REVIEW

Mesenchymal stem cell therapy as a game-changer in liver diseases: review of current clinical trials

Wei-Chen Huang[1,2], Yuan-Chi Li[3], Pin-Xuan Chen[3], Kevin Sheng-Kai Ma[4] and Li-Tzu Wang[3,5*]

Summary

Chronic liver diseases, including cirrhosis and liver failure, remain formidable challenges due to their complex progression and limited therapeutic options. Mesenchymal stem cell (MSC) therapy has emerged as a game-changing approach, leveraging its potent immunomodulatory, anti-fibrotic, and regenerative capabilities, along with the ability to transdifferentiate into hepatocytes. This review delves into the latest advances in MSC-based treatments for chronic and end-stage liver diseases, as highlighted in current clinical trials. MSCs derived from bone marrow and umbilical cord have shown remarkable promise in reversing liver damage, improving liver function, and providing hope for patients who do not respond to conventional therapies. When administered through hepatic, portal, or peripheral veins, MSCs have significantly improved liver histology, reduced fibrosis, and restored functional capacity. Furthermore, MSC-derived materials, such as extracellular vesicles and exosomes, are emerging as cutting-edge tools for treating liver failure and mitigating post-transplant complications. While autologous MSC-derived hepatocytes hold promise for non-fatal cirrhosis, allogeneic MSCs are being applied in more severe conditions, including liver failure and transplantation cases. Despite these promising early outcomes, larger trials and long-term studies are essential to fully harness MSCs as a transformative, off-the-shelf alternative to liver transplantation, heralding a new era in regenerative liver therapies.

Keywords Mesenchymal stem cells (MSCs), Immunomodulation, Anti-fibrosis, Transdifferentiation, Liver cirrhosis, End-stage liver diseases

*Correspondence:
Li-Tzu Wang
lizwang@tmu.edu.tw
[1]Division of Gastroenterology, Department of Internal Medicine, Tri-Service General Hospital, National Defense Medical Center, Taipei, Taiwan
[2]Laboratory of Clinical Immunology, National Defense Medical Center, Taipei, Taiwan
[3]School of Medical Laboratory Science and Biotechnology, College of Medical Science and Technology, Taipei Medical University, 10F., Teaching & Research Building, Shuang-Ho Campus, No. 301, Yuantong Rd., Zhonghe Dist., Taipei 235, Taiwan
[4]Center for Global Health, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA
[5]Medical Biotechnology, College of Medical Science and Technology, Taipei Medical University, Taipei, Taiwan

Introduction

Liver disease accounts for two million deaths annually, representing 4% of all fatalities worldwide (1 in every 25 deaths) [1]. Hepatic diseases, including specific conditions, cirrhosis, liver failure, and transplantation complications, present significant challenges due to their complex pathogenesis and the irreversible damage that occurs before symptoms emerge [2]. Specific conditions, such as autoimmune hepatitis, Wilson's disease, and biliary atresia, involve persistent inflammation and fibrosis, leading to progressive liver dysfunction. Cirrhosis is marked by extensive fibrosis and disruption of normal liver architecture, often progressing unnoticed

until severe damage occurs. Liver failure, whether acute or chronic, represents the terminal stage of severe liver disease and is life-threatening. Currently, biliary atresia is treated surgically (Kasai procedure) or with transplant [3]. Wilson's disease is treated with chelation and dietary modifications [4]; autoimmune hepatitis is treated with immunosuppressants [5]. Liver cirrhosis management includes lifestyle modifications, with transplantation for severe cases [6]. Liver failure requires urgent treatment, potentially including transplantation [7]. Liver transplantation involves risks like rejection, infection, and disease recurrence, requiring long-term immunosuppressive therapy [8, 9]. Mesenchymal stem cell (MSC) therapy has emerged as a promising treatment for these liver diseases, with immunomodulatory, anti-fibrotic, and regenerative properties. Clinical trials have explored the therapeutic potential of MSCs for various liver diseases, offering new therapeutic avenues for conditions that are currently difficult to treat [10–12].

