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**Current understanding of mesenchymal stem cells in liver diseases**

Wu MC *et al*. MSCs and liver diseases

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**Abstract**

Liver diseases caused by various factors have become a significant threat to public health worldwide. Liver transplantation has been considered as the only effective treatment for end-stage liver diseases; however, it is limited by the shortage of donor organs, postoperative complications, long-term immunosuppression, and high cost of treatment. Thus, it is not available for all patients. Recently, mesenchymal stem cells (MSCs) transplantation has been extensively explored for repairing hepatic injury in various liver diseases. MSCs are multipotent adult progenitor cells originated from the embryonic mesoderm, and can be found in mesenchymal tissues including the bone marrow, umbilical cord blood, adipose tissue, liver, lung, and others. Although the precise mechanisms of MSC transplantation remain mysterious, MSCs have been demonstrated to be able to prevent the progression of liver injury and improve liver function. MSCs can self-renew by dividing, migrating to injury sites and differentiating into multiple cell types including hepatocytes. Additionally, MSCs have immune-modulatory properties and release paracrine soluble factors. Indeed, the safety and effectiveness of MSC therapy for liver diseases have been demonstrated in animals. However, pre-clinical and clinical trials are largely required to confirm its safety and efficacy before large scale clinical application. In this review, we will explore the molecular mechanisms underlying therapeutic effects of MSCs on liver diseases. We also summarize clinical advances in MSC-based therapies.

**Key Words:** Mesenchymal stem cell; Liver disease; Clinical trial; Treatment; Safety; Efficacy

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**Core Tip:** Liver diseases are major threats that endanger public health globally. Mesenchymal stem cell (MSC) transplantation has been proposed as an attractive therapeutic option for liver diseases due to their differentiation potential, immune-modulatory properties, and paracrine release. Here, we will summarize the molecular mechanisms underlying therapeutic effects of MSCs on liver diseases and clinical trials in MSC-based therapies.

**INTRODUCTION**

Mesenchymal stem cells (MSCs) can be isolated easily from a wide variety of tissues including umbilical cord blood, adipose tissue, the liver, lung, dermis, and amniotic membrane, and menstrual blood[1]. Notably, MSCs play important roles in tissue repair and regeneration because of their high potential for multipotent differentiation, capacity for self-renewal, and low immunogenicity[2]. In recent years, application of MSCs in liver diseases has attracted considerable attention. First, MSCs can self-renew and differentiate into various types of cells, including hepatocyte-like cells (HLCs), which possess similar functions of normal hepatocytes[3]. Second, MSCs have low immunogenicity and low expression of major histocompatibility complex class II and costimulatory molecules, which provides a possibility for allogeneic transplantation[4]. Third, MSCs can secrete a series of cytokines and signaling molecules, which favor injury repair and regeneration[5]. Indeed, accumulating evidence has supported that MSC transplantation is effective for the treatment of various liver diseases. Here, we will discuss the molecular mechanisms of MSCs in the treatment of liver diseases and summarize potential therapeutic efficacy of MSCs in both animal models and clinical trials.

**MECHANISMS OF MSC THERAPY FOR LIVER DISEASES**

***Differentiation capability of MSCs***

MSCs can self-renew and differentiate into various progenitors, including hepatic progenitor cells. Indeed, a variety of studies have demonstrated that MSCs could differentiate into HLCs both *in vitro* and *in vivo*[6,7]. Under appropriate conditions, in particular with specific growth factors, such as hepatocyte growth factor (HGF), epidermal growth factor (EGF), fibroblast growth factor (FGF), and oncostatin M (OSM), MSCs are able to differentiate into HLCs with a liver-specific morphology and function[8,9]. In line with these findings, Zhang *et al*[3] transplanted human umbilical cord-derived MSCs (UC-MSCs) into fibrotic livers of rats and observed improvement in transaminase, synthetase, human albumin (ALB), alpha-fetoprotein, cytokeratin 18 (CK18), and CK19, suggesting that MSCs could differentiate into HLCs *in vivo*. Furthermore, MSCs might fully differentiate into hepatocytes with liver functions, such as low-density lipoprotein uptake, glucose storage, and ammonia detoxification. However, this notion is debated. For example, differentiated MSCs could not express markers of mature hepatocytes, including hepatocyte nuclear factor 4 α and hepatocyte paraffin 1[10]. Similarly, only a small fraction of MSCs (less than 3% of the total liver mass) underwent hepatocyte trans-differentiation[11]. Collectively, MSCs-mediated therapeutic effects most likely rely on other mechanisms other than fully functional complementation from direct differentiation (Figure 1).

