



Mesenchymal stem cell therapy for cirrhosis: Present and future perspectives

Young Woo Eom, Gaeun Kim, Soon Koo Baik

Young Woo Eom, Soon Koo Baik, Cell Therapy and Tissue Engineering Center, Yonsei University Wonju College of Medicine, Wonju 220-701, South Korea

Gaeun Kim, College of Nursing - Research Institute for Nursing Science, Keimyung University, Daegu 704-701, South Korea

Soon Koo Baik, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital, Wonju 220-701, South Korea

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Correspondence to: Soon Koo Baik, MD, PhD, Professor, Department of Internal Medicine, Yonsei University Wonju College of Medicine, Wonju Severance Christian Hospital, 20, Ilsanro, Wonju 220-701, South Korea. baiksk@yonsei.ac.kr
Telephone: +82-33-7411229
Fax: +82-33-7451228

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Abstract

Cirrhosis occurs as a result of various chronic liver injuries, which may be caused by viral infections, alcohol abuse and the administration of drugs and chemicals. Recently, bone marrow cells (BMCs), hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs) have been used for developing treatments for cirrhosis. Clinical trials have investigated the therapeutic potential of BMCs, HSCs and MSCs for the treatment of cirrhosis based on their potential to differentiate into hepatocytes. Although the therapeutic mechanisms of BMC, HSC and MSC treatments are still not fully characterized, the evidence thus far has indicated that the potential therapeutic mechanisms of MSCs are clearer than those of BMCs or HSCs with respect to liver regenerative medicine. MSCs suppress inflammatory responses, reduce hepatocyte apoptosis, increase hepatocyte regeneration, reverse liver fibrosis and enhance liver functionality. This paper summarizes the clinical studies that have used BMCs, HSCs and MSCs in patients with liver failure or cirrhosis. We also present the potential therapeutic mechanisms of BMCs, HSCs and MSCs for the improvement of liver function.

Key words: Cirrhosis; Cell therapy; Bone marrow cells; Mesenchymal stem cells; Hematopoietic stem cells; Immune-modulation; Trophic factors; Anti-fibrosis

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Core tip: Mesenchymal stem cells (MSCs) are considered to be a potential therapeutic agent for the treatment of cirrhosis because of their potential to differentiate into hepatocytes, their immune-modulatory properties and their ability to secrete

trophic factors. Nevertheless, several issues, including the fibrogenic potential of MSCs and their ability to promote pre-existing tumor cell growth, must be carefully considered.

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INTRODUCTION

Cirrhosis is the end stage of chronic liver disease, which may lead to severe hepatic dysfunction and even life-threatening conditions. Currently, liver transplantation is the only curative remedy for end-stage cirrhosis^[1], but this treatment is associated with many problems, such as donor shortage, surgical complications, immunological rejection and high medical costs. In 2000, Theise *et al.*^[2] reported that Y chromosome-positive hepatocytes were observed in autopsied women who had received therapeutic bone marrow transplantations from male donors, which implies the existence of pluripotent stem cells among bone marrow cells. Since then, attention has been focused on bone marrow cells as a cell source for liver regenerative therapies^[3-9]. As of December 16, 2014, more than 216 clinical trials had been registered or were in proof when ClinicalTrials.gov was searched for the terms "stem cells AND liver diseases". Bone marrow contains both hematopoietic stem cells (HSCs) and mesenchymal stem cells (MSCs), which can differentiate into hepatocyte-like cells both *in vitro* and *in vivo*. Recently, MSCs have also been isolated from adipose tissue, umbilical cord blood, peripheral blood, brain, lung, liver, dermis, and skeletal muscle^[10-15]. This paper summarizes the clinical studies that have used unsorted bone marrow cells (BMCs), HSCs and MSCs in patients with liver failure or cirrhosis and presents the potential therapeutic mechanisms proposed for these cell types.

CELL THERAPY FOR CIRRHOSIS

Cell therapies for liver disease can be broadly classified into bio-artificial liver devices that contain hepatocytes or the direct infusion of cells. Bio-artificial liver devices have been used in patients with acute liver failure. Regarding direct infusion, cells such as primary hepatocytes, BMCs, HSCs and MSCs have all been used. Of these cell types, the transplantation of hepatocytes has been shown to be unsuitable because human hepatocytes are difficult to obtain and because it is difficult to maintain their viability and function when they are cryo-preserved or cultured *in vitro*.