Challenges of hepatic diseases

Specific chronic liver disease

Hepatic diseases encompass a broad spectrum of disorders, each characterized by unique mechanisms, progression patterns, and distinct pathogenesis. Understanding the complexity of these conditions is crucial, as the liver is a vital organ with multifaceted roles, including metabolism, detoxification, and immune regulation [13]. Autoimmune hepatitis is characterized by aberrant immune responses against hepatocytes, leading to chronic inflammation, fibrosis, and eventually cirrhosis if untreated [14]. Wilson's disease, on the other hand, is a genetic disorder caused by mutations in the ATP7B gene, leading to impaired copper metabolism [15, 16]. This results in copper accumulation in the liver and other organs, causing oxidative stress, cell damage, and liver function impairment. Biliary atresia is a developmental disorder of the biliary system where the bile ducts are abnormally narrowed or absent, leading to neonatal cholestasis, progressive liver injury, and cirrhosis in infancy [17, 18].

End-stage liver disease (liver cirrhosis)

Cirrhosis represents the end stage of many chronic liver diseases and is characterized by extensive fibrosis and the formation of regenerative nodules, leading to the disruption of normal liver architecture [19, 20]. The progression to cirrhosis is marked by the activation of hepatic stellate cells, which are the primary source of extracellular matrix components in the liver [21]. Persistent liver injury, as seen in chronic hepatitis or alcohol abuse, leads to the continuous activation of these cells, resulting in excessive fibrosis. As cirrhosis advances, liver function deteriorates and resistance in the portal venous system increases, leading to severe complications such as coagulopathy,

portal hypertension, ascites, and hepatic encephalopathy. The disease typically progresses slowly over months to years, and its insidious nature complicates early diagnosis and treatment.

Liver failure (liver decompensation)

Liver failure is a severe and life-threatening liver condition presenting with sudden or progressive loss of liver function [22, 23]. It can be the result of acute causes such as drug-induced liver injury, viral hepatitis, or ischemia, or it can occur as a consequence of the progression of chronic liver disease to decompensation. The development of liver failure involves extensive liver damage, significant hepatocyte necrosis, and inadequate liver function to meet physical needs, ultimately leading to multi-system dysfunction. This condition often requires urgent medical intervention, including liver transplantation.

Transplantation complications

Transplantation complications present another set of challenges in managing hepatic diseases [24, 25]. Despite being a life-saving procedure, liver transplantation is associated with an array of risks, including organ rejection, infection, and recurrence of the original liver disease. The host immune reaction to the grafted liver can lead to acute or chronic rejection, requiring long-term immunosuppressive therapy and assessment. Moreover, disease recurrence after liver transplantation including HBV/HCV re-infection, malignancy, or autoimmune hepatitis further complicates the prognosis [26].

The nature of the liver and its non-specific symptoms often make it difficult to promptly detect and manage liver problems. The remarkable regeneration capability of the liver has both pros and cons, as it can mask underlying pathology and produce irrevocable damage. Despite advances in medical science, liver disease remains a critical challenge due to its complex pathogenesis, the tolerability of disease onset, and limited treatment alternatives in advanced stages.

Overall, immune cells are central to the pathogenesis of liver inflammation, fibrosis, and cirrhosis. Hepatocyte injury triggers Kupffer cells, the liver's resident macrophages (MΦs) to release inflammatory mediators, activating other immune cells, including infiltrating MΦs, inflammatory T lymphocytes, neutrophils, and dendritic cells (DCs) [27]. These cells amplify inflammation through cytokine and chemokine production, stimulating hepatic stellate cells to transform into myofibroblasts. Myofibroblasts produce excessive extracellular matrix, leading to fibrosis and, ultimately, cirrhosis if inflammation persists. Additionally, liver sinusoidal endothelial cells play a crucial role in orchestrating the recruitment and activation of natural killer (NK) cells during acute

inflammatory liver injury [28]. The complex interplay of these cells and their signaling pathways drives a cycle of injury and inflammation. Therefore, effective therapies for inflammation-mediated liver diseases must address both tissue repair and immune modulation to prevent fibrosis progression.

Therapeutic potential of MSCs in treating liver diseases

MSCs have emerged as a promising therapeutic option for treating liver diseases due to their unique biological properties, including their ability to differentiate into various cell types, modulate immune responses, and promote tissue repair. MSCs are multipotent stromal cells that can be isolated from a variety of tissues, including bone marrow (BM), adipose tissue (Ad), and birth-associated tissue like umbilical cord (UC) [11, 29]. Their therapeutic potential in liver diseases lies in their capability to treat multiple pathological processes, including inflammation, fibrosis, and hepatocyte loss, which are central to the progression of many hepatic disorders [30–32].

