November 11, 2014

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 14364-edited-reviewed.doc).

Title: Mesenchymal stem cells as a therapeutic tool to treat sepsis. A review of the literature

Author: Eleuterio Lombardo, Tom van der Poll, Olga delaRosa, Wilfried Dalemans

Name of Journal: *World Journal of Stem Cells*

ESPS Manuscript NO: 14364

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 reviewers
Reviewer 02446025

(1) "In the section of effect of MSC treatment on mortality and organ injury induced by sepsis", it would be much better if the source of MSC, the route of administration could be listed and discussed..."
Reply: Where missing, MSC source and route of administration have been included in the text (highlighted in bold).

(2)"It would be very interesting to know if there was any side effect such as lung trap occurred in different models"

Reply: The following text has been added in page 14 (highlighted in bold): "**No specific side effects of MSC treatment have been reported in sepsis models (only Chang et al reported increased mortality when using living rat ASCs compared to the untreated group in a rat model of CLP [69]). The fate of MSCs in sepsis models have been also investigated in some studies. When MSCs were administered intravenously, cells were always detected in the lungs and eventually, to a lesser extent, in spleen, liver, kidney or lymph nodes [61,66,74]. When MSCs were administered intramuscularly, cells were only detected in the muscle up to 24h after administration [76].**"

(3)"Table 1 needs to be modified in order to read and understand".

Reply: We were not sure what the reviewer wanted. We have structured the table differently so now it is organized by model and source of MSC and not chronologically (LPS mouse, LPS rat, CLP mouse, CLP rat, etc). We also copied the table horizontal.

(4)"...it would be helpful to reader if the authors could give their perspective on what should be considered or pay more attentions when design the randomized trial..."

Reply: The following text has been added in page 19 (highlighted in bold): "...**Such clinical trials should be prospective, controlled, and randomized so to guarantee a clear outcome of the MSC treatment effect. Moreover, taking into consideration the complexity and heterogeneity of sepsis and the poor results up to now in sepsis clinical trials, we believe that such trials should first be done in well defined and homogeneous sepsis patient populations.**"

(5)" ... an "an" should be "a" in the first paragraph on page 6".
Reply: It has been modified.

Reviewer 00462683

(1) "...the authors should emphasize the need for an animal model whose inflammatory response may be more similar to that which occurs in humans..."
Reply: The following text has been added in page 19 (highlighted in bold): "...**The promising results obtained in these, small animal, preclinical efficacy studies are encouraging and suggest that MSCs might be a therapeutic option to treat sepsis in patients. Importantly, efficacy of MSCs in large animal models that better replicate the inflammatory response, organ failure and disease in humans (e.g. sheep models) will be additionally relevant to support further testing of the therapeutic potential of allogeneic MSC treatment in humans...**"

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

Sincerely yours,

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