Therefore, bone marrow-derived cells (*i.e.*, BMCs, HSCs and MSCs) appear to be viable alternatives. Because stem cells present among BMCs are known to differentiate into hepatocytes, clinical studies have used both unsorted BMCs and stem cells (*i.e.*, HSCs and MSCs) isolated from BMCs.

Unsorted autologous BMC infusion

The infusion of autologous BMCs into the hepatic artery or the peripheral veins of patients with cirrhosis has been reported to be safe and feasible. Moreover, the infusion of autologous BMCs increases the serum albumin level and improves liver function^[16-23]. Terai *et al.*^[24] reported that the infusion of BMCs repopulated the damaged liver and differentiated into albumin-producing hepatocytes in a mouse model of chronic liver injury induced by continuous administration of carbon tetrachloride (CCl₄). These authors also showed that the infusion of BMCs elevated the levels of matrix metalloproteinase (MMP)-2, MMP-9 and MMP-14, reduced liver fibrosis and improved the survival rate^[25-28]. Currently, MMPs are considered beneficial factors associated with a reduction in liver fibrosis, and several reports have indicated that adenoviral delivery of MMPs into the liver ameliorates experimental cirrhosis^[29-31]. However, the therapeutic mechanism of BMC infusion remains controversial. Several studies have suggested that hematopoietic cells among BMCs may generate hepatocyte-like cells, whereas others have hypothesized that they act primarily by fusion with hepatocytes or through a paracrine effect^[32-35]. To generate a greater beneficial effect of BMC infusion, granulocyte-colony-stimulating factor (G-CSF) has been used to mobilize BMCs (monitored by the number of CD34⁺ cells) into the peripheral blood^[36].

HSC transplantation

HSCs can be isolated from the bone marrow or peripheral blood after the administration of G-CSF, which induces the mobilization of CD34⁺ cells into the peripheral blood. HSCs express hematopoietic markers^[37-39], such as c-kit, Sca-1, Thy-1, CD34, CD45 and CD133, and can differentiate into hepatocytes. Gordon and colleagues reported that the infusion of CD34⁺ cells isolated from the peripheral blood after the administration of G-CSF *via* the hepatic artery or portal vein improves the level of serum albumin^[40]. Moreover, Pai *et al.*^[41] reported that the autologous infusion of expanded mobilized CD34⁺ cells improves the level of serum albumin and the Child-Pugh score. However, the therapeutic mechanism by which HSC infusion ameliorates liver damage remains unclear, although some authors have proposed that infused HSCs can differentiate into hepatocytes through cell fusion or through a paracrine effect^[32-35].

MSC transplantation

More recently, clinical studies using bone marrow-

derived MSCs have been conducted. MSCs have several advantages over other cell types, such as their relatively simple acquisition and strong proliferative capacity. Moreover, a sufficient number of MSCs required for clinical trials may be expanded *ex vivo*, without a loss of differentiation or proliferation potential, and then cryo-preserved until needed. Therefore, MSCs can be injected repeatedly without a concomitant loss of their viability and function. In one study, autologous bone marrow-derived MSCs were infused through the peripheral veins of 4 patients with decompensated cirrhosis. No side effects were observed, and the Mayo End-Stage Liver Disease (MELD) score was improved in half of the patients. Furthermore, the quality of life for all four patients improved by the end of the follow-up period^[42]. Kharaziha *et al.*^[43] also reported improved liver function in patients with cirrhosis who were injected with autologous MSCs *via* the peripheral or portal veins. In another study, Jang *et al.*^[44] demonstrated the beneficial effects of transplanting autologous bone marrow MSCs for the treatment of alcoholic cirrhosis. MSCs (5×10^7 cells) were injected into the hepatic artery twice at weeks 4 and 8. According to the Laennec fibrosis system, histological improvement was observed in 6 of the 11 patients (54.5%).