One of the key mechanisms by which MSCs exert their therapeutic effects in liver diseases is through immunomodulation (Fig. 1) [33]. Chronic liver diseases are
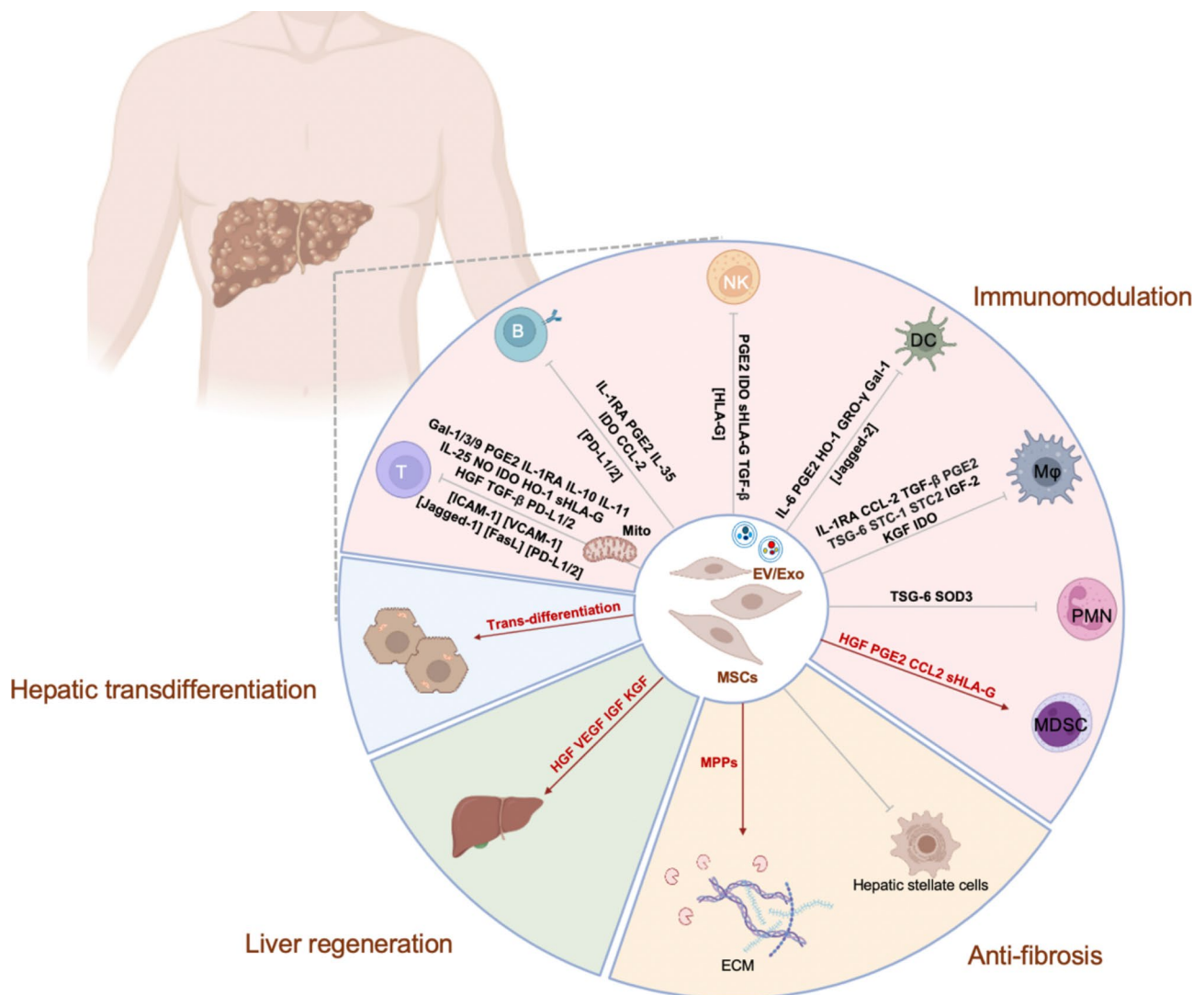
Fig. 1 Mechanisms of mesenchymal stem cell (MSC) immunomodulation on both lymphoid and myeloid cells, along with their roles in anti-fibrotic effects, liver regeneration, and hepatic transdifferentiation. NK, natural killer cell; PMN, polymorphonuclear neutrophil; MΦ, macrophage; MDSC, myeloid-derived suppressor cell; DC, dendritic cell; Gal, galectin; PGE2, prostaglandin E2; IL, interleukin; NO, nitric oxide; IDO, indoleamine 2, 3-dioxygenase; HO-1, heme oxygenase-1, HLA-G, human leukocyte antigen G; HGF, hepatocyte growth factor; TGF-β, transforming growth factor beta; FasL, Fas ligand; PD-L, programmed death-ligands; ICAM-1, Intercellular Adhesion Molecule-1; VCAM-1, vascular cell adhesion molecule 1; IL-1RA, IL-1 receptor antagonist (IL-1RA); CCL2, chemokine ligand 2; GRO)- γ, growth-regulated oncogene-γ, TSG-6, tumor necrosis factor-α-stimulated gene/protein-6; STC1, stanniocalcin 1; IGF, insulin-like growth factor; KGF, keratinocyte growth factor; SOD-3, superoxide dismutase-3; VEGA, vascular endothelial growth factor; Mito, mitochondria; MMP, matrix metalloproteinases. Cell-contact factors are denoted in brackets. Figure was created with BioRender.com, with permission