***MSC-mediated immunomodulation***

MSCs may modulate effector cells of innate and adaptive immune systems[12]. MSC–immune cell interaction and paracrine release may enable successful treatment of liver diseases. MSCs can regulate immune responses mediated by macrophages, dendritic cells (DCs), T cells, regulatory T cells (Tregs), B cells, and regulatory B cells (Bregs), to establish a stable and balanced microenvironment[13] (Figure 1).

**Effects of MSCs on adaptive immune response**: MSCs can inhibit T cell proliferation either by directly interacting with T cells or by secreting soluble factors, including indoleamine 2,3-dioxygenase (IDO), prostaglandin E2 (PGE2)[12], and transforming growth factor-β1 (TGF-β1)[14,15]. On one hand, MSCs induced cell-cycle arrest by downregulation of cyclin D2 and upregulation of p27kip1[16]. On the other hand, in the presence of interferon-γ, MSCs upregulated IDO, which conversed tryptophan into kynurenine, consequently depleted tryptophan, and enhanced apoptosis of T cells[17,18]. Furthermore, Ding *et al*[19] demonstrated that MSCs could secrete matrix metalloproteinases (MMP), such as MMP-2 and MMP-9, to suppress T cell activation by cleaving surface CD25. Of note, imbalance between Tregs and T helper 17 (Th17) cells might be associated with a variety of liver diseases[20]. MSCs could play an immunoregulatory role by inducing Tregs and suppressing Th17 cells[21,22]. Also, Cahill *et al*[23] observed that MSCs expressed Jagged-1, which is responsible for Tregs accumulation. Consistently, there was a significant increase in Tregs and a markable decrease in Th17 cells after MSC infusion. Moreover, compared with the control group, liver function of patients in the MSC-transplantation group was improved, partially attributed to regulation of the Treg/Th17 cell balance[24]. In addition, B cells participate in the pathogenesis of liver fibrosis. MSCs could block the proliferation of B cells by inducing cell cycle arrest at G0/G1 phase. Also, the differentiation and chemotactic cytokine production of B cells were inhibited[25].

**Effects of MSCs on innate immune response:** Macrophages exert profound effects in the pathogenesis of chronic liver injury[26]. There are two types of macrophages: M1 inflammatory and M2 anti-inflammatory. Importantly, imbalance in M1/M2 polarization could lead to hepatocyte injury and fibrosis[27]. Intriguingly, MSCs could induce conversion of M1 into M2 tissue-resident macrophages in a PGE2-dependent manner, which was mediated by signal transducer and activator of transcription 6 and mechanistic target of rapamycin signaling[28]. Furthermore, MSCs could inhibit the activation and maturation of DCs by downregulating interleukin 12 (IL-12) production[13].