We conducted a systematic review to evaluate the safety, feasibility and effects of MSC therapy in patients with liver disease and to explore possible future directions (Table 1). We searched the OVID-Medline, EMBASE and Cochrane library databases for studies published through November 2014 to identify studies in which MSC therapy was administered to patients with liver disease. The main search strategy combined the terms that indicated MSC and liver disease. The methodological quality of the studies was assessed with the SIGN (Scottish Intercollegiate Guidelines Network) checklist. Two authors independently extracted the studies with predefined data fields and included indicators of study quality. Of the 568 studies identified, 14 were eligible for inclusion. These studies evaluated a mean sample size of 32 patients and a mean follow-up of 11.6 mo. The publication year of the studies ranged from 2007 to 2014. The majority of the study designs were small single-cohort studies, clinical trials, or case control studies. Overall, the study quality was moderate or poor. Most of the studies used bone marrow-derived MSCs, and 3 used umbilical cord-derived cells. The majority of the studies used the peripheral route, two used the hepatic artery, one used the portal vein, and one used the intrasplenic route for cell delivery. One study compared the administration of cells by intrasplenic injection and by peripheral administration, whereas another investigation compared the intrasplenic and intrahepatic administration of cells. Although marked heterogeneity was observed among studies with respect to the injection dose, cell source, delivery route and study design, MSC therapy was shown

to be safe and feasible. The majority of analyzed studies demonstrated improved liver function, which was measured by biochemical outcome, changes in liver function or associated prognostic indicators. The bilirubin, albumin, aspartate aminotransferase [AST, serum glutamic oxaloacetic transaminase (SGOT)], alanine aminotransferase [ALT, serum glutamic pyruvic transaminase (SGPT)], MELD, Child-Pugh and histological scores (Laennec system) demonstrated a statistically significant improvement in 9/10, 11/11, 7/8, 9/9, 8/8, 4/4 and 1/1 studies, respectively. Additionally, critical adverse events or complications were not observed in any of the studies. Hence, although MSC therapy is a much-needed possibility for treating liver disease, further robust clinical trials and evidence regarding the preferred source of cells, dose and route of delivery are required.

POSSIBLE THERAPEUTIC MECHANISMS OF BMCS, HSCS AND MSCS FOR CIRRHOSIS

Although cell therapy for cirrhosis has demonstrated that BMCs, HSCs and MSCs can improve liver function and deliver beneficial effects in terms of liver regeneration, the therapeutic mechanisms responsible for these effects are still far from being fully characterized. Several mechanisms by which these cells might contribute to liver regeneration have been proposed, including their differentiation into hepatocytes, their fusion with endogenous hepatocytes and a proliferative paracrine effect on hepatocytes^[32,34,45-47].

Unsorted autologous BMCs

Teraï *et al.*^[46] demonstrated that BMCs could differentiate into albumin-producing hepatocytes in a mouse model of chronic liver injury. These authors also showed that the infusion of BMCs caused an elevation in the levels of MMP-2, MMP-9 and MMP-14, which was associated with reduced liver fibrosis^[25,26]. Furthermore, MSCs present among cultured BMCs may represent candidates for treating cirrhosis^[17]. However, Thomas *et al.*^[48] reported that macrophages among BMCs were beneficial for repairing cirrhosis. Indeed, macrophages, cells of hematopoietic origin, are known to play a critical role in the regulation of liver fibrosis in murine models^[48,49]. Furthermore, the intravenous administration of autologous BMCs caused hepatic homing of the injected cells, which suggests that this easy, safe route may represent an adequate option for BMC infusion in patients with cirrhosis^[25,50].

HSCs

Although HSCs can differentiate into hepatocyte-like cells under specified culture conditions *in vitro* or in animals with liver injury^[24,51-54], controversy still exists concerning the therapeutic mechanisms by

Table 1 Summary of the clinical studies that have used mesenchymal stem cells in patients with cirrhosis

