Stem Cell Therapies for Chronic Liver Diseases: Progress and Challenges

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Abstract

Chronic liver diseases have become a significant health issue worldwide and urgently require the development of novel therapeutic approaches, in addition to liver transplantation. Recent clinical and preclinical studies have shown that cell-based therapeutic strategies may contribute to the improvement of chronic liver diseases and offer new therapeutic options to restore liver function through their roles in tissue impairment and immunomodulation. In this review, we summarize the current progress and analyze the challenges for different types of cell therapies used in the treatment of chronic liver diseases currently explored in clinical trials and preclinical studies in animal models. We also discuss some critical issues regarding the use of mesenchymal stem cells (MSCs, the most extensive cell source of stem cells), including therapeutic dosage, transfusion routine, and pharmacokinetics/pharmacodynamics (PK/PD) of transfused MSCs.

Key words: chronic liver disease; cell therapy; stem cells; mesenchymal stem cell; clinical trial

Graphical Abstract
Introduction
Liver diseases are a serious threat to human health. It is estimated that up to 800 million people have been affected by chronic liver diseases worldwide, including more than 300 million in China.1,3 Besides viral hepatitis, other common causes of chronic liver disease are obesity, metabolic-associated fatty liver disease, alcoholic liver disease, autoimmune liver disease (primary biliary cholangitis, autoimmune hepatitis, and primary sclerosing cholangitis), genetics, and other metabolic diseases.4,6 End-stage liver diseases, including decompensated cirrhosis and liver failure, are characterized by portal hypertension and severely impaired liver function, with a series of complications such as ascites, spontaneous peritonitis, coagulation dysfunction, gastrointestinal bleeding, hepatic encephalopathy, and hepatorenal syndrome.7,8 The one-year mortality rate of liver cirrhosis was estimated to be 57%,9 causing 1.32 million deaths worldwide in 2017, accounting for 2.4% of mortalities in the world.5,10 Chronic liver diseases, including decompensated cirrhosis, can develop into acute-on-chronic liver failure, with a further significant increase in mortality (33% at 28 days; 50% at 90 days).11

Current treatments for decompensated cirrhosis or liver failure are still limited, and liver transplantation remains the only available approach to improve survival but is restricted by a shortage of organ resources, rejection after transplantation, and heavy financial costs.12,13 In the past decade, a series of new applications based on cell therapy, including stem cell infusion, hepatocyte transplantation, in vitro artificial liver, and implantation of tissue-engineered organs have been studied as an alternative interventional method for chronic liver diseases. A series of preclinical and clinical studies on cell therapy have shown promising data. However, several gaps remain in the clinical application of MSC treatment for chronic liver diseases. This review focuses on cell therapy for severe liver diseases, summarizes the current progress, and discusses the challenges and unmet issues in this field.

Types of Cells Used for the Treatment of Chronic Liver Diseases
Recently, cell-based therapies, particularly stem cell therapy, are receiving increasing attention. Stem cells and adult liver-originated hepatocytes are often the main cell sources, and they include a type of cell with potential properties of self-renewal and multi-directional differentiation. They can be classified as totipotent, multipotent, and specialized stem cells. They can develop into a complete living organism, various kinds of tissues, and human organs or cells of a certain lineage, under specific conditions. In recent years, with the progress of regenerative medicine and basic research on stem cells, an increasing number of preclinical and clinical studies have been conducted using different types of stem cells,14 as shown in Table 1.

