**Name of journal: World Journal of Gastroenterology**

**ESPS Manuscript NO: 14974**

**Columns: META-ANALYSIS**

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

Pankaj P *et al*. Bone marrow transplantation in decompensated liver

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

**Prasoon Pankaj, Qi Zhang, Xue-Li Bai, Ting-Bo Liang,** Department of Hepatobiliary and Pancreatic Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine, Hangzhou 310009, Zhejiang Province, China

**Author contributions:** Pankaj P and Zhang Q contributed equally to this work; Liang TB conceived the idea; Pankaj P and Bai XL performed the literature search; Pankaj P and Zhang Q extracted the data; Zhang Q analyzed the data; Pankaj P and Zhang Q drafted the manuscript; all authors approved the final version to be published.

**Supported by** National Natural Science Foundation of China, No. 81171884 and No. 81401954; and Innovation and High-Level Talent Training Program of Department of Health of Zhejiang Province, China.

**Conflict-of-interest:** The authors declared no conflict of interest.

**Data sharing:** No additional data are available.

**Open-Access:** This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/

**Correspondence to: Ting-Bo Liang, MD, PhD, Professor,** Department of Hepatobiliary and Pancreatic Surgery, the Second Affiliated Hospital, Zhejiang University School of Medicine, 88 Jiefang Road, Hangzhou 310009, Zhejiang Province, China. liangtingbo@zju.edu.cn

**Telephone:** +86-571-8731500

**Fax:** +86-571-87315005

**Received:** November 2, 2014

**Peer-review started:** November 3, 2014

**First decision:** March 10, 2015

**Revised:** March 27, 2015

**Accepted:** April 28, 2015

**Article in press:**

**Published online:**

**Abstract**

**AIM:** To evaluate the efficacy of autologous bone marrow mononuclear cell or mononuclear stem cell transplantation in decompensated liver disease.

**METHODS:** Medline, Embase, PubMed, Science Direct and The Cochrane Library were searched for relevant studies. Retrospective case-control studies were included along with randomized clinical trials. Meta-analysis was performed in line with recommendations from the Cochrane Collaboration software review manager. Heterogeneity was assessed using a random-effects model.

**RESULTS:** Four randomized controlled trials and four retrospective studies were included. Cell transplantation increased serum albumin level by 1.96 g/L (95%CI: 0.74-3.17; *P* = 0.002], 2.55 g/L (95%CI: 0.32-4.79; *P* = 0.03), and 3.65 g/L (95%CI: 0.76-6.54; *P* = 0.01) after 1, 3, and 6 mo, respectively. Patients undergone cell transplantation also had a lower level of total bilirubin [mean difference (MD): -1.37 mg/dL; 95%CI: -2.68-(-0.06); *P* = 0.04] after 6 mo. The decreased after 1 year when compared to that with standard treatment (MD: -1.26; 95%CI: -2.48-(-0.03); *P* = 0.04]. Besides, temporary decrease in alanine transaminase and aspartate transaminase were significant in cell transplantation group. However, after 6 mo treatment, patients undergone cell transplantation had a slightly longer prothrombin time (MD: 5.66 s, 95%CI: 0.04-11.28; *P* = 0.05). Changes in model for end-stage liver disease score and Child-Pugh score were not statistically significant.

**CONCLUSION:** Autologous bone marrow transplantation showed some benefits in patients with decompensated liver disease. However, further studies are still needed to verify its role in clinical treatment for end-stage liver disease.

**Key words:** Autologous transplantation; Bone marrow; Cirrhosis; Decompensated liver disease

**© The Author(s) 2015.** Published by Baishideng Publishing Group Inc. All rights reserved.

**Core tip:** Autologous bone marrow mononuclear cells prevent immune rejection. In this systematic review and meta-analysis, we attempted to gather evidence for the therapeutic use of autologous bone marrow mononuclear cell transplantation for decompensated liver disease and cirrhosis. We found that autologous bone marrow transplantation is satisfactory in patients with decompensated liver disease. Some important issues need to be verified by large-volume centers.