Ref.	Publication year	Country	Study design	Mean age (yr) range (mean ± SD)	Sample size	Follow-up (mo)	Cell source	Injection route	Dose (cells/kg)	Main outcome	Side effects or complications
Amin <i>et al</i> ^[83]	2013	Egypt	Cohort	42-60 (51.3 ± 6.2)	n = 20 (M:F = 14:6)	6	Bone marrow	Intrasplenic	A mean of 10 × 10 ⁶	I	None
Jang <i>et al</i> ^[44]	2014	South Korea	Clinical trials	37-60 (50 ± 8)	n = 11 (M:F = 10:1)	45	Bone marrow	Hepatic artery	5 × 10 ⁶	I	None
Kharazmiha <i>et al</i> ^[43]	2009	Sweden	Cohort	38-67 (55.63)	n = 8 (M:F = 4:4)	6	Bone marrow	Portal vein (n = 6) or Peripheal vein (n = 2)	3 × 10 ⁷ -5 × 10 ⁷	I	None
Mohamadnejad <i>et al</i> ^[84]	2013	Iran	RCT	MSC 43.1 ± 17.6 Placebo 34.6 ± 13.8	n = 25 (M:F = 13:12) MSC (n = 14) Placebo (n = 11)	12	Bone marrow	Peripheal vein	Median of 1.95 × 10 ⁸ (range: 1.2-2.95)	I	None
Mohamadnejad <i>et al</i> ^[42]	2007	Iran	Case series	34-56 (47.3)	n = 4 (M:F = 1:3)	12	Bone marrow	Peripheal vein	(5.2 ± 0.63) × 10 ⁹	I	None
Salama <i>et al</i> ^[85]	2014	Egypt	RCT	(1) MSC 50.27 ± 6.05 (2) Control 50.9 ± 7.23	n = 40 (M:F = 33:7) (1) MSC (n = 20) (2) Control (n = 20)	6	Bone marrow	Peripheal vein	1 × 10 ⁶	I	None
Wang <i>et al</i> ^[86]	2013	China	Clinical trial	33-58 (40)	n = 7 (M:F=1:6)	12	Umbilical cord	Peripheal vein	0.5 × 10 ⁶	NR	None
Zhang <i>et al</i> ^[87]	2012	China	Case control	(1) MSC: 48 (2) Control: 47	n = 45 (M:F = 40:5) (1) MSC (n = 30) (2) Control (n = 15)	12	Umbilical cord	Peripheal vein	0.5 × 10 ⁶	I	None
Wang <i>et al</i> ^[88]	2014	China	Cohort	30-60 (50)	n = 10 (M:F=1:9)	12	Bone marrow	Peripheal vein		I	None
EL-Ansary <i>et al</i> ^[89]	2010	Egypt	RCT	Intrasplenic 48.50 ± 11.09 Peripheal 50.83 ± 6.88	n = 12 (M:F = 8:4) intrasplenic (n = 6) peripheal (n = 6)	6	Bone marrow	Intrasplenic Peripheal vein	1 × 10 ⁶ /5 mL	I	None
Shi <i>et al</i> ^[90]	2012	China	Case control	(1) MSC 24-59 (2) Control 26-62	n = 43 (M:F = 35:8) MSC (n = 24) Control (n = 21)	18	Umbilical cord	Peripheal vein	0.5 × 10 ⁶	I	None
Peng <i>et al</i> ^[91]	2011	China	Case control	MSC 42.19 ± 10.80 Control 42.22 ± 11.37	n = 158 (M:F=149:9) MSC (n = 53) Control (n = 105)	45 (195 wk)	Bone marrow	Hepatic artery	3.4 × 10 ⁶ -3.8 × 10 ⁸	I	None
El-Ansary <i>et al</i> ^[92]	2012	Egypt	Case control	MSC 48.0 ± 7.4 Control 51.6 ± 7.2	n = 25 (M:F=19:6) MSC (n = 15) Control (n = 10)	6	Bone marrow	Peripheal vein	1 × 10 ⁶	I	None
Amer <i>et al</i> ^[23]	2011	Egypt	RCT	MSC 50.5 ± 4.1 Control (45-55) ± 3.6	n = 40 (M:F=33:7) MSC (n = 20) Control (n = 20)	6	Bone marrow	1) Intrasplenic 2) Intrahepatic	2 × 10 ⁷	I	None

I: Improved; NR: Not reported; None: Not observed.

which HSCs contribute to hepatocyte regeneration or liver repair. Some authors have proposed that conversion to hepatocytes may occur *via* cell fusion *in vivo*^[32,33,55]. Other possible explanations for target organ regeneration and improvements in function include the activation of endogenous hepatic progenitor cells and the release of vascular endothelial growth factor (VEGF), which would increase the blood supply to the cells and aid in the repair of the damaged tissue^[33,56]. It has also been suggested that HSCs may act in a regenerative capacity simply through upregulating the expression of the B-cell leukemia/lymphoma-2 gene (*Bcl-2*), which would