Mesenchymal Stem Cells (MSCs)
Mesenchymal stem cells (MSCs) are pluripotent stem cells derived from the mesoderm and can be isolated or prepared from the bone marrow, umbilical cord, fat, pulp, placenta, endometrial tissue, limbus, and amniotic membrane. In the 1960s, Freidenstein et al discovered a group of colony-forming unit-fibroblast cells from bone marrow that can adhere and grow in vitro, with similar morphology to fibroblasts.15,16 Later, these types of cells with the ability of bone and cartilage differentiation were named mesenchymal stem cells, and this name has been widely used17 since then. Properties of MSCs include multi-directional differentiation, immunomodulatory and pro-angiogenic effects, and secretion of various types of growth factors, cytokines, and regulators through paracrine signaling and other pathways, while generally not causing host immune responses due to their low immunogenicity.18,19 Therefore, after being first used in clinical trials for hematological diseases in 1995, approximately a thousand clinical trials have been carried out with MSCs around the world to explore new ways to treat various refractory diseases. At present, MSCs that function as a type of cell-based drug have been approved for the treatment of graft-versus-host disease (GVHD), Crohn’s disease complicated with anal fistula, spinal cord injury, limb ischemia, amyotrophic lateral sclerosis, and other illnesses in the European Union, Canada, South Korea, and Japan.

Table 1. Cell-infusion clinical studies of liver diseases, based on cell-type.

| Cell type   | Research phase             | Advantages or limitations                                                                 |
|-------------|----------------------------|------------------------------------------------------------------------------------------|
| MSCs        | Human study (Phase I and II trials) | • No ethical restriction.                                                                  |
|             |                            | • Easy expansion.                                                                         |
|             |                            | • Immune regulation, anti-fibrosis, regeneration.                                         |
|             |                            | • Most clinical research evidence.                                                        |
| ESCs        | Preclinical study          | • Ethical concern.                                                                       |
|             |                            | • Risk of tumorigenicity and immune rejection.                                            |
| iPSCs       | Preclinical study          | • Tumorigenicity                                                                         |
|             |                            | • Immunogenicity                                                                         |
| BTSCs       | Human study (Case report)  | • Multipotent stem cells.                                                                 |
|             |                            | • Differentiate into hepatocytes and biliary epithelial cells.                            |
|             |                            | • Limited source.                                                                        |
| Hepatocyte  | Human study (Small sample size, randomized controlled trial) | • Limited cell source from liver donor.                                                  |
|             |                            | • Difficult to expand.                                                                   |
|             |                            | • Difficult to cryopreserve.                                                             |
|             |                            | • Immune rejection.                                                                      |

Abbreviations: MSCs, mesenchymal stem cells; ESCs, embryonic stem cells; iPSCs, Induced pluripotent stem cells; BTSCs, biliary tree stem cells; HSCs, hematopoietic stem cells.
Human Embryonic Stem Cells (hESCs)

Human embryonic stem cells (hESCs) are pluripotent stem cells from the blastocyst stage of the cell population in the embryo, with unlimited potential for self-proliferation and differentiation into different cell types in vitro.28 hESCs have recently been used in the treatment of many diseases through their induction into a certain spectrum of stem cells in vitro, and hESC-derived cells are commonly used in clinical trials for the treatment of subacute spinal cord injury, age-related macular degeneration, type 1 diabetes, Parkinson's disease, retinitis pigmentosa, amyotrophic lateral sclerosis, type 1 citrullinemia, and intrauterine adhesions.21,22 For the treatment of liver disease, hESCs have been induced to differentiate into hepatocyte-like cells with the characteristics of mature hepatocytes in vitro.23 The induction of hESCs into hepatocytes and bile duct cells led to the formation of organoids, which shows promise for the construction of liver disease models and the exploration of new therapeutic approaches for liver diseases.24,25 However, due to the ethical and legal issues concerning the source of hESCs, together with the risk of tumorigenicity and immune rejection after cell infusion, there have been no clinical trials involving hESCs for the treatment of chronic liver diseases.

Induced Pluripotent Stem Cells (iPSCs)

