

ANSWERING REVIEWERS

March 27, 2015



Dear Editor,

Please find enclosed the edited manuscript in Word format.

Title: Autologous bone marrow transplantation in decompensated liver: Systematic review and meta-analysis

Author: Prasoon Pankaj, Xue-Li Bai , Qi Zhang, Ting-Bo Liang

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 14974

The manuscript has been improved according to the suggestions of reviewers. In the current version, we have made substantial revision as per the reviewer's comments.

Reviewer No :503536

The systematic review and meta-analysis written by Pankaj et al. describes the effectiveness of autologous bone marrow transplantation for the treatment of decompensated liver disease. The data show that autologous bone marrow transplantation is an effective treatment to restore liver function in patients with advanced liver cirrhosis, but with limited duration. The data are well-analyzed and well-written. However, there are some concerns that need to be addressed. Major points 1. The effect of autologous bone marrow transplantation is observed for relatively short time. For instance, the preferable effect on serum albumin levels disappeared after 12 months. The authors should discuss on that point with any idea to overcome the problem. Are there any reports in which the treatment was repeatedly performed? 2. The possible cellular or molecular mechanisms for the effectiveness of the treatment should be explained. 2. It is unclear why serum AST or ALT levels were decreased after autologous bone marrow transplantation. The author

should discuss on that point. Minor point 1. English editing by native speaker is needed.

Answer: These comments have been responded, and the manuscript has been revised according to Reviewer No. 503536 last time.

Reviewer No :12216

Panjak et al, carry-out a meta-analysis of nine papers about autologous bone marrow transplantation as strategy to improve liver function in decompensated liver disease. They perform a systematic review of different data-bases to select the papers of the study. Only four out of nine selected papers were randomized studies, which could decrease the evidence level. It could be interesting to know if the meta-analysis would be the same including only the randomized studies. The obtained results show a short-term improvement in some variables, such as albumin or transaminases. It could be great to see a table showing the included study features and the clinical features of the experimental and control groups in each study. Statistical methods should be described in more detail since they are essential in a meta-analysis study In my opinion, the discussion is too general, similar to what would be expected in a review article. I think authors should comment about the statistical and methodological issues of the meta-analysis that could affect the conclusions, such as the heterogeneity and inclusion of non-randomized studies.

Answer: Thank you for these suggestions.

- (1) Four randomized controlled trials (RCTs) were included. We have listed them as a separate subgroup in the meta-analysis. Results acquired from all included studies and those from only RCTs were showed in the revised figures. Most results were similar with or without non-RCTs included. However, some results were not significant any more if non-RCTs were excluded, mostly due to the decrease of numbers of included studies.
- (2) The table showing features of the included studies was included as Table 1.
- (3) The data extraction and statistical analysis section have been revised to show more details. Hope this would be fine.
- (4) We have rearranged the discussion. In particular, we focused on the statistical and methodological issue as per your request.

Reviewer No: 12386

Etiology influences the prognosis of cirrhosis. Authors should describe the etiology of cirrhosis. Invasive methods of autologous bone marrow mononuclear cell or mononuclear stem cell transplantation seems limited to certain patients with decompensated cirrhosis such as better liver function, because they need general anesthesia not but local anesthesia. So, authors should mention these things and revise their manuscript.

Answer: We appreciate the reviewer's comments. In the revised manuscript, the etiology of liver disease in each included studies was described in Table 1. We were especially thankful for the comment that patients underwent BM-MNC transplantation were prone to be with better liver function in non-RCTs. We have added this to our discussion.

Reviewer No: 11164

To my understanding the article entitled 'Autologous bone marrow transplantation in decompensated cirrhosis' by Pankaj et al. is a time endeavor as there is lack of appropriate treatment modality for this intractable liver disease. Although some innovative therapeutic regimens have been proposed for this pathological condition, critical analyses of these approaches are still lacking. The present article seems to provide an analysis of bone marrow transplantation in decompensated cirrhosis in this communication that may be worthy in clinics. However, the authors should note the limitation of their article and study design so that it may be a viable one for the readers and clinicians. Comment 1. The systemic review and meta-analysis revealed that autologous bone marrow transplantation improved serum albumin level and down regulated MELD score without any significant impact on prothrombin time in patients with decompensated cirrhosis due to bone marrow transplantation. If we look at the study design, a total of 9 studies were analyzed out of a total of 630 plus 40 studies were preliminary selected. In Fig. 1, the authors have demonstrated why several hundred studies were excluded. Definitely, this has been done due to the impact of inclusion and exclusion criteria. However, the authors should discuss the logics of exclusion of 101 studies that were excluded at the final state. In fact, a meta-analysis with 9 studies may not be a proper sample size and any meta-analysis may be too early for this subject. 2. The title of the

article is 'bone marrow transplantation'. Bone marrow is a mixture of highly heterogeneous population of different cells. In fact, patients receiving transplantation of bone marrow mononuclear cell (BMMNC) and bone marrow stem cell (BMSC) have been included in this analysis. The outcomes of bone marrow transplantation also show marked heterogeneity, especially regarding prothrombin time. If you show the result of BMMNC transplantation and BMSC transplantation separately, how the overall picture is visualized? Please try to do that, and then the overall outcome may be discussed in Discussion and your comments. 3. Please take cautionary measure to use term like 'appropriate' in conclusion of Abstract. The impact of BMT is far from an appropriate therapeutic measure and a meta-analysis with improvement of some marker for a short duration is not endowed to use the term 'appropriate'. 4. Check the discrepancy of Table 1 versus Fig. 1 in Text and Figure. 5. The future research direction of BMT transplantation should be shown from the experience of this article.