often marked by excessive and persistent inflammation, and MSCs possess potent immunomodulatory properties. These effects are largely mediated by the secretion of bioactive molecules, including anti-inflammatory cytokines and growth factors. MSCs modulate T cells by secreting galectins (Gal) 1, 3, and 9 [34, 35], prostaglandin E2 (PGE2) [36], interleukin (IL)-10 [37], IL-11 [38], IL-25 [39], IL-1 receptor antagonist (IL-1RA) [40], nitric oxide [41], indoleamine 2, 3-dioxygenase (IDO) [42], heme oxygenase (HO)-1 [43], human leukocyte antigen G (HLA-G) [44–46], hepatocyte growth factor (HGF) [47], transforming growth factor beta (TGF-β) [48], programmed death-ligands (PD-L) 1 and 2 [49], or through cell-cell contact via molecules such as Jagged-1 [50], Fas ligand (FasL) [51], PD-L1 and 2 [52, 53], intercellular adhesion molecule-1, and vascular cell adhesion molecule 1 [54]. Additionally, MSCs promote regulatory T cell (Treg) induction [55] while inhibiting T helper (Th) 1 [56] and Th17 cells [57] through mitochondrial transfer. In terms of B cell modulation, MSCs secrete IL-1RA [58], PGE2 [59], IL-35 [60], IDO [61], and chemokine ligand 2 (CCL2) [62], or act through cell-cell contact via PD-L1 and 2 [52]. For NK cells, MSCs secrete PGE2, IDO [63], HLA-G [45], TGF-β [64], and also directly interact through HLA-G [65]. MSCs modulate DCs by secreting IL-6 [66], PGE2 [67], HO-1 [68], growth-regulated oncogene-γ [69], Gal-1, or through Jagged-2-mediated contact [70]. In MΦs, MSCs exert effects by secreting IL-1RA [58], CCL2 [71], TGF-β [72], PGE2 [73], tumor necrosis factor-α-stimulated gene/protein (TSG)-6 [74], stanniocalcin (STC)-1 [75] and STC-2 [76], insulin-like growth factor (IGF)-2 [77], keratinocyte growth factor (KGF) [78], and IDO [79]. Moreover, MSCs release TSG-6 to inhibit polymorphonuclear neutrophil (PMN) infiltration [74], while superoxide dismutase-3 reduces PMN respiratory burst [80]. Additionally, MSCs secrete HGF [81], PGE2 [82], CCL2 [83], and HLA-G [84] to enhance the induction of myeloid-derived suppressor cells. By creating an immunosuppressive environment, MSCs mitigate the chronic inflammation driving liver damage, thereby slowing disease progression and promoting tissue repair.

Fibrosis, a hallmark of chronic liver disease leading to cirrhosis, is another important target for MSC therapy. Fibrosis results from the excessive deposition of extracellular matrix (ECM) components, primarily collagen, produced by activated hepatic stellate cells in response to chronic liver injury. MSCs have been shown to attenuate liver fibrosis through several mechanisms (Fig. 1). Firstly, they can directly inhibit the activation of hepatic stellate cells, reducing the synthesis and deposition of ECM components [85]. Secondly, MSCs secrete matrix metalloproteinases, enzymes that degrade the ECM, thereby promoting the resolution of fibrosis [86]. Furthermore,

MSCs can induce apoptosis in activated hepatic stellate cells, further contributing to the reduction of fibrotic tissue [87]. By targeting the fibrosis process, MSCs help preserve liver structure and function and may even delay or prevent the onset of cirrhosis [88, 89].