Induced pluripotent stem cells (iPSCs) can be derived from various adult somatic cells in vitro through reverse differentiation via a reprogramming technique first reported in 2007.29,30 They present a pluripotent ability similar to that of hESCs. Since first described, the reprogramming technique has been widely used in disease modeling, drug screening, tissue engineering, and new therapeutic strategies for the treatment of illnesses.27,28 Such as Parkinson's disease, macular degeneration, retinitis pigmentosa, spinal cord injury, platelet transfusion, GVHD, and cartilage defects.22 iPSCs can be induced into human hepatocytes that resemble normal-functioning hepatocytes. In an animal model of liver injury, iPSCs were reprogrammed into hepatocyte-like cells and the survival rate of mice with acute liver failure.28 iPSCs-derived hepatocyte-like cells have also been used in the development of disease models such as fatty liver disease and ornithine transcarboxylase deficiency.29,30 Bloor et al performed a dose-escalation phase I trial to evaluate the safety and efficacy of iPSC-derived cells by using human peripheral blood monocyte-derived iPSCs for the treatment of steroid-resistant GVHD.31 However, considering their tumorigenicity and immunogenicity, the safety and efficacy of iPSCs need to be thoroughly evaluated before clinical application.32 Thus, there have been no clinical trials on iPSCs for the treatment of chronic liver diseases.

Notably, Taniguchi's team first developed the human liver bud including endothelial cells,33 later generated human iPSCs-derived liver organoids that were successfully transplanted into infantile piglets through the portal vein with a good safety.34 The preclinical data demonstrated that transplantation of human liver organoids may present a promising therapeutic strategy in the treatment of severe chronic liver diseases; however, the safety and efficacy of transplantation of human liver organoids need to be confirmed in the future clinical trials.

Biliary Tree Stem Cells (BTSCs)

Biliary tree stem cells (BTSCs) are multipotent stem cells located in both extramural peribiliary glands tethered to the exterior surface of bile ducts and intramural peribiliary glands within bile duct walls or in the villi base of the gallbladder. BTSCs express endoderm-specific transcription factors and early surface molecular markers of stem cells.35 BTSCs have the capacity to differentiate into functional liver cells, bile duct, and pancreatic endocrine glands, and play an important role in the development, maturation, and organ regeneration and maintenance of the liver, pancreas, and gallbladder.36 In animal models of drug-induced liver injury, a transfusion of BTSCs was found to promote the repair and regeneration of the injured liver.37 In a clinical trial, Vincenzo et al found that BTSCs could improve the model for end-stage liver disease (MELD) scores, quality of life, and prolong the survival time in patients with decompensated cirrhosis, without significant post-transplant rejection.38 However, there is an ethical concern that limits their clinical application, as the main source of BTSCs is the fetal biliary tree. Thus, they are not extensively used in clinical trials.

Human Hepatocytes

Human hepatocytes from adult donors have been utilized in various attempts to treat liver diseases39 since Mito et al first performed hepatocyte transplantation in a patient with metabolic liver disease in 1992.40 Transplanted hepatocytes were usually prepared from donor livers that were not suitable for transplantation. However, many factors, including inadequate liver supply, varying quality, immunogenicity, the impaired proliferative ability of hepatocytes, inefficient cell migration, and limited space within a severely pathological liver limit the applications of hepatocyte transplant.31 Hepatocytes are usually more suitable for the treatment of inherited metabolic diseases, such as Wilson’s disease, familial cholestasis, and phenylketonuria. Fox et al found that a pre-treatment of irradiating the host liver could improve the engraftment efficiency of transplanted hepatocytes in an animal model, indicating that pre-treatment radiation was safe and could improve the engraftment of transplanted hepatocytes and the long-term survival of patients.41 In addition, trans-differentiation strategy was developed to generate functional hepatocyte-like cells (iHep) from mature cells, which may, in part, solve the limitation of insufficient human primary hepatocytes for the purpose of cell therapy. Two teams reported that transplantation of iHep cells could rescue mice with liver failure respectively in preclinical studies.42,43 Because transplantation of human hepatocytes is with some disadvantages that significantly limit their clinical application, therefore, it is necessary to develop new sources for functional hepatic cell supply or other novel therapeutic approaches in the treatment of severe chronic liver diseases.44