***Anti-fibrotic activities of MSCs***

Liver fibrosis is characterized by an imbalance between synthesis and degradation of the extracellular matrix (ECM)[29]. When the liver is damaged, pro-fibrotic factors are secreted to promote the activation and proliferation of hepatic stellate cells (HSCs), and thus contribute to ECM deposition. How can MSCs participate in fibrosis? First, MSCs produce several molecules, such as HGF, IL-10, and tumor necrosis factor α[30], to inhibit HSC activation and collagen production. Accordingly, when MSCs were transfected with the *HGF* gene[31,32], a decrease in collagen levels and improvement in hepatocyte function were observed. Therefore, HGF-overexpressing MSCs might alleviate liver fibrosis. In addition, MSCs have the potential to reverse the fibrotic process by upregulating MMPs, such as MMP-13 and MMP-9, to degrade the ECM directly[33]. Finally, TGF-β1 is a primary mediator in liver fibrogenesis as it stimulates the synthesis but inhibits the degradation of the ECM. More importantly, TGF-β1 functions by activating drosophila mothers against decapentaplegic protein 3 (Smad3). Thus, the TGF-β/Smad signaling pathway plays a critical role in ECM accumulation and liver fibrosis progression[34]. Of note, MSC-derived milk factor globule EGF 8 (MFGE8), an anti-fibrotic protein, could reduce ECM deposition and suppress HSC activation through the TGF-β signaling pathway[35] (Figure 1).

**MSC TRANSPLANTATION IN ANIMAL MODELS OF LIVER DISEASE**

Recently, MSC transplantation has been applied in the treatment of acute liver injury (ALF), chronic liver disease, non-alcoholic fatty liver disease (NAFLD), and hepatocellular carcinoma (HCC). Notably, MSC transplantation can partially restore liver function, ameliorate symptoms, and increase survival rates. Major findings regarding MSC transplantation in animal models of liver diseases are summarized in Table 1.

***Acute liver injury***

ALF is characterized by rapid loss of function and tissue necrosis[36]. Its treatment should focus on restoration of function and prevention of disease progression. Thus, MSCs may provide functional substitution and restoration[37]. Accordingly, the therapeutic potential of MSCs in ALF has been reported in mice[38], rats[39] and monkeys[40]. For example, in a murine model of acetaminophen (APAP) induced ALF[38], intravenously transplanted human UC-MSCs significantly alleviated hepatic injury and improved survival rates. Chen *et al*[39] demonstrated that MSCs could prevent the release of liver injury biomarkers and promote the recovery of liver structure in ALF rats. Furthermore, transplantation of cocultured MSCs with hepatocytes provides better restoration of liver function, resulting in a primary decrease in aspartate aminotransferase, alanine aminotransferase (ALT), and total bilirubin (TBIL). On one hand, co-transplanted hepatocytes could provide timely support of liver functions. On the other hand, MSCs could not only reduce immune rejection of hepatocytes by the host but also improve the viability and function of hepatocytes. Similarly, in a large, non-human primate model, human UC-MSCs mitigated the progression of ALF. Guo *et al*[40] demonstrated that early peripheral infusion of human UC-MSCs could markedly improve hepatic histology, systemic homeostasis, and survival of monkeys. Mechanistically, IL-6 was critical to initiate and accelerate ALF development, while human UC-MSCs could disrupt the inflammatory cascade by inhibiting monocyte activation. Overall, in ALF, MSC transplantation might exert beneficial effects.

***Chronic liver injury***

Chronic liver diseases are attributed to tissue deterioration as a result of fibrosis or cirrhosis associated with persistent chronic inflammation. Therapies aim at inhibition of inflammation and restoration of tissue architecture[37]. The beneficial effects of MSC transplantation on chronic liver diseases have been well documented in animal models. For example, infusion of bone marrow-derived MSCs (BM-MSCs) could safely ameliorate liver fibrosis in a thioacetamide-induced cirrhotic rat model[41]. Interestingly, the collagen proportionate area and content of hepatic hydroxyproline were significantly decreased. BM-MSC administration could downregulate the TGF-β1/Smad signaling pathway. Consistently, BM-MSC transplantation obviously improved liver function[42]. Moreover, liver fibrosis progression and hepatocyte necrosis were attenuated after BM-MSC administration, partially due to paracrine action of MSCs.