In addition to their immunomodulatory and antifibrotic effects, MSCs have the potential to contribute to liver regeneration (Fig. 1). MSCs can differentiate into hepatocyte-like cells under certain conditions [90, 91], providing a source of new functional hepatocytes to replace damaged or lost liver cells. Although the efficiency of MSC differentiation into fully functional hepatocytes remains an area of ongoing research, their ability to enhance liver regeneration is also supported by paracrine effects. MSCs secrete a variety of growth factors [92, 93], such as HGF, vascular endothelial growth factor, IGF, and KGF, which stimulate the proliferation of endogenous liver progenitor cells and mature hepatocytes. This regenerative capability is particularly valuable in patients with extensive hepatic injury or liver failure, whose liver functions are compromised.

Another significant aspect of MSC therapy is their low immunogenicity and relative safety profile. Unlike many other cell types, MSCs do not express high levels of major histocompatibility complex class II molecules, which allows them to evade recognition and attack by the host immune system. This property makes allogeneic MSC infusion a viable recourse, expanding the availability of MSC-based therapies to a broader patient population [94, 95].

Despite the promising results seen in preclinical studies and early clinical trials, challenges remain in optimizing MSC therapy for liver diseases. These include improving the migratory efficiency of MSCs to the liver [96], ensuring their long-term survival and function postinfusion, and understanding the mechanisms underlying their therapeutic effects in greater detail. Nevertheless, the multifaceted roles of MSCs in modulating immune responses, reducing fibrosis, and promoting liver regeneration make them a compelling therapeutic candidate for a wide range of liver diseases [97]. As research progresses, MSC-based therapies have the potential to offer new hope for patients with conditions that are currently difficult to treat.

Current clinical trials of MSC therapy for liver diseases: overview

Numerous reviews have summarized ClinicalTrials.gov data on MSC therapy for liver diseases [98, 99]. However, this field is rapidly evolving. This study provides an updated overview, incorporating data from 62 trials reported in 2022 [100]. Our analysis considers key factors influencing treatment outcomes, including the source of MSCs, and the route of administration. This

comprehensive approach allows for a more nuanced understanding of current MSC therapies and identifies areas for future research and development in this promising area of liver disease treatment. As of August 2024, a total of 73 clinical studies involving MSCs for treating liver disorders have been registered on NIH Clinical Trial Database (https://ClinicalTrials.gov/). The primary focus of these trials is on end-stage liver diseases or liver cirrhosis (31 trials) and liver failure or decompensation (34 trials), with fewer trials targeting other liver diseases, including transplantation complications (5 trials), and single trials for autoimmune hepatitis, Wilson's disease, and biliary atresia (Fig. 2).

The sources of MSCs used in these studies are diverse (Fig. 3). The most common sources are UCMSCs (35 trials) including one exosome trial, and BMMSCs (24 trials) including one trial using BMMSC-derived hepatocytes. Additionally, two trials use both UCMSCs and BMMSCs. AdMSCs were utilized in 2 trials, whereas skin tissue MSCs and menstrual blood MSCs were each used in 1 trial. Seven trials involve MSCs without specifying the donor or tissue source, including 2 trials that explore MSC-derived extracellular vesicles (EVs). One trial uses autologous MSC-derived hepatocyte progenitors from an unspecified tissue source. Among the 37 UCMSC

trials, all are considered allogeneic. Allogeneic BMMSCs are used in 10 trials, while allogeneic AdMSCs and skin tissue MSCs are each used in 1 trial. Autologous MSCs are employed in 19 trials, primarily from BMMSCs (16 trials), with one trial using autologous AdMSCs and another one using autologous menstrual blood MSCs.

The majority of these trials are in early phases, with 16 phase 1 trials, 28 combined phase 1/2 trials, 15 phase 2 trials, 1 combined phase 2/3 trial, 2 phase 3 trials, 1 phase 4 trial; 10 trials are unspecified (Table 1). A significant number of participants are involved across these phases, totaling 6,013, with 261 in phase 1 trials, 2,121 in combined phase 1/2 trials, 1,673 in phase 2 trials, 66 in the combined phase 2/3 trial, 730 in phase 3 trials, 5 participants in the phase 4 trial; 1,157 participants are unspecified (Table 2). These trials highlight a strong interest in the immunomodulatory and regenerative potential of MSCs, particularly in the use of allogeneic sources.