Clinical Trials and Rationale of MSC Therapy for Chronic Liver Diseases

Mesenchymal stem cells (MSCs) are the most commonly used cell source in clinical studies of cell therapy for liver diseases. By searching for “mesenchymal stem cell OR mesenchymal stromal cell AND liver [Title]” on PubMed, 1290 publications were retrieved (year distribution shown in Fig. 1A). Similarly, a search of “mesenchymal stem cell and liver diseases” shows that 63 clinical trials have been registered on ClinicalTrials.gov up to 29 April 2022 (Fig. 1B, 1C).
It has been reported that the MELD score, prothrombin time, serum albumin, and total bilirubin were improved in patients with liver cirrhosis or liver failure when they received an MSC infusion. Suk KT et al conducted a multicenter, open-label, phase II clinical trial to evaluate the treatment of alcoholic liver cirrhosis with autologous bone marrow-derived MSCs. A total of 72 patients were randomized into 3 groups, namely, control group, single-infusion group, or double-infusion group. The primary endpoint was the improvement of the fibrosis score, and the secondary endpoints were liver function, Child-Pugh score, and MELD score. Compared to the control group, MSCs significantly improved the fibrosis score and Child-Pugh score at week 24, but there was no significant difference between the single-infusion and double-infusion groups. There was also no significant difference in adverse events among the 3 groups, indicating that MSC infusion is safe and well-tolerated in alcoholic liver cirrhosis patients.

Figure 1. A summary of MSCs studies of liver diseases. A. Number of published papers associated with studies on mesenchymal stem cells or mesenchymal stromal cells in liver diseases. These data were obtained on 29 April 2022 (Total = 1290). B. Country and regional distribution of 63 clinical trials registered on ClinicalTrials.gov. C. Country and regional distribution of 22 completed clinical trials shown in Table 2. D. Dosage of MSCs for peripheral intravenous infusion in 14 completed clinical trials shown in Table 2. E. MSC-therapy cell infusion route of 22 completed clinical trials shown in Table 2.
that treatment with MSCs could improve the patients’ liver function, increase hepatic functional reserve, reduce post-transplant rejection and complications, and improve quality of life and survival time. In a 75-month follow-up study of 219 cirrhotic patients who had received an MSC infusion, we found that MSCs could significantly improve patient survival and liver function without increasing tumor incidence and other adverse events. However, some studies have also found that MSC infusion did not improve liver function. The inconsistency in these conclusions may be caused by the varying inclusion and exclusion criteria, endpoints, and sources of MSCs, as well as the small sample size in the majority of trials. In Table 2 and Fig. 1D, we have summarized 22 reported MSC clinical trials for liver cirrhosis and liver failure (11 studies had not been registered on ClinicalTrials.gov).

The rationale for MSC therapy for chronic liver diseases is as follows: (1) owing to the differentiation and regenerative properties of MSCs, they can be stimulated to differentiate into hepatocytes in vitro. MSCs can also replenish and repair a pathological liver in an animal model; (2) MSCs exert a range of immunomodulatory effects and regulate innate and adaptive differentiation in vivo including natural killer cells, Kupffer cells, macrophages, dendritic cells, helper T cells, regulatory T cells, and B cells, via direct contact or paracrine signaling to reduce hepatic inflammation and improve host tissue impairment. (3) MSCs can play a role in improving the hepatic microenvironment and anti-fibrosis. For example, MSCs can secrete interleukin 10 and tumor necrosis factor, which inhibit the activation of hepatic stellate cells (HSCs) and simultaneously induce HSCs apoptosis through the Fas-FasL pathways, but they can also induce the regeneration of liver stem cells via hepatocyte growth factor. MSCs can also induce immune cells to produce or directly secrete matrix metalloproteinases for degradation of the extracellular matrix. Ferroptosis is a new form of non-apoptotic cell death that plays a role in the progression of liver diseases. MSCs protect the liver and inhibit the ferroptotic process of hepatocytes through the decrease of intracellular reactive oxygen species (ROS) and Fe levels. Additionally, Li et al demonstrated that bone marrow MSCs were able to prolong the survival time for fulminant liver failure in a porcine model by blocking the cytokine storm. During the COVID-19 pandemic (early 2020), a series of clinical trials were conducted to evaluate the efficiency of MSC therapy for patients with severe COVID-19. Some trials demonstrated that an MSC transfusion could reduce pulmonary inflammation and lesion, improve the convalescence of severe patients, and shorten the length of hospitalization time. In a multicenter, randomized, double-blind, placebo-controlled trial of 101 patients, we found that MSCs accelerated the restoration of lung lesions and had alleviated pulmonary fibrosis at a one-year follow-up visit. These findings are consistent with the anti-fibrotic properties of MSCs.

