therapy. This should be done and it would be interesting to study the outcomes in a Crohn animal model.

Response: Thank you for your comments. We chose the ip administration to facilitate direct effects of MSCs in inflamed colon. We had previously tested intravenous (iv) administration of MSCs in the DSS-induced colitis model; however, we observed similar results to ip administration. There was no clinical benefit of intravenously administered MSCs compared to untreated mice.

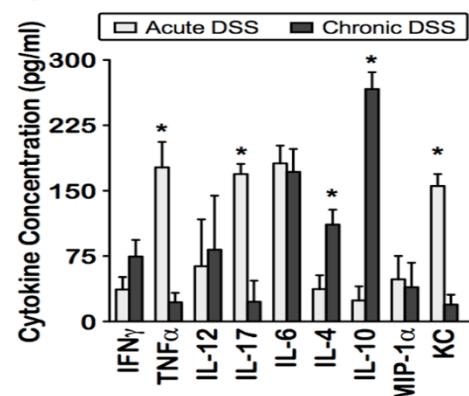


There is evidence from a previous study that ip injection of MSCs could be more efficient than iv injection in TNBS-induced colitis model (**Morgana T.L. Castelo-Branco**, Igor D.P. Soares, Daiana V. Lopes, Fernanda Buongusto, Cesonia A. Martinusso, Alyson do Rosario Jr., Serigio A.L. Souza, Bianca Gutfilen, Lea Mirian B. Fonseca, Celeste Elia, Kalil Madi, Alberto Schanaider, Maria Isabel D. Rossi, Heitor S.P. Souza. Intraperitoneal but not intravenous cryopreserved mesenchymal stromal cells home to the inflamed colon and ameliorate experimental colitis. *Plos one* 2012; 7(3): e33360 [PMID: 22432015]). Furthermore, many clinical studies have focused on the local administration of MSCs rather than systemic administration in IBD patients, as shown in table 2.

(2) In addition, this is an “acute colitis” model, and results may not be generalizable to other, e.g. chronic colitis models. Authors should consider repeating the experiments at least in another colitis model.

Response: We agree with these important points. Currently, there are no reports on MSC therapy in mouse chronic colitis model. According to a study which compares the cytokine profile between acute DSS-induced colitis model and chronic DSS-induced colitis model, the proinflammatory cytokine levels including TNF- α and IL-17 decreased and the levels of IL-4 and IL-10 increased significantly in chronic DSS-induced colitis model (**Philip Alex**, Nicholas C. Zachos, Thuan Nguyen, Liberty Gonzales, Tian E. Chen, Laurie S. Conklin, Michael Centola, Xuhang Li. Distinct cytokine patterns identified from multiplex profiles of murine DSS and TNBS-induced colitis. *Inflammatory bowel disease* 2009; 15(3): 341-352. [PMID: 18942757 DOI: 10.1002/ibd20753]). Due to different cytokine profiles, we believe that MSCs may function differently in chronic DSS-induced colitis compared to acute DSS-induced colitis model. In future studies we will investigate the effects of MSC therapy in a chronic colitis model.

Fig 3B



(3) Authors should add animal numbers for each assessment/Figures/subgroup.

Response: Thank you for your comments. We added animal numbers for each assessment and figure legends. Each group consisted of ten mice and two mice were sacrificed for assessment. Each assessment was performed in triplicates. Furthermore, results are representative of 3 repeated experiments.

(4) The paper is too long; results should be more focused and compact, delete duplicate information presented also as Figures, additionally, some figures should be also omitted.

Response: As you have pointed out, we revised to delete duplicate information presented in figure legends. We removed figure 1 and also omitted figure 2 c indicating body weight, because body weight is included in DAI score.

3 References and typesetting were corrected

4 The English in this document has been checked by at least two professional editors, both native speakers of English. For a certificate, please see:
<http://www.textcheck.com/certificate/HdHngS>

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

Sincerely yours,
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