Pankaj P, Zhang Q, Bai XL, Liang TB. Autologous bone marrow transplantation in decompensated liver: Systematic review and meta-analysis. *World J Gastroenterol* 2015; In press

**INTRODUCTION**

Liver disease is a global health problem and hepatitis B and C are two of the most epidemic and serious types[1]. As the disease advances, the liver function may be decompensated, leading to decompensated liver diseases, mostly cirrhosis. Currently, there are few therapeutic options for decompensated liver disease, and new strategies have been explored for several decades. Regeneration of functional hepatocytes is believed to be the key for maintaining liver function in these patients. Autologous bone marrow mononuclear cells (BM-MNCs), include mesenchymal stem cells, hematopoietic stem cells, endothelial progenitor cells, and stromal cells, are beneficial for patients with decompensated liver disease[2]. Due to the contribution of non-hematopoietic stem cells, BM-MNCs can generate various types of cells in different tissues[3-5]. Other cell components of BM-MNCs may facilitate stem cell differentiation by secreting cytokines, modeling microenvironments, or interacting with stem cells.

In autologous transplantation, cells are derived from the patients themselves, which theoretically can prevent the possibility of immune rejection. At present, autologous BM-MNCs have been widely applied in the treatment of liver diseases[6-9]. It is proposed that pluripotent nonhematopoietic stem cells from BM might participate in the repopulation of a damaged liver and may even improve its function[10]. The combination of mobilization, isolation, and direct infusion of BM stem cells into the liver via the hepatic artery or portal vein, or autologous human BM stem cell transplantation, showed inconsistent improvement in liver function[10-12]. However, the evidence for autologous BM-MNCs transplantation for decompensated liver disease is controversial. This systematic review aimed to summarize the currently available literature on this topic.

**MATERIALS AND METHODS**

***Literature search strategies and selection***

Five electronic databases (Medline, Embase, PubMed, Science Direct, and The Cochrane Library) were searched from dates of inceptions up to October 2014. The following key words were used: “bone marrow”, “autologous”, “transfusion”, “liver OR hepatic”, and “systematic review”; similar headings were also searched such as “treatment of decompensated liver disease”, “treatment option for cirrhosis”, and “meta-analysis”. Further articles were identified by a manual search of reference lists from the retrieved publications. The databases were used again to retrieve the abstracts, and if favorable, the full text was downloaded for the final review. All articles included in this study were published in English.

Two reviewers independently screened the title and abstract of each identified publication. Citations with suspected compliance with our eligibility criteria underwent a full review. If either of the two reviewers identified a citation to be potentially relevant, we obtained the full text for a full review. Any disagreements were resolved through discussions with a third reviewer.

***Eligibility criteria and outcome evaluation***

This study compared autologous BM stem cell therapy in decompensated liver disease, regardless of blinding and concealment of allocation. Retrospective studies were included along with randomized clinical trails. Eligibility criteria were as follows: (1) explicitly reporting the indications for BM-MNCs; (2) comparing at least one of the following outcomes: albumin, total bilirubin, coagulation function tests (prothrombin time and activity), Child-Pugh score, model for end-stage liver disease (MELD) score, alanine transaminase (ALT), and aspartate transaminase (AST); and (3) when two studies were published by the same institution or authors and data were repeated, the higher quality or the most recent was included.

***Exclusion criteria***

Studies were excluded if: (1) it was impossible to extract or reasonably estimate the data from the published articles; and (2) there was considerable overlap among patients in the studies published.

***Data extraction and analysis***

Data presented as changes were preferred. When changes were unavailable but could be calculated from the data before and after treatment, we calculated them using appropriate methods[13]. In brief, we calculated a correlation coefficient from a comparable study with considerable detail using the formula suggested by The Cochrane Collaboration[13]. The desired SD of certain study could then be calculated using transformation of the same formula. When no correlation coefficient could be acquired from other comparable studies could be found, which meant that calculation was impossible for the missing data, we evaluated the SD using the most conservative way (assuming that the correlation coefficient was -1). The influence of the evaluation was then discussed.

Meta-analysis was performed using Review Manager (version 5.3) and followed the recommendations from The Cochrane Collaboration. Heterogeneity was assessed using a random-effects model, and *P* < 0.10 with *I*2 > 50% was considered statistically significant. A statistical analysis of continuous variables was carried out using the mean difference (MD) as the summary statistic by the Inverse-Variance method and was reported with a 95% confidential interval (CI). The MD was considered to be statistically significant at *P* < 0.05.