### Facing Challenges in MSC Therapy

The treatment of chronic liver diseases with MSCs has yielded some promising findings, but some critical issues in the current protocols remain to be addressed in future studies, including study design, the dosage of transfused MSCs, infusion route of MSCs, and pharmacokinetics and pharmacodynamics (PK/PD) of transfused MSCs in vivo.

### Dosage of MSCs

The dosage of MSCs used clinically is a critical issue. Appropriate cell dosage should be carefully determined in the study design based on the source of the cells, patient indication, transfusion time, and infusion route. Phase I clinical studies are often initiated to establish the optimal cell dosages for different indications and infusion routes. Of these, the dose of MSCs administered by peripheral intravenous infusion generally ranges from $5 \times 10^5$ to $1 \times 10^6$ cells/kg. In a phase I trial of MSC treatment in acute respiratory distress syndrome (ARDS) patients, the low-, medium-, and high-dose groups were $1 \times 10^6$ cells/kg, $5 \times 10^6$ cells/kg, and $1 \times 10^7$ cells/kg, respectively. No infusion-related adverse events were observed in the high-dose group, suggesting that a dose of $1 \times 10^7$ cells/kg is safe for ARDS patients. As for the treatment of liver diseases, in a dose-escalation study of stem cells, which included a total of 20 patients with decompensated cirrhosis, no adverse events related to cell infusion were observed after 3 rounds of intravenous infusion of umbilical cord stem cells at the highest dose of $2 \times 10^6$ cells/time. However, the optimal dose for each clinical trial needs to be explored according to the different stages of the disease and administration routine. Figure 2 shows the intravenous infusion dosage used in 14 different clinical studies.

### Efficiency and Infusion Route of MSCs

Although unmanipulated, conventional MSCs have been the most widely used in therapeutic studies, extensive efforts have been made to improve the safety and efficiency of MSC transusions. Some of these strategies, including sorting MSCs to be enriched for stronger functionality, priming MSCs with cytokines, and genetic modification of MSCs, have been developed to enhance the MSCs immunomodulatory potential and/or their homing when they migrate into the target organ with inflammation and loss. MSCs, a heterogeneous population of cells, can be classified into several subgroups. Therefore, pacified and enriched MSCs with selected markers may be more suitable for special conditions than conventional MSCs. For example, MSCs capabilities of chemotaxis, anti-aging, and differentiation could be improved after MSC identification via CD146, CD73, CD271, and CD200. Furthermore, after coculture with interferon-$\gamma$, interleukin-7, and transforming growth factor, the effector cytokines produced by MSCs were increased and their modulation role on immune cells, as well as chemotaxis and proliferative ability, were strengthened. The gene-editing technique has also been applied to specifically upregulate or silence certain genes (insulin growth factor-like-1, CXCR4, Let7a, etc.) that could result in gene-modified MSCs with stronger anti-fibrotic, immunomodulatory, chemotaxis, anti-apoptotic, differentiated regenerative abilities, and organ-restoration functions. Although purification methods and gene editing are feasible for MSCs in preclinical studies, there is still a long way to go in terms of cell stability, safety, and compliance with drug-related production specifications. Therefore, the challenge is to balance additional costs and potential logistical/safety concerns.

