September 5th, 2014

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Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 12954-review.doc).

Title: Use of mesenchymal stem cells to treat liver fibrosis: Current situation and future prospects

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Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 12954

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

- (1) "I would evaluate more the role of HSC and especially their transformation from quiescent to active form. Also, please, highlight the role of a-SMA."

The following paragraphs have been included in the revised version of the manuscript:

HSC activation has been well identified as a key event in the fibrotic response to liver injury. Proliferating activated HSC are typically located in the regions of greatest injury. This phenomenon is preceded by an influx of inflammatory cells and is associated with extracellular matrix accumulation {Friedman, 2008}.

During fibrosis, the enhanced expression of the cytoskeletal protein a-SMA confers a contractile potential to HSCs, which is a determinant of increased portal resistance {Friedman, 2008}. High expression level of a-SMA correlates with an extent of disease progression. Some particularites have been documented as in kidney. Indeed, renal fibrosis progression (in experimental glomerulonephritis model) was enhanced in mice lacking this protein in myofibroblasts, while tissue fibrosis was ameliorated by forced expression of a-SMA in renal interstitial myofibroblasts {Takeji, 2006}. These data suggest that a-SMA expression could play a role in moderating chronic organ fibrosis.

- (2)" On the paragraph about cellular sources of fibrogenesis I would recommend to write more about hepatocytes"

The following paragraph has been included in the revised version of the manuscript:

TGFb induces the acquisition of a fibroblastoid phenotype by hepatocytes and their expression of

proteins characteristic for EMT and fibrogenesis. After EMT, hepatocytes will contribute to the population of myofibroblasts and consequently, participate to fibrogenesis {Dooley, 2008}.

- (3) "The paragraph about histology of the liver fibrosis is somehow confusing and should be rewritten."

This paragraph has been rewritten into the revised version of the manuscript.

- (4) "Note that these studies are primarily allogeneic ESc, iPCS and MSC cell transplantation. Where autologous, it should be stated."

It has been stated in the corresponding tables.

- (5) "It is not clear that tissue based MSCs are advantageous over BM MSCs."

The following paragraph has been included in the revised version of the manuscript:

To our knowledge, tissue based MSCs and bone marrow-derived MSCs have not been compared in terms of efficacy for liver fibrosis treatment until now. The beneficial effects were observed regardless of the origin of MSCs, even if the superiority in terms of immunomodulation has been demonstrated in vitro for adipose tissue-derived MSCs in comparison with bone marrow-derived MSCs {Schubert, 2011}.

- (6) "In vivo MSC differentiation to hepatocytes has been demonstrated in sheep."

This study has been included in the revised version of the manuscript.

- (7) "The MELD score needs to be defined."

The following paragraph has been included in the revised version of the manuscript:

The MELD score (Model for End-Stage Liver Disease) is based on objective variables (INR, serum albumin and serum bilirubin) and has been validated as a predictor of survival among patients with advanced liver disease {Kamath, 2007}.

- (8) "Although liver fibrosis has been considered as a progressive and irreversible change, liver fibrosis due to HBV and/or HCV can be improved with the current antiviral treatments. I think they should briefly describe the recent changes in the clinical course of the hepatitis virus-associated liver fibrosis."

The following paragraph has been included in the revised version of the manuscript:

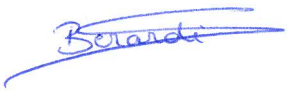
For chronic viral hepatitis, anti-viral treatment efficacy has been recently documented to improve liver fibrosis. In the context of chronic hepatitis B, prevention of developing cirrhosis and fibrosis regression has been demonstrated for Entecavir and Tenofovir, two third-generation nucleotide

analogues. Chang and Colleagues firstly documented histological improvements and reversal of fibrosis/cirrhosis in patients with chronic hepatitis B treated with Entecavir for a period of at least 3 years {Chang, 2010}. More recently, Marcellin and colleagues reported a regression of fibrosis and cirrhosis among patients with chronic hepatitis B infection treated during 5 years with Tenofovir disoproxil fumarate. 74% of the patients with cirrhosis were no longer cirrhotic at year 5 {Marcellin, 2013}. With respect to chronic hepatitis C, a significant regression of fibrosis has been shown among patients presenting mild-to-moderate fibrosis after treatment with Peginterferon alpha-2a or alpha-2b plus ribavirin during 24 or 48 weeks, depending on genotype {Vokobrat-Bijedic, 2014}. However, beyond the strict enrolment criteria of the studies, the long term efficacy and safety of these anti-viral treatments have to be confirmed with older patients presenting several comorbidities and treated with other medications.

3 References and typesetting were corrected

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

Sincerely yours,



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