**RESULTS**

***Literature search results and general characteristics***

A totally of 610 nonduplicated publications were identified and underwent abstract screen. 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, six studies did not report the interested outcomes, two studies were one-arm study, and one study was a further report of the previous one (Figure 1). Finally, eight studies were included for quantitative analysis[2,14-21], and four of them were randomized clinical trials[2,14,19,20]. The characteristics of the included studies are shown in Table 1.

***Outcome evaluation***

Indicators for liver function such as serum albumin, total bilirubin, ALT, and AST were assessed by most studies. MELD score[2,15,19,20] and Child-Pugh score[2,19] were used in some articles to evaluate the effects of cell transplantation. Meta-analysis showed that compared to the control group, the patients who had undergone cell transplantation had a higher level of serum albumin within 6 mo after treatment. The additional increase in serum albumin by cell transplantation was 1.96 g/L (95%CI: 0.74-3.17; *P* = 0.002), 2.55 g/L (95%CI: 0.32-4.79; *P* = 0.03), and 3.65 g/L (95% CI 0.75-6.54; *P* = 0.01) g/L after 1, 3, and 6 mo[2,14-17,19,21], respectively (Figure 2A-C). However, this effect disappeared after 1 year (Figure 2D), by which time there was no difference regarding serum albumin between the experimental and control groups (MD: 1.43 g/L; 95%CI: -2.27-5.14; *P* = 0.45). However, heterogeneity was high among these studies (*I*2: 88%-97%), and could not be explained by only one or two studies.

With regard to total bilirubin, meta-analysis of six studies[2,14,15,17,19,21] did not show any significant difference between the two groups, except at 6 mo (Figure 3A-D). At 6 mo after cell transplantation, patients had a lower level of total bilirubin (MD: -1.37 mg/dL; 95%CI: -2.68-(-0.06); *P* = 0.04). Heterogeneity was high (I2: 66%-79%), and was mainly contributed by Lyra’s study[2]. Exclusion of Lyra’s study did not change the conclusions.

Two studies reported changes in AST after treatment[14,17]. There was a decrease in AST level at 3 mo after cell transplantation (MD: -16.30 U/L; 95%CI: -22.52-(-10.08); *P* < 0.00001; Figure 4A) and after 6 mo (MD: -13.80 U/L; 95%CI: -17.98-(-9.61); *P* < 0.00001; Figure 4B). No heterogeneity was detected (*P* > 0.10, with *I*2 = 0). Three studies reported changes in ALT after cell transplantation[14,17,19]. Similarly, cell transplantation showed a lower ALT level at 3 mo (MD: -9.11 U/L; 95%CI: -16.35-(-1.88); *P* = 0.01; Figure 5A), but it failed to show a consistent effect at 6 mo (MD: -9.60 U/L; 95%CI: -21.82-2.62; *P* = 0.12; Figure 5B). No heterogeneity was detected regarding ALT level at 3 mo (*P* = 0.22), but heterogeneity should be taken into consideration regarding ALT level at 6 mo (*P* = 0.06, with *I*2 =72%)

MELD score was reported by two to four studies, depending on the time point assessed**[**2,15,19,20**]**. Meta-analysis did not show any difference within 12 mo of treatment (Figure 6A-D). Two studies reported that Child-Pugh score could be incorporated into meta-analysis[2,19]. No significant difference was detected at up to 1 year after treatment (Figure 7A-C).

Four studies reported changes in prothrombin time[14,15,17,21]. Changes in prothrombin time were noted only at 6 mo after therapy, when patients with cell transplantation showed a slight increase (MD: 5.66 s, 95%CI: 0.04-11.28; *P* = 0.05; Figure 8A-C). However, the heterogeneity was high (*P* < 0.00001, with *I*2 = 95%). Only one study followed changes in prothrombin time up to 24 mo[21], and suggested no statistically difference (MD: -1.3 s, 95%CI: -2.67-0.07; *P* = 0.06).