Different infusion routes may affect the efficacy of MSC treatment. Intravenous infusion is the most common route of MSC administration. Other routes include the hepatic artery, portal vein, and intrahepatic or intra-splenic (Fig. 3) transfusion of MSCs. However, given the differences in the enrolled...
| Country                  | Author registration number | Years         | Type of study design timing of follow-up visit at endpoint | Liver disease Sample size | Cell source                       | Cell dose/each transfusion | Times of infusions | Interval | Infusion route | Endpoints                          | Major improvements                           |
|-------------------------|----------------------------|---------------|------------------------------------------------------------|---------------------------|----------------------------------|---------------------------|---------------------|----------|---------------|-----------------------------------|---------------------------------------------|
| Iran                    | Mohamadnejad et al50       | 2007          | Case series 12 months                                       | Decompensated liver cirrhosis \(n = 4\) | Autologous bone marrow MSC       | \(3.173 \times 10^7\)      | 1                   | –        | Peripheral vein | Safety and feasibility          | Creatinine and MELD score                  |
| Switzerland             | Kharaziha et al62          | 2009          | Single arm 6 months                                        | Cirrhosis \(n = 8\)      | Autologous bone marrow MSC       | \(3-5 \times 10^7\)        | 1                   | –        | Portal or peripheral vein | Feasibility, safety and efficacy (LFT and MELD scores) | Creatinine, prothrombin time, and MELD score |
| Egypt                   | El-Ansary et al63          | 2010          | Case-control 6 months                                      | Decompensated liver cirrhosis \(n = 12\) | Autologous bone marrow MSC       | \(1 \times 10^7\)          | 1                   | –        | Intra-splenic or peripheral vein | LFT and MELD score improvement             | Creatinine, prothrombin time, albumin, bilirubin and MELD score |
| People’s Republic of China | Zhang et al64             | 2012          | Case-control 24 months                                     | HBV-related decompensated cirrhosis \(n = 45\) | Allogeneic umbilical cord-derived MSC | \(0.5 \times 10^5\)kg       | 3                   | Every 4 weeks | Peripheral vein | Safety and efficacy (LFT and MELD scores) | Albumin, bilirubin, MELD score and ascites |
| Egypt                   | El-Ansary et al67          | 2012          | Case-control 6 months                                      | HCV-related decompensated cirrhosis \(n = 25\) | Autologous bone marrow MSC       | \(1 \times 10^5\)kg        | 1                   | –        | Peripheral vein | Improvement in LFT and MELD scores | Albumin and MELD score                     |
| People’s Republic of China | Wang et al65             | 2013          | Single arm 12 months                                       | primary biliary cirrhosis \(n = 7\) | Allogeneic umbilical cord MSC     | \(0.5 \times 10^5\)kg       | 3                   | Every 4 weeks | Peripheral vein | Safety and efficacy               | Alkaline phosphatase and GGT               |
| Iran                    | Mohamadnejad et al69       | 2013          | Randomized controlled 12 months                            | Decompensated cirrhosis \(n = 25\) | Autologous bone marrow MSC       | \(1.20-2.95 \times 10^7\)  | 1                   | –        | Peripheral vein | Absolute change in MELD score    | No improvements                            |
| Egypt                   | Amin et al66              | 2013          | Single arm 6 months                                        | HCV related cirrhosis \(n = 20\) | Autologous bone marrow MSC       | \(1 \times 10^7\)          | 1                   | /        | Intrasplenic injection | Safety and efficacy               | Albumin, prothrombin time, bilirubin, AST, ALT, and MELD scores |
| People’s Republic of China | Wang et al64             | 2014          | Single arm 12 months                                       | Primary Biliary Cirrhosis \(n = 10\) | Allogeneic bone marrowMSC        | \(3 to 5 \times 10^5\)kg   | 1                   | /        | Peripheral vein | Safety and efficacy               | Patient quality of life, ALT, AST, GGT and IgM |
| Egypt                   | Salama et al69            | 2014          | Randomized controlled 6 months                            | HCV-related decompensated cirrhosis \(n = 40\) | Autologous bone marrow MSC       | \(1 \times 10^6\)kg        | 1                   | /        | Peripheral vein | Safety and efficacy               | Albumin, bilirubin, international normalized ratio, prothrombin, ALT and MELD scores |
| Korea                   | Jang et al66              | 2014          | Single arm 6 months                                        | Alcoholic cirrhosis \(n = 11\) | Autologous bone marrow-derived MSC | \(5 \times 10^7\)          | 2                   | Every 4 or 8 weeks | Hepatic artery | Improvement of patients’ liver histological features | Child-Pugh score and liver histology |
| People’s Republic of China | Xu et al67               | 2014          | Randomized controlled 6 months                            | HBV related cirrhosis \(n = 56\) | Autologous bone marrow-derived MSC | \(0.75 \pm 0.50 \times 10^6\) | 1                   | –        | Hepatic artery | Absolute change in MELD score and improvement of liver function | Liver function, Treg cells and Th17 cells |