***Non-alcoholic fatty liver disease***

NAFLD is characterized by abnormal lipid accumulation in hepatocytes in the absence of alcohol abuse[43]. Of note, MSCs could relieve lipid and glucose metabolism disorders. In a rat model of type 2 diabetes mellitus, MSCs alleviated insulin resistance and improved glucose homeostasis by inducing phenotypic transition of macrophages[44]. In recent years, the therapeutic potential of MSCs has been explored in NAFLD. Indeed, MSCs exhibit therapeutic effects on NAFLD by improving carbohydrate and lipid metabolism, as demonstrated by a marked decrease in glucose and lipid profile, including triglyceride, total cholesterol, and low-density lipoprotein cholesterol. Moreover, UC-MSC infusion significantly attenuated histological hepatic lesions, as evidenced by decreased lipid accumulation and hepatic steatosis. These findings were explained by upregulation of fatty acid oxidation-related genes and downregulation of lipogenesis-related genes[45]. Previously, Ezquer *et al*[46] transplanted BM-MSCs into mice that were fed a high-fat diet (HFD). Interestingly, the mice were obese, hypercholesterolemic, hyperglycemic, and insulin resistant; however, fibrosis markers and pro-inflammatory cytokines were substantially reduced. Therefore, this controversy is not related to a reversion of metabolic syndrome but to preclusion of inflammatory process. In addition, in a mouse model ofHFD-induced NAFLD, MSC transplantation relieved weight gain, expansion of subcutaneous adipose tissue, steatosis, lobular inflammation, and liver fibrosis, through suppressing the proliferation of CD4+ T lymphocytes in the spleen[47]. These findings indicated that MSCs could have clinical value in NAFLD therapy *via* immune regulation. Of note, NAFLD can stem from simple steatosis, subsequently progressing to non-alcoholic steatohepatitis (NASH). NASH presents with hepatic inflammation, fibrosis, and cirrhosis, and eventually progresses to HCC[48]. It is noteworthy that insulin resistance is a hallmark for NAFLD progression to NASH[49]. Chen *et al*[50] reported that MSC therapy improved lipid metabolism in HFD-fed rats, as reflected by substantially decreased lipid droplet accumulation in hepatocytes. Also, MSCs could reduce fasting insulin level in serum. These results indicated that MSCs have potential in preventing the development of NASH. Furthermore, MSCs could remarkably improve intracellular calcium homeostasis and endoplasmic reticulum (ER) stress *in vitro*, and the latter might be involved in the pathology of NAFLD.

***Hepatocellular carcinoma***

MSCs can rapidly respond to “damage signals” and mobilize from bone marrow or other tissues to inflammatory or fibrotic microenvironment[51]. Specific signals mediating MSCs migration mainly include pro-inflammatory growth factors and chemokines, such as insulin growth factor, HGF, FGF, and TGF-β[52]. Furthermore, CXC motif chemokine receptor type 4 (CXCR4) could regulate MSC migration from bone marrow to the liver[53]. For example, genetically modified MSCs overexpressing CXCR4 exhibited higher migratory activity towards and functional improvement of the liver, likely relying on upregulation of stromal cell-derived factor (SDF-1) (the ligand for CXCR4) that is typically present at inflammatory sites and highly expressed in an injured liver[54]. HCC can be caused by chronic liver diseases with varying degrees of chronic inflammatory fibrosis, which enable MSCs to migrate to HCC microenvironment. Garcia *et al*[55]reported that MSCs could migrate and home to HCC and fibrotic microenvironment. Also, HCC cells secreted autocrine motility factor could induce MSCs migration towards them[56]. Furthermore, HCC-released factors including IL-8, growth-regulated oncogene (GRO), and monocyte chemotactic protein-1 can enhance MSC migration after exposure to conditioned media (CM) from HCC[57]. Multipotent MSCs can block HCC progression by spurring apoptosis and inhibiting proliferation *in vitro*, as well as suppressing tumor growth and metastasis *in vivo*[58,59]. Qiao *et al*[60] suggested that CM from MSCs were able to inhibit HepG2 proliferation by downregulating nuclear factor-κB. Similarly[61], when severe combined immunodeficiency disease mice were injected with equal numbers of MSCs and H7402 human hepatoma cells, tumor formation was delayed and hepatoma growth inhibited. However, increasing evidence suggests that MSCs as a doble-bladed sword may promote HCC progression. For instance, soluble factors from MSCs could promote the proliferation and invasion of canine HCC cells[62]. In agreement with this finding, Gong *et al*[63] reported that BM-MSCs could promote microvascular formation in transplanted hepatoma area in nude mice.