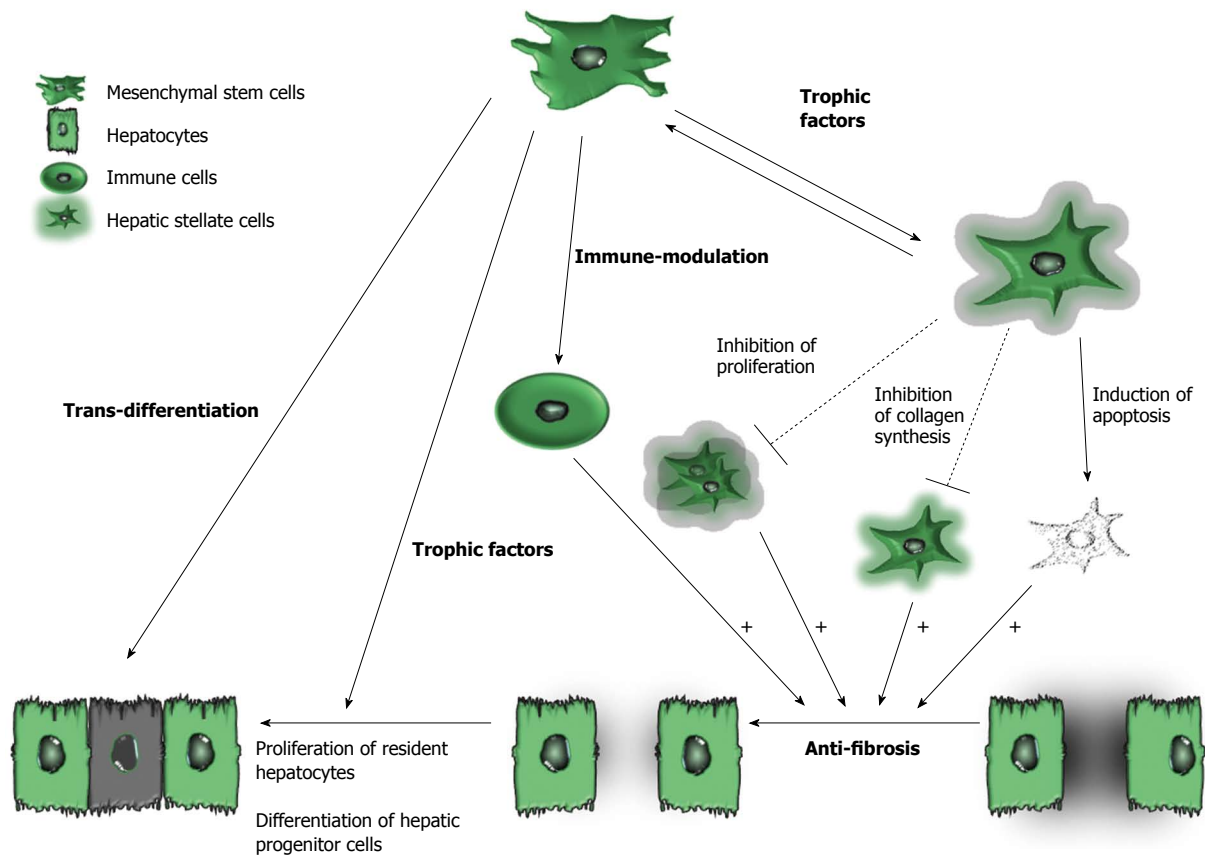


Figure 1 Potential role of mesenchymal stem cells in cirrhosis. Potential protective mechanisms of mesenchymal stem cells (MSCs) include the following: (1) trans-differentiation into hepatocyte-like cells; (2) suppression of immune reactions; (3) secretion of trophic factors to suppress activated hepatic stellate cells and to increase the proliferation of both resident hepatocytes and hepatic progenitor cells; and (4) anti-fibrotic action that results from the regulation of activated hepatic stellate cells and immune cells. Solid lines and dashed lines indicate stimulatory and inhibitory modifications, respectively. The + sign represents tentative stimulatory effects. The shadows represent extracellular matrix (ECM) that is secreted from hepatic stellate cells.

suppress apoptosis^[57,58], and downregulating immune responses in the diseased organ *via* the interleukin-6 (IL-6) pathway^[59].

MSCs

Recently, several studies have emphasized the critical importance of cell types other than hepatocytes, such as macrophages, hepatic stellate cells and lymphocytes, in the regulation of liver regeneration^[60-62]. Moreover, unbalanced immune cell populations or infiltration of the liver by immune cells can disrupt the immune-privileged state of the liver, which may cause liver injury or fibrosis. Accumulating evidence indicates that the therapeutic mechanisms of MSC treatments are better defined than those of BMCs or HSCs in terms of liver regeneration (Figure 1). For instance, MSCs can differentiate into hepatocyte-like cells both *in vitro* and *in vivo*^[63-65] and can secrete trophic factors, including growth factors, cytokines and chemokines, which promote the regeneration of the impaired liver. Trophic factors expressed by MSCs are known not only to reduce the inflammation, apoptosis and fibrosis of damaged tissues but also to stimulate angiogenesis and tissue regeneration^[66-68]. Moreover, trophic factors [*i.e.*, IL-10, hepatocyte growth factor (HGF),