| Country                  | Author registration number | Years          | Type of study design | Timing of follow-up visit at endpoint | Liver disease | Sample size | Cell source                                                                 | Cell dose/each transfusion | Times of infusions | Interval | Infusion route | Endpoints                                         | Major improvements                                                                 |
|------------------------|---------------------------|----------------|----------------------|---------------------------------------|---------------|-------------|-----------------------------------------------------------------------------|----------------------------|-------------------|----------|----------------|-----------------------------------------------|--------------------------------------------------------------------------------|
| Turkey                 | Kantarcıoğlu et al68      | 2015           | Single arm          | 12 months                             | Liver disease | \( n = 25 \) | Autologous bone marrow-derived MSC                                          | \( 1 \times 10^6 \)          | 1                 | –        | Peripheral vein | Safety and efficacy                                | Albumin, MELD scores, hepatitis activity index scores                         |
| Korea                  | Suk et al69               | 2016           | Randomized controlled | 12 months                           | Alcoholic cirrhosis | \( n = 72 \) | Autologous bone marrow MSC                                                  | \( 5 \times 10^7 \)          | 1 or 2             | Every 1 month | Hepatic artery | Safety and efficacy                                | Liver fibrosis and Child-Pugh score                                              |
| People’s Republic of China | Liang et al70            | 2017           | Single arm          | 8-70 months                          | Cirrhosis associated with autoimmune liver disease | \( n = 26 \) | Allogeneic umbilical cord (or cord blood or bone marrow) MSC               | \( 1 \times 10^6/kg \)       | 1                 | –        | Peripheral vein | Safety and efficacy                                | ALT, bilirubin, prothrombin time, MELD score                                    |
| Switzerland            | Lanthier et al64          | 2017           | Randomized controlled | 12 months                           | Alcoholic decompensated cirrhosis | \( n = 58 \) | Autologous bone marrow MSC                                                  | \( 0.47 \pm 0.15 \times 10^{5}/kg \)     | 1                 | –        | Hepatic artery | Safety and efficacy                                | No improvement                                                                |
| People’s Republic of China | Shi et al71              | 2021           | Randomized controlled | 75 months                           | HBV-related decompensated cirrhosis | \( n = 219 \) | Umbilical cord-derived MSC                                                  | \( 0.5 \times 10^6/kg \)       | 3                 | Every 4 weeks | Peripheral vein | Overall survival and liver cancer-free survival | Overall survival, albumin, prothrombin activity, cholinesterase, and total bilirubin |
| People’s Republic of China | Peng et al72             | 2011           | Case-control        | 48 months                            | Chronic hepatitis B liver failure | \( n = 527 \) | Autologous bone marrow MSC                                                  | \( 3.4 \pm 3.8 \times 10^4 \)        | 1                 | –        | Hepatic artery | Short-term and long-term efficacy                  | Albumin, total bilirubin, MELD score, prothrombin time                          |
| People’s Republic of China | Shi et al73              | 2012           | Case-control        | 18 months                            | Chronic hepatic failure | \( n = 43 \) | Umbilical cord-derived MSC                                                  | \( 0.5 \times 10^6/kg \)       | 3                 | Every 4 weeks | Peripheral vein | Safety and efficacy                                | Survival rate, MELD score, globulin, prothrombin activity, direct bilirubin, alanine aminotransferase |
| People’s Republic of China | Li et al75               | 2016           | Case-control        | 24 months                            | Hepatitis B chronic plus acute liver failure | \( n = 45 \) | Umbilical cord stem cell MSC                                                | \( 0.2 \times 10^5 \)          | 1                 | –        | Peripheral vein | Safety and efficacy                                | Albumin, alanine aminotransferase, aspartate aminotransferase, total bilirubin, direct bilirubin, prothrombin time (PT), international normalized ratio (INR), Model for End-stage Liver Disease score |
| People’s Republic of China | Lin et al74               | 2017           | Randomized controlled | 6 months                            | Hepatitis B chronic acute liver failure | \( n = 110 \) | Allogeneic bone marrow MSC                                                  | \( 1 \text{ to } 10 \times 10^5/kg \) | 4                 | Every 1 week | Peripheral vein | Safety and efficacy                                | 24-week survival rate, MELD score, total bilirubin                              |
population, the most suitable source, dosage, and transfusion route of MSC medication have not been confirmed in the reported clinical trials so far, and further randomized, controlled clinical trials with larger sample sizes are needed.