**CLINICAL TRIALS USING MSCS FOR TREATMENT OF LIVER DISEASES**

Numerous clinical studies have been initiated to investigate the therapeutic potential of MSCs in the treatment of liver diseases. Main findings regarding MSC transplantation in liver diseases are summarized in Table 2.

A phase I–II clinical trial included eight patients with liver cirrhosis[64]. All patients received an injection of autologous BM-MSCs previously transdifferentiated in hepatocytes *via* the peripheral or portal vein. No severe side-effects were observed until the end of follow-up at 24 wk after transplantation, which emphasized the safety of using autologous BM-MSCs as a treatment. All patients had improved performance status and quality of life partially because of reduced volumes of ascites. Furthermore, liver function was ameliorated as verified by model for end-stage liver disease (MELD) score, prothrombin complex from international normalized ratio (INR), and serum creatinine. Four out of eight patients had significantly decreased MELD score whereas seven had normalized creatinine levels in 8 wk after treatment. In another phase I–II clinical trial, Zhang *et al*[65] randomized 45 patients with decompensated liver cirrhosis resulting from chronic hepatitis B into two groups: 30 patients received UC-MSC transfusion, and 15 received saline as controls. The patients receiving MSCs had significantly reduced volumes of ascites and levels of serum liver cirrhosis markers when compared to the control group. Importantly, UC-MSC transfusion could improve liver function, as evidenced by an increase in ALB whereas a reduction in TBIL, prothrombin time activity (PTA), or MELD-sodium (MELD-Na) score. Of note, MELD-Na score has been demonstrated as a marker for better prognosis of liver diseases. In a phase II trial, Suk *et al*[66] transplanted BM-MSCs in 48 patients with alcoholic cirrhosis. Child-Pugh scores and histologic fibrosis were improved after BM-MSC transplantation compared with 24 control patients. However, two-time injections failed to display better effects on fibrosis in comparison with one-time injection of BM-MSCs, which indicated that one-time injection of BM-MSCs might be sufficient for inducing regression of fibrosis. In general, these trials shed light on the safety and efficacy of MSCs in patients with liver cirrhosis. Similarly, several trials on end-stage liver diseases, especially acute-on-chronic liver failure (ACLF), were performed. In a phase II trial, Peng *et al*[67] transplanted autologous MSCs from iliac bone aspirates to patients with hepatitis B-related liver failure. Follow-up of patients receiving MSCs-transplantation identified a significant improvement in ALB and TBIL in 2 wk, whereas prothrombin time (PT) and MELD score in 3 wk. However, during the 192-wk follow-up, long-term outcome was not markedly improved after transplantation. Notably, no significant difference in the incidence of HCC or survival rate was observed between the cirrhosis and non-cirrhosis groups, indicating that autologous BM-MSC transplantation might be preferable for cirrhosis with regard to the development of HCC and mortality. Thus, this clinical trial proposed that BM-MSC transplantation was safe with favorable short-term efficacy in the treatment of end-stage liver diseases; however, survival rate was not markedly improved. Additionally, MSCs derived from hepatitis B patients presented impaired function as reflected by weakened proliferation, reduced activity, and fastened aging/senescence[68]. Allogeneic MSC transplantation might overcome major limitations of autologous MSC treatment. In a trial[69], allogeneic BM-MSC transplantation was employed in patients with HBV-related ACLF: 56 patients were infused weekly for 4 wk with 1-10 × 105 cells/kg allogeneic BM-MSCs while 54 patients were treated with standard medical therapy as a control group. Interestingly, allogeneic BM-MSC treatment could markedly ameliorate laboratory parameters, such as ALT, ALB, TBIL, and MELD scores. More importantly, mortality from multiple organ failure and severe infection was significantly decreased. In addition, no severe side-effects were observed until the end of follow-up at 24 wk after treatment. In another trial[70], 24 patients received 0.5 × 106 cells/kg UC-MSCs *via* the cubital vein. Those patients receiving MSC transplantation had better liver function as indicated by increased ALB and PTA levels. In particular, they exhibited a decreased MELD score and increased survival rate, inconsistent with previous finding (Peng *et al*[67]). The difference might be caused by different sources of MSCs. Compared with BM-MSCs, UC-MSCs had higher proliferation and clonality capacity[71]. Furthermore, UC-MSCs expressed lower levels of senescence markers, which made UC-MSCs more advantageous over BM-MSCs for therapy of end-stage liver diseases[72]. Based on the data, MSC therapy in the treatment of liver disease is limited by the quality of MSCs and therapeutic strategies. Although these results demonstrated that MSC transfusion is safe and may serve as a novel therapy for patients with liver diseases, some limitations remain in these studies. For example, follow-up time is not long enough and larger-scale studies are needed. Overall, there are still some problems that need to be clarified about the clinical application of MSC in the future, for example, the contraindications for MSC therapy in liver disease. Of note, in clinical trials, patients with the following conditions should be excluded, including pregnant and lactating women, severe heart or lung function failure, other important organ dysfunctions, proven other malignancies, spontaneous peritonitis or concomitant infection, active gastrointestinal bleeding, and active substance abuse.