**DISCUSSION**

In this systematic review and meta-analysis, we attempted to collect evidence for BM-MNC, or particularly, bone marrow stem cell (BMSC) transplantation as a potential therapeutic approach for patients with decompensated liver disease. It is suggested that pluripotent nonhematopoietic stem cells derived from the BM may be able to repopulate the impaired liver and improve its function[10]. Genomic plasticity is the intrinsic foundation of trans-differentiation of BMSCs[22]. Besides, BM-MNCs may facilitate differentiation of BM nonhemetopoietic stem cells into hepatoblasts and hepatocytes by remodeling the liver microenrivonment[23]. Many growth factors such as granulocyte colony-stimulating factor and hepatic growth factor were also found faciliate the effectiveness of BM-MNC transplantation by stimulating cell proliferation or suppressing liver inflammation and fibrosis[24,25]. In addition, transplanted BM-MNCs may have different roles according to the etiology of liver disease, which may influence the clinical effects of BM transplantation. Most patients in the included studies have hepatitis virus (either HBV or HCV) infection and/or alcholic explosure, and were suffer from decompensate liver cirrhosis (see Table 1). Limited evidence has shown that BM-MNC transplantation might help remove the viruses. In Salama‘s study, there was a negative correlation between HCV titer changes and changes in AST at 3 and 6 mo after cell transplantation, and a moderate negative correlation between HCV titer changes and changes in ALT at 2 mo after cell transplantation[13]. However, another study has demonstrated that the severity of liver disease is independent of serum levels of HCV[26]. To date, no direct antivirus effect of BM-MNCs has been clearly demonstrated, and this possible role, if it exists, could be due to enhancement of hepatic local immune function induced by BM-MNCs. In general, autologous BM-MNC transplantation may restore liver function from two aspects: help repair the damaged liver, and may be beneficial for hepatitis virus clearance. However, the exact process whereby BM-MNCs promote hepatocyte regeneration or liver restoration remains to be determined.

There usually was a gradual improvement in the hepatic functional reserve in the patients who underwent BM-MNC transplantation. For instance, the maximum improvement in Child-Pugh score occurred after 6 mo in the largest cohort of HCV-associated end-stage liver disease patients[14]. On the other hand, the long-term benefits of BM-MNC transplantation were not as convincible as the short-term ones. Peng *et al*[15] documented the positive results of short-term analysis; however, a longer investigation revealed these beneficial effects failed to last more than 2 years. Indeed, most relevant studies only reported short-term benefits, and for the studies containing long-term results, beneficial effects failed to last for long. Many reasons involved in the ambiguous results in long-term follow up. For instance, the parameters used to assess the clinical improvement are different. These parameters have different clinical implications, and some of them are more sensible than others. Another reason is that the details of autologous BM-MNC transplantation are actually distinct among the studies, causing different long-term results. Thirdly, the activity of transplanted cells and whether they have induced the process of liver repopulation are critical to preserve long-term effects of this therapy. Accordingly, two strategies are needed to verity and improve the long-term effects. On one hand, basic researchers need to understand the biological process of BMSC-induced liver repopulation, and find appropriate methods to boost it. On the other hand, clinical investigators should use more parameters to comprehensively evaluate the clinical improvement.

Given the undetermined role of BM-MNC transplantation in long-term follow-up, some investigators have tried to assess whether repetitive transplantation of autologous BM-MNCs at regular intervals could be a strategy for improving the conditions of decompensated cirrhosis[21]. Repeated autologous BMSC infusions or the combination of cell therapy with granulocyte colony-stimulating factor might be a promising treatment option for patients with advanced chronic liver disease[2]. Nevertheless, it has been shown that transfusion through peripheral veins might results in promising outcomes[6,8]. However, Mohamadnejad and colleagues recommended that infusion of BMSCs through peripheral veins was probably not beneficial in decompensated cirrhosis by concluding that “liver transplantation is still considered the standard treatment for decompensated cirrhosis”[19].We needs to be reminded that the natural history of cirrhosis is often varying. How to improve the infusion method, and optimize the cell transplant type and transplantation strategy remains to be further studied[21][Khurana, 2008 #2341;Bai, 2014 #2356]. Long-term studies are needed to improve BM-MNC transplantation for treatment of cirrhosis.