Answer: We appreciate the reviewer's helpful comments.

- (1) We apologize for our mistake. Actually, only eight studies were included in this meta-analysis. In the revised version, we have added the reasons for exclusion of studies in each step. For the 110 publications underwent full-text screen, 40 of them were excluded because they were irrelevant to our topic, 13 studies were not eligible due to unexpected inclusion of participants or undesired treatment, 6 studies did not report the interested outcomes, 2 studies were one-arm study, and 1 study was a further report of the previous one.
- (2) This is a fantastic ideal. From Table 1 we can see that four studies (Lyra 2010, Spahr 2012, Bai 2004, and Saito 2011) using mononuclear cells, and the left four studies using stem cells for transplantation. We have tried to separate studies using BM-MNCs or BMSCs. In all the outcomes we assessed, the conclusion did not change. Actually, in most cases, the study conducted by Mohanmadnejad et al. showed marked difference with other studies, and contributed a lot to the heterogeneity. The reason could be the distinct race (probably Iranians), etiology (nearly a half patients has cryptogenic cirrhosis), or study design. However, due to limited space, it is difficult to show all these results. This has been discussed in the revised manuscript.

(3) Thank you very much for this comment. We have revised our conclusion of Abstract to avoid using the term 'appropriate'.

(4) The discrepancy has been corrected. Thank you for reminding.

(5) We appreciate this suggestion. The major concerns and future research direction of BM transplantation has been mentioned in the last paragraph of the manuscript.

Reviewer No: 39518

This meta-analysis describes the effectiveness of autologous bone marrow transplantation for the treatment of decompensated liver disease. Although the study shows that autologous bone marrow transplantation is an effective treatment to improve liver function scores and some hematochemical parameters in patients with advanced liver cirrhosis, this effect seems to be of limited duration. Furthermore, the conclusion of the study may be hampered by the heterogeneity of the methods used and by the limited number of patients evaluated in the studies taken into account. The data are appropriately analyzed, the method of the meta-analysis is right and the paper is well-written. No major changes are requested. However, Table 1, summarizing the main features of the 9 studies evaluated, is lacking and the Discussion can be shortened. There are some typographical errors that should be corrected.

Answer: Thank you for the comments.

(1) Last time the Table 1 was submitted as a separate Excel file as per the editor's request. This time we include Table 1 in the Word file.

(2) We have rewritten the Discussion and have tried to shorten it.

(3) Typos and grammatical errors were corrected. We apologize for the mistakes.

Reviewer No: 52899

In this meta-analysis, the author evaluated the efficacy of autologous bone marrow transplantation in the treatment of decompensated liver disease. The

author found that autologous bone marrow transplantation could improve liver function and was an effective therapy for decompensated liver disease. Overall, the meta-analysis is carefully prepared and the manuscript is well organized. However, there are still some problems. They are given below. 1. Where is the Table 1? 2. Clarify the exclusion reasons for the 101 articles in Figure 1. 3. In paragraph 2 of "outcome evaluation", "At 6 mo after cell transplantation, patients had a lower level of total bilirubin (MD: -1.32 mg/dL; 95% CI: -3.39 to 0.75; P = 0.04)". The data of total bilirubin in text and Figure 3C were not consistent. 4. In the last paragraph of "outcome evaluation", "P < 0.00001" should be "P=0.05" according to Figure 8B. 5. Heterogeneity was high in several studies.

Answer: Thank you for the comments.

- (1) Last time the Table 1 was submitted as a separate Excel file as per the editor's request. This time we include Table 1 in the Word file.
- (2) We are sorry for that. The reason of exclusions has been provided in the revised manuscript.
- (3) Thank you for reminding. The correction has been made.
- (4) We apologize for this error, and corrected the text in the revised manuscript.
- (5) Indeed, both clinical and statistical heterogeneity were high among the included studies. We have assessed the heterogeneity and discussed its the influence on the conclusion. Accordingly, we used the most conservative method (assuming the correlation coefficient was -1) to evaluate standard deviation, and used a random-effects model for meta-analysis. However, given the high heterogeneity, some outcomes (such as albumin and bilirubin) still showed benefits compared to the control group. This means BM transplantation is clinically valuable, but needs further study to improve its efficient.

Finally, we shall thank again for all the reviewers' comments.

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

Sincerely yours,

A handwritten signature in black ink, appearing to be the name 'Liang Tingbo' in a cursive style.

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Dear editor,

Please see the revised manuscript in the attachment. We have revised the manuscript as per the suggestion of journal editor-in-chief. In addition, we reshuffled the author list a little according to the contribution during the revision. All authors approve this change, and the new copyright transfer file are resigned as the new order of author list.