**CONCLUSION**

MSCs have emerged as a promising treatment for liver diseases due to their hepatic differentiation potential, as well as anti-fibrotic activities and immunomodulatory properties. Currently, accumulating evidence has indicated the efficacy of MSC in animals. However, many concerns remain to be addressed in clinical use of MSCs for liver diseases, including optimal timing of injection, optimal types of stem cells, the minimum number of effective cells, as well as the best route of administration. Recently, MSC-secreted exosomes have attracted attention. Exosomes are safe with controllable outcomes. Thus, this cell-free therapy may become a new therapeutic strategy for patients with liver diseases. In conclusion, using MSCs as a therapy for treating liver diseases holds great promise although requires large randomized and controlled clinical trials to confirm their safety and efficacy in the clinic.

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**Figure Legends**



**Figure 1 The mechanism of mesenchymal stem cells in liver diseases.** A: Mesenchymal stem cell (MSCs) differentiate into hepatocyte-like cells both *in vitro* and *in vivo*; B: MSCs modulate effector cells of innate and adaptive immune systems; C: MSCs alleviate liver fibrosis. MSC: Mesenchymal stem cell; UC-MSC: Human umbilical cord-derived MSC; HGF: Hepatocyte growth factor; EGF: Epidermal growth factor; FGF: Fibroblast growth factor; OSM: Oncostatin M; HLCs: Hepatocyte-like cells; ALB: Albumin; AFP: Alpha-fetoprotein; CK18: Cytokeratin 18; CK19: Cytokeratin 19; DC: Dendritic cell; M1: M1 macrophage; M2: M1 macrophage; IL-12: Interleukin 12; PGE2: Prostaglandin E2; IDO: Indoleamine 2,3-dioxygenase; MMP: Matrix metalloproteinases; TGF-β1: Transforming growth factor-β1; Th17: T helper cells 17; Treg: Regulatory T cells; HSC: Hepatic stellate cell; IL-10: Interleukin 10; TNFα: Tumor necrosis factor α; MFGE8: Milk factor globule EGF 8; ECM: Extracellular matrix.