Due to the considerable clinical and statistical heterogeneity among these studies, the results of the meta-analysis should be cautiously interpreted. Several reasons contributed to the heterogeneity. Firstly, only a half of the included studies were RCTs, and the inclusion of non-RCTs reduced the quality of evidence. Particularly, since BM transplantation is an invasive procedure and needs general anesthesia, patients underwent BM transplantation were prone to be with relatively better liver function in non-RCTs. This could introduce bias. Although most results were similar with or without inclusion of non-RCTs, some results became insignificant after exclusion of non-RCTs. This was mostly because the decrease of numbers of included studies. Secondly, the exact type (BM-MNCs or BMSCs) and number of cells transplanted were different among studies (see Table 1), let alone the heterogeneity of etiology and severity of the diseases. Even among the RCTs, contradictory results were reported. For instance, Mohamadnejad’s study showed relatively poor prognosis in experimental group compared to that of control group with regard to albumin and Child-Pugh score[19]. Thirdly, there was a lack of clinical follow-up details to ascertain the specific results at certain time points in some studies, and we had to calculate or estimate these data using appropriate means. Although we carefully performed the estimation, this could make the results deviate from the actual values. Besides, some parameters were not comparable among studies, which led to a painstaking work to evaluate the particular connection in view of the numerous outcomes. To be conventional, we simulated that the correlation coefficient equaled -1 when mandatory. This assumption resulted in a large SD and a wide range of 95%CI, which made the meta-analysis more insensitive with the minimized type II error, and thus could have underestimated the efficacy of this treatment.

In conclusion, our study implies that the short-term outcomes of autologous BM transplantation were satisfactory in patients with decompensated liver disease. However, many concerns need to be addressed by further basic research and clinical trials in large-volume centers. For instance, the type and number of cell transplanted, the route of transplantation (*e.g.*, portal vein, or hepatic artery), pretreatment of cells, repeat cell transplantation, and concomitant adjuvant therapy are important to authenticate autologous BM-MNC transplantation. In addition, well-designed randomized controlled trials are required to verify and enhance the effectiveness, especially for long-term outcomes, by addressing these issues. Cell transplantation is an innovative intervention for end-stage liver disease, and we should be cautious when advocating its effectiveness in clinical practice with current evidence.

**COMMENTS**

***Background***

Bone marrow mononuclear cells (BM-MNCs), including non-hematopoietic stem cells, were found to help liver regeneration, and BM-MNCs transplantation is a potential treatment for decompensated liver disease. However, some contradictory results existed.

***Research frontiers***

The cells used for treating decompensated liver disease varied from mesenchymal stem cells to BM stem cells and BM-MNCs. These types of cells can acquired from BM, however, they have different components. In addition, the purity, routes, and repeated cycles were distinct in different studies. Most studies demonstrated positive short-term result, however, the long-term efficacy was inconclusive.

***Applications***

BM-MNC transplantation, if proved beneficial for liver regeneration, will be a promising strategy for improving prognosis of patients with decompensated liver disease.

***Terminology***

BM-MNCs include mesenchymal stem cells, hematopoietic stem cells, endothelial progenitor cells, and stromal cells, are beneficial for patients with decompensated liver disease. Bone marrow stem cell transplantation is a potential therapeutic approach for patients with decompensated liver disease.

***Peer-review***

This systematic review and meta-analysis written describes the effectiveness of autologous bone marrow transplantation for the treatment of decompensated liver disease. The data showed that autologus 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.

**References**

1 **Lee WM**. Hepatitis B virus infection. *N Engl J Med* 1997; **337**: 1733-1745 [PMID: 9392700 DOI: 10.1056/NEJM199712113372406]

2 **Lyra AC**, Soares MB, da Silva LF, Braga EL, Oliveira SA, Fortes MF, Silva AG, Brustolim D, Genser B, Dos Santos RR, Lyra LG. Infusion of autologous bone marrow mononuclear cells through hepatic artery results in a short-term improvement of liver function in patients with chronic liver disease: a pilot randomized controlled study. *Eur J Gastroenterol Hepatol* 2010; **22**: 33-42 [PMID: 19654548 DOI: 10.1097/MEG.0b013e32832eb69a]

3 **Khurana S**, Mukhopadhyay A. In vitro transdifferentiation of adult hematopoietic stem cells: an alternative source of engraftable hepatocytes. *J Hepatol* 2008; **49**: 998-1007 [PMID: 18657875 DOI: 10.1016/j.jhep.2008.05.019]