transforming growth factor-beta 3 (TGF- β 3) and tumor necrosis factor alpha (TNF- α)] secreted by MSCs inhibit the proliferation of hepatic stellate cells and decrease collagen synthesis^[69,70]. In addition, MSCs have immune-modulatory properties and are able to migrate to damaged tissues. MSCs can also express various soluble factors, such as nitric oxide (NO), prostaglandin E2 (PGE2), indoleamine 2,3-dioxygenase (IDO), IL-6, IL-10 and human leukocyte antigen G (HLA-G). These soluble factors regulate the proliferation and functions of a variety of immune cells, and they have also been shown to induce regulatory T (Treg) cells^[71]. The beneficial effects of autologous bone marrow MSC transplantation in patients with cirrhosis are listed in Table 1.

FUTURE PERSPECTIVES

For patients with cirrhosis, autologous BMCs, HSCs or MSCs may be excellent candidates for use in cell therapies to stimulate the production of functional hepatocytes that can replenish diminished liver function. However, it is uncertain whether these cells can differentiate into hepatocytes *in vivo* at a clinically useful and stable level because the trans-differentiation

of BMCs, HSCs or MSCs into hepatocytes has not been commonly observed in animal models^[72]. In addition, it is difficult to distinguish trans-differentiated hepatocytes from resident hepatocytes in patients. Nevertheless, the beneficial effects of these cells have been reported in patients with cirrhosis. Several critical issues in clinical trials require further investigation, such as the optimal cell type for infusion, the optimal therapeutic timing, the most effective number of cells, the best route of administration and the optimal period or number of injections. Before these issues can be solved, we must consider what types of cells among the bone marrow cells are primarily responsible for liver regeneration. Accumulating evidence has revealed that resident stem cells (*i.e.*, HSCs and MSCs) among the bone marrow cells may differentiate into hepatocytes and improve liver function. Of the different types of stem cells, MSCs can be easily isolated due to their plastic and adhesive properties, and they can be expanded to a sufficient cell number for clinical application without a loss of stemness. In addition, the length of survival of the engrafted cells is important to achieve a sustained efficacy. To detect the infused cells in many pre-clinical animal studies, human cells have been observed by immunohistochemical analysis using human-specific markers^[73-75]; however, for clinical translation, more sophisticated techniques will be required to identify and follow the fates of the injected cells. For instance, infused cells can be labeled with superparamagnetic iron oxide nanoparticles or reporter genes, which may allow them to be traced with advanced imaging technologies^[76-80]. Because nanoparticles or reporter genes can modify the properties of cells, biomarkers specific to the injected cells, as well as other identifiers that do not cause cell damage, must be developed, even if the development of such tools requires an extended period of time.

In addition, the transplantation of BMCs, HSCs and MSCs is considered safe and has been widely tested in clinical trials in individuals with liver diseases with encouraging results. However, the development of cell therapy for cirrhosis requires larger clinical studies to obtain meaningful insights into the safety and clinical efficacy of cell infusion^[81,82]. This is especially true in the case of MSC transplantation, for which reports on the efficacy of MSCs are controversial and are dependent on the research group; however, we expect that issues concerning the efficacy of these cells will be resolved in the near future by a large multicenter randomized clinical trial that is currently being conducted in Korea. Moreover, multicenter international clinical studies on the safety and efficacy of MSC treatments for cirrhosis can help clinicians reach a consensus regarding the treatment of liver fibrosis, which will ultimately improve the prognosis of patients.

CONCLUSION

Cell therapy with autologous BMCs, HSCs or MSCs has

been suggested as an effective strategy for patients with cirrhosis. Accumulating evidence has revealed that the potential therapeutic mechanisms of MSC treatments are better defined than those of BMCs or HSCs in terms of liver regenerative medicine. Furthermore, MSCs are considered a potential agent for treating cirrhosis because of their potential to differentiate into hepatocytes, as well as their immunomodulatory properties and their ability to secrete trophic factors. Nevertheless, several issues, including those that involve the fibrogenic potential of MSCs and their ability to promote pre-existing tumor cell growth, must be carefully considered.

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