**Table 1 Experiments using mesenchymal stem cell transplantation in animals**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Disease** | **Treatment** | **Source** | **Animal** | **Main results** | **Mechanism** | **Ref.** |
| ALF | APAP | Human UC-MSCs | Mice | Alleviate hepatic injury and improve survival rates | Mediate paracrine effects, regulate inflammatory response | Liu *et al*[38], 2014 |
| ALF | LPS | Human UC-MSCs | Monkeys | Improve the hepatic histology, systemic homeostasis, and survival | Suppress the hepatic aggregation and maturation of circulating monocytes and their IL-6 secretion | Guo *et al*[40], 2019 |
| LC | CCl4 | Human UC-MSCs | Rats | Improve liver transaminases and synthetic function, reduce liver histopathology, and reverse hepatobiliary fibrosis | Differentiate into hepatocytes | Zhang *et al*[3], 2017 |
| LC | CCl4 | Monkey BM-MSCs | Mice | Decrease liver fibrosis, progression, and hepatocyte necrosis | Mediate paracrine effects | Fu *et al*[42], 2018 |
| LC | TAA | Human BM-MSCs | Rats | Decrease collagen proportionate area and the content of hepatic hydroxyproline | Mediate TGF-β1/Smad signaling pathway | Jang *et al*[41], 2014 |
| NAFLD | HFD | MiceBM-MSCs | Mice | Decrease fibrosis markers and pro-inflammatory cytokines | Regulate inflammatory process | Ezquer *et al*[46], 2011 |
| NAFLD | HFD | MiceBM-MSCs | Mice | Decrease weight gain, expansion of subcutaneous adipose tissue, steatosis, lobular inflammation, and liver fibrosis | Suppress the proliferation of CD 4+ T cells | Wang *et al*[47], 2018 |

MSCs: Mesenchymal stem cells; AFL: Acute liver failure; LC: Liver cirrhosis; NAFLD: Non-alcoholic fatty liver disease; APAP: Acetaminophen; LPS: α-amatoxin and lipopolysaccharide; TAA: Thioacetamide; HFD: High-fat diet; BM-MSCs: Bone marrow-derived MSCs; UC-MSCs: Umbilical cord-derived MSCs.

**Table 2 Clinical trials using mesenchymal stem cells to treat liver disease**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Disease** | **Phase** | **No.** | **Stage** | **Source** | **Dose** | **Route of****delivery** | **Main results** | **Ref.** |
| LC | I–II | 8 | MELD score ≥ 10 | Autologous BM-MSCs | 30-50 million cells | Peripheral or the portal vein | Reduce volumes of ascites; improve MELD scores, INR, and serum creatinine | Kharaziha *et al*[64], 2009 |
| LC | I–II | 30 | MELD Na score approximately 14 | UC-MSCs | 0.5 × 106 cells/kg | Peripheral | Reduce volumes; improve ALB, TBIL, PTA, and MELD Na scores | Zhang *et al*[65], 2012 |
| ALC | II | 48 | Child-Pugh B/C | BM-MSCs | 5 × 107 cells/kg | Hepatic artery | Improve Child-Pugh scores and histologic fibrosis | Suk *et al*[66], 2016 |
| Liver failure | II | 53 | MELD score: CG: 29.15 ± 3.72; EG: 30.01 ± 3.99 | Autologous BM-MSCs | None | Hepatic artery | Improve ALB, TBIL, PT, and MELD scores | Peng *et al*[67], 2011 |
| ACLF | II | 56 | 17 ≤ MELD score ≤ 30 | Allogeneic BM-MSCs | 1.0-10 × 105 cells/kg | Peripheral veins | Improve ALT, ALB, TBIL, and MELD scores; decrease mortality | Lin *et al*[69], 2017 |
| ACLF | II | 24 | MELD score: CG: 26.32; EG: 24.05 | UC-MSCs | 0.5 × 106 cells/kg | Cubital vein | Improve ALB, CHE, PTA, and MELD score; increase survival rate | Shi *et al*[70], 2012 |

LC: Liver cirrhosis; ALC: Alcoholic liver cirrhosis; ACLF: Acute-on-chronic liver failure; CG: Control group; EG: Experimental group; BM-MSCs: Bone marrow-derived MSCs; UC-MSCs: Umbilical cord-derived MSCs; MELD: End-stage liver disease; ALB: Albumin; ALT: Alanine aminotransferase; TBIL: Total bilirubin; PT: Prothrombin time; PTA: Prothrombin time activity; INR: International normalized ratio; CHE: Cholinesterase.



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