Pharmacokinetics/Pharmacodynamics (PK/PD)
PK/PD measures the distribution of tested drugs and biomarkers in normal or disease models and is further used to analyze the dynamic course of drug absorption, distribution, metabolism, and excretion after drug administration. Therefore, this is an integral part of drug development. PK/PD studies contribute to a better understanding of the relationship between drug exposure, efficacy, and toxicity, and are significant tools to guide the study design for further preclinical and clinical evaluations. Of these, PK/PD-related cell tracking after cell infusion is a key component for evaluating the safety and efficacy of cellular therapy products. Recently, quantitative three-dimensional cryo-imaging, multiple imaging methods, including quantitative magnetic particle imaging, and near-infrared fluorescent semiconductor polymer imaging have been successively used to trace cells after their infusion to evaluate their distribution across different organs and their changes over time in vivo. These studies, in which MSCs were administered via peripheral intravenous infusion, demonstrated that MSCs were frequently distributed in the liver and lungs of animal models.

Given the characteristics of cell-based products, PK/PD research for application in humans is still in its infancy compared to traditional drugs and may pose uncertain risks to healthy subjects. Therefore, stem cell clinical trials have rarely been conducted in healthy volunteers. In their study, Gholamrezanezhad et al used 125In-oxine-labeled MSCs in decompensated cirrhosis patients and tracked them using MRI. MSCs were largely concentrated in the lungs 20 minutes after infusion, and after 2 h, MSCs could be detected in the liver and spleen until 10 days after baseline. These findings are consistent with the conclusions obtained in animal studies and provide a basis for the application of MSCs in the treatment of liver diseases. Accounting for the PK-PD relationship in MSC translational research, combined with better bio-distribution studies, could allow the realization of the potential of a more robust MSC clinical translation.

Perspective
Stem cell therapy, and especially MSC therapy, is generally considered a safe and potentially relevant therapeutic strategy for patients with acute or acute-on-chronic liver failure and decompensated liver cirrhosis. Although these studies provided preliminary evidence on the safety and efficacy of MSC infusions, most clinical trials have been conducted at a single center and with small sample sizes. Further robust, randomized, and controlled clinical studies with a large sample size are required to increase the reliability of MSC therapy and to establish a clinical alternative to treat severe liver diseases. At the same time, owing to the complexity of the clinical process of end-stage liver diseases, the design of the cell-infusion protocol, the time and duration of clinical treatment, and the endpoints at the trials need to be further optimized. The mechanisms of MSC therapy in liver diseases have been studied in vitro; however, cell distribution and related mechanisms in humans have not been fully clarified.
We believe that in the near future, several clinical trials will be conducted or completed to generate high-level evidence, which will continuously promote the development of stem cell infusion for the treatment of liver diseases and ultimately benefit the outcome and prognosis of patients with severe liver diseases.

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**Conflict of Interest**
The authors indicated no potential conflicts of interest.

**Author Contributions**
F.S.W. proposed initial proposal. F.S.W, L.S. conceived the structure of paper; L.S., T.L., Z.W., and E.L. collected materials and suggested additional information for the table; F.S.W and L.S. critically revised the manuscript. All authors read and approved the final paper.

**Data Availability**
No new data were generated or analyzed in support of this research.

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