4 **Banas A**, Teratani T, Yamamoto Y, Tokuhara M, Takeshita F, Osaki M, Kato T, Okochi H, Ochiya T. Rapid hepatic fate specification of adipose-derived stem cells and their therapeutic potential for liver failure. *J Gastroenterol Hepatol* 2009; **24**: 70-77 [PMID: 18624899 DOI: 10.1111/j.1440-1746.2008.05496.x]

5 **Yan Y**, Xu W, Qian H, Si Y, Zhu W, Cao H, Zhou H, Mao F. Mesenchymal stem cells from human umbilical cords ameliorate mouse hepatic injury in vivo. *Liver Int* 2009; **29**: 356-365 [PMID: 19141029 DOI: 10.1111/j.1478-3231.2008.01855.x]

6 **Terai S**, Ishikawa T, Omori K, Aoyama K, Marumoto Y, Urata Y, Yokoyama Y, Uchida K, Yamasaki T, Fujii Y, Okita K, Sakaida I. Improved liver function in patients with liver cirrhosis after autologous bone marrow cell infusion therapy. *Stem Cells* 2006; **24**: 2292-2298 [PMID: 16778155 DOI: 10.1634/stemcells.2005-0542]

7 **Pai M**, Zacharoulis D, Milicevic MN, Helmy S, Jiao LR, Levicar N, Tait P, Scott M, Marley SB, Jestice K, Glibetic M, Bansi D, Khan SA, Kyriakou D, Rountas C, Thillainayagam A, Nicholls JP, Jensen S, Apperley JF, Gordon MY, Habib NA. Autologous infusion of expanded mobilized adult bone marrow-derived CD34+ cells into patients with alcoholic liver cirrhosis. *Am J Gastroenterol* 2008; **103**: 1952-1958 [PMID: 18637092 DOI: 10.1111/j.1572-0241.2008.01993.x]

8 **Kharaziha P**, Hellström PM, Noorinayer B, Farzaneh F, Aghajani K, Jafari F, Telkabadi M, Atashi A, Honardoost M, Zali MR, Soleimani M. Improvement of liver function in liver cirrhosis patients after autologous mesenchymal stem cell injection: a phase I-II clinical trial. *Eur J Gastroenterol Hepatol* 2009; **21**: 1199-1205 [PMID: 19455046 DOI: 10.1097/MEG.0b013e32832a1f6c]

9 **Gilchrist ES**, Plevris JN. Bone marrow-derived stem cells in liver repair: 10 years down the line. *Liver Transpl* 2010; **16**: 118-129 [PMID: 20104479 DOI: 10.1002/lt.21965]

10 **Fausto N**. Liver regeneration and repair: hepatocytes, progenitor cells, and stem cells. *Hepatology* 2004; **39**: 1477-1487 [PMID: 15185286 DOI: 10.1002/hep.20214]

11 **Houlihan DD**, Newsome PN. Critical review of clinical trials of bone marrow stem cells in liver disease. *Gastroenterology* 2008; **135**: 438-450 [PMID: 18585384 DOI: 10.1053/j.gastro.2008.05.040]

12 **Almeida-Porada G**, Zanjani ED, Porada CD. Bone marrow stem cells and liver regeneration. *Exp Hematol* 2010; **38**: 574-580 [PMID: 20417684 DOI: 10.1016/j.exphem.2010.04.007]

13 **Higgins JPT**, Green S (editors). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from: URL: http:// www.cochrane-handbook.org

14 **Salama H**, Zekri AR, Bahnassy AA, Medhat E, Halim HA, Ahmed OS, Mohamed G, Al Alim SA, Sherif GM. Autologous CD34+ and CD133+ stem cells transplantation in patients with end stage liver disease. *World J Gastroenterol* 2010; **16**: 5297-5305 [PMID: 21072892 DOI: 10.3748/wjg.v16.i42.5297]

15 **Peng L**, Xie DY, Lin BL, Liu J, Zhu HP, Xie C, Zheng YB, Gao ZL. Autologous bone marrow mesenchymal stem cell transplantation in liver failure patients caused by hepatitis B: short-term and long-term outcomes. *Hepatology* 2011; **54**: 820-828 [PMID: 21608000 DOI: 10.1002/hep.24434]

16 **Saito T**, Okumoto K, Haga H, Nishise Y, Ishii R, Sato C, Watanabe H, Okada A, Ikeda M, Togashi H, Ishikawa T, Terai S, Sakaida I, Kawata S. Potential therapeutic application of intravenous autologous bone marrow infusion in patients with alcoholic liver cirrhosis. *Stem Cells Dev* 2011; **20**: 1503-1510 [PMID: 21417817 DOI: 10.1089/scd.2011.0074]

17 **El-Ansary M**, Abdel-Aziz I, Mogawer S, Abdel-Hamid S, Hammam O, Teaema S, Wahdan M. Phase II trial: undifferentiated versus differentiated autologous mesenchymal stem cells transplantation in Egyptian patients with HCV induced liver cirrhosis. *Stem Cell Rev* 2012; **8**: 972-981 [PMID: 21989829 DOI: 10.1007/s12015-011-9322-y]

18 **Amin MA**, Sabry D, Rashed LA, Aref WM, el-Ghobary MA, Farhan MS, Fouad HA, Youssef YA. Short-term evaluation of autologous transplantation of bone marrow-derived mesenchymal stem cells in patients with cirrhosis: Egyptian study. *Clin Transplant* 2013; **27**: 607-612 [PMID: 23923970 DOI: 10.1111/ctr.12179]

19 **Mohamadnejad M**, Alimoghaddam K, Bagheri M, Ashrafi M, Abdollahzadeh L, Akhlaghpoor S, Bashtar M, Ghavamzadeh A, Malekzadeh R. Randomized placebo-controlled trial of mesenchymal stem cell transplantation in decompensated cirrhosis. *Liver Int* 2013; **33**: 1490-1496 [PMID: 23763455 DOI: 10.1111/liv.12228]

20 **Spahr L**, Chalandon Y, Terraz S, Kindler V, Rubbia-Brandt L, Frossard JL, Breguet R, Lanthier N, Farina A, Passweg J, Becker CD, Hadengue A. Autologous bone marrow mononuclear cell transplantation in patients with decompensated alcoholic liver disease: a randomized controlled trial. *PLoS One* 2013; **8**: e53719 [PMID: 23341981 DOI: 10.1371/journal.pone.0053719]

21 **Bai YQ**, Yang YX, Yang YG, Ding SZ, Jin FL, Cao MB, Zhang YR, Zhang BY. Outcomes of autologous bone marrow mononuclear cell transplantation in decompensated liver cirrhosis. *World J Gastroenterol* 2014; **20**: 8660-8666 [PMID: 25024623 DOI: 10.3748/wjg.v20.i26.8660]

22 **Cho KA**, Lim GW, Joo SY, Woo SY, Seoh JY, Cho SJ, Han HS, Ryu KH. Transplantation of bone marrow cells reduces CCl4 -induced liver fibrosis in mice. *Liver Int* 2011; **31**: 932-939 [PMID: 21092070 DOI: 10.1111/j.1478-3231.2010.02364.x]

23 **Terai S**, Sakaida I, Yamamoto N, Omori K, Watanabe T, Ohata S, Katada T, Miyamoto K, Shinoda K, Nishina H, Okita K. An in vivo model for monitoring trans-differentiation of bone marrow cells into functional hepatocytes. *J Biochem* 2003; **134**: 551-558 [PMID: 14607982 DOI: 10.1093/jb/mvg173]

24 **Piscaglia AC**, Shupe TD, Oh SH, Gasbarrini A, Petersen BE. Granulocyte-colony stimulating factor promotes liver repair and induces oval cell migration and proliferation in rats. *Gastroenterology* 2007; **133**: 619-631 [PMID: 17681181 DOI: 10.1053/j.gastro.2007.05.018]

25 **Oyagi S**, Hirose M, Kojima M, Okuyama M, Kawase M, Nakamura T, Ohgushi H, Yagi K. Therapeutic effect of transplanting HGF-treated bone marrow mesenchymal cells into CCl4-injured rats. *J Hepatol* 2006; **44**: 742-748 [PMID: 16469408 DOI: 10.1016/j.jhep.2005.10.026]

26 **Duvoux C**, Pawlotsky JM, Bastie A, Cherqui D, Soussy CJ, Dhumeaux D. Low HCV replication levels in end-stage hepatitis C virus-related liver disease. *J Hepatol* 1999; **31**: 593-597 [PMID: 10551380]

**P-Reviewer:** Akbar SMF, Kanda T, Larrubia jr, Pompili M, Shimizu Y, Wang k **S-Editor:** Ma YJ **L-Editor: E-Editor:**

**Table 1 Most patients in the included studies have hepatitis virus infection and/or alcholic explosure, and were suffer from decompensate liver cirrhosis**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trials** | | **Region** | **Design** | **Duration** | **No. of patients** | **Etiology of liver disease** | **Intervention** | **Follow-up** |
| Lyra  2010 | | Brazil | RCT | 2006.1-2006.4 | 15 *vs* 15 | Chronic liver disease waiting for liver transplantation, mainly alcoholic and/or hepatitis C | About 3.78 × 108 BM-MNCs, through hepatic artery | Up to 12 mo |
| Salama  2010 | | Egypt | RCT | 2008.6-2009.5 | 90 *vs* 50 | Post HCV liver cirrhosis | Autologous BM-derived CD34+ and CD133+ stem cell infusion in the portal vein | Up to 6 mo |
| Spahr  2012 | | Switzerland | RCT | 2008.2-2011.3 | 28 *vs* 30 | Decompensated alcoholic liver disease | About 4.7 × 107/kg BM-MNCs, including CD34+ cells and MSCs | Up to 3 mo |
| Mohanmadnejad  2013 | | Iran | RCT | 2007.7-2010.8 | 15 *vs* 12 | 2 PBC, 2 HBV, 1 HCV, 9 AIH, 11 unknown | About 1.95 × 108 MSCs through cubital vein | Up to 12 mo |
| Bai  2004 | China | | Case-control | 2009.3-2011.3 | 32 *vs* 15 | Decompensated liver cirrohsis, 91.5% with HBV infection | BM-MNCs through hepatic artery | Up to 24 mo |
| Peng  2011 | China | | Case-control | 2005.5-2009.6 | 53 *vs* 105 | Chronic hepatitis B induced liver disease, 73% with cirrhosis | BM-derived MSCs through proper hepatic artery | Up to 192 wk |
| Saito  2011 | Japan | | Case-control | NA | 5 *vs* 5 | Alcoholic liver cirrhosis | About 8 × 109 BM-MNCs through cubital vein | Up to 48 wk |
| El-Ansary  2012 | Egypt | | Prospetive cohort study | NA | 15 *vs* 10 | HCV induced liver cirrhosis | About 1 × 106 MSCs/kg, intravenosly | Up to 6 mo |

PBC: Primary biliary cirrhosis; HBV: Hepatitis B virus; HCV: Hepatitis C virus; AIH: Autoimmune hepatitis; BM-MNCs: Bone marrow mononuclear cells; MSC: Mesenchyme stem cell; RCT: Randomized controlled trial; NA: Not available.

****

**Figure 1 Study flow diagram.**

****

**Figure 2 Changes in albumin level at 1 mo (A), 3 mo (B), 6 mo (C), and 12 mo (D) after autologous bone marrow transplantation.**

****

**Figure 3 Changes in total bilirubin level at 1 mo (A), 3 mo (B), 6 mo (C), and 12 mo (D) after autologous bone marrow transplantation.**

****

**Figure 4 Changes in aspartate transaminase level at 3 mo (A) and 6 mo (B) after autologous bone marrow transplant.**

****

**Figure 5 Changes in alanine transaminase level at 3 mo (A) and 6 mo (B) after autologous bone marrow transplantation.**

****

**Figure 6 Changes in model for end-stage liver disease score at 1 mo (A), 3 mo (B), 6 mo (C), and 12 mo (D) after autologous bone marrow transplantation.**

****

**Figure 7 Changes in Child–Pugh score at 3 mo (A), 6 mo (B), 12 mo (C) after autologous bone marrow transplantation.**

****

**Figure 8 Changes in prothrombin time at 1 mo (A), 6 mo (B), and 12 mo (C) after autologous bone marrow transplantation.**