Current clinical trials of MSC therapy for liver diseases
Specific chronic liver disease
MSC therapy is being explored in clinical trials for its potential to treat various chronic liver diseases, including Wilson's disease, autoimmune hepatitis, and biliary
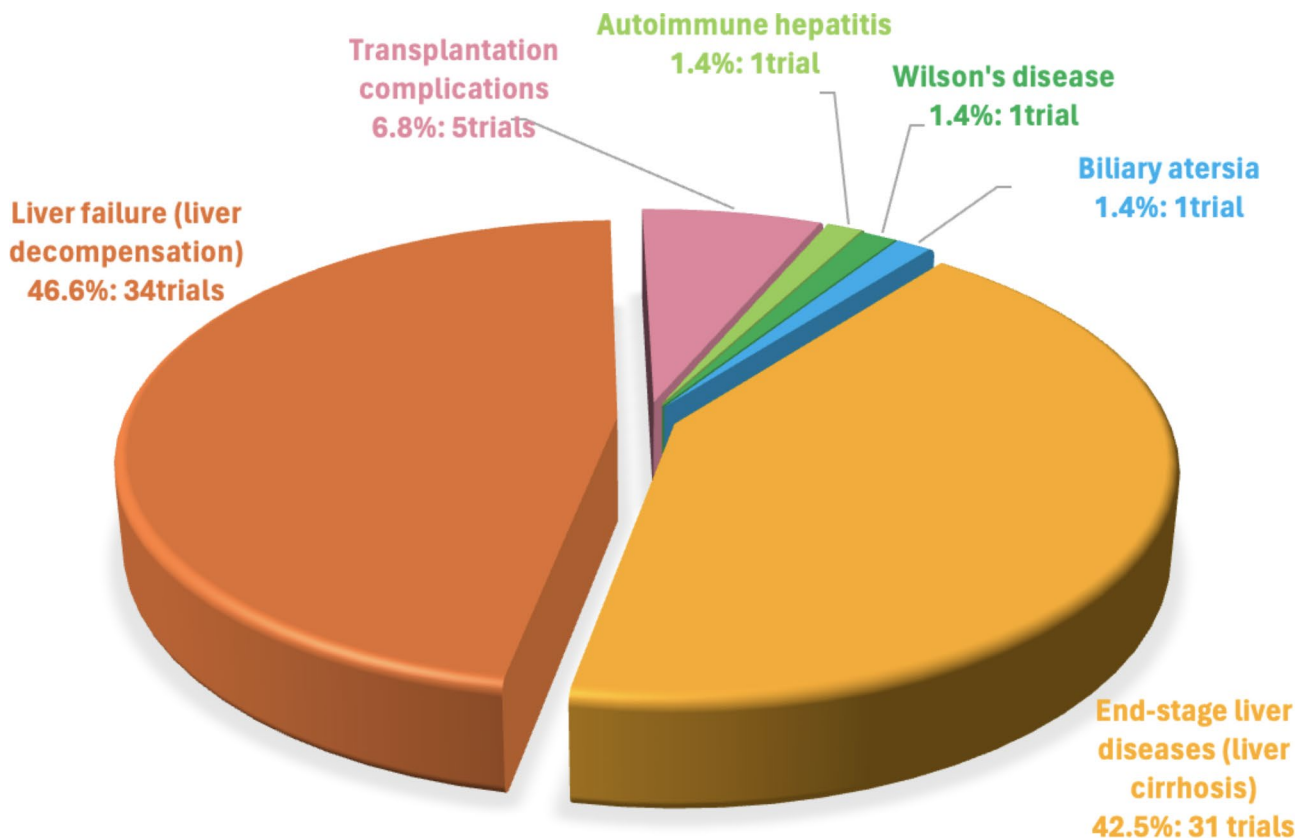
Fig. 2 Distribution of clinical trials using human MSCs for liver diseases. The number of MSC clinical trials treating various liver conditions was retrieved from the NIH Clinical Trial website (https://ClinicalTrials.gov/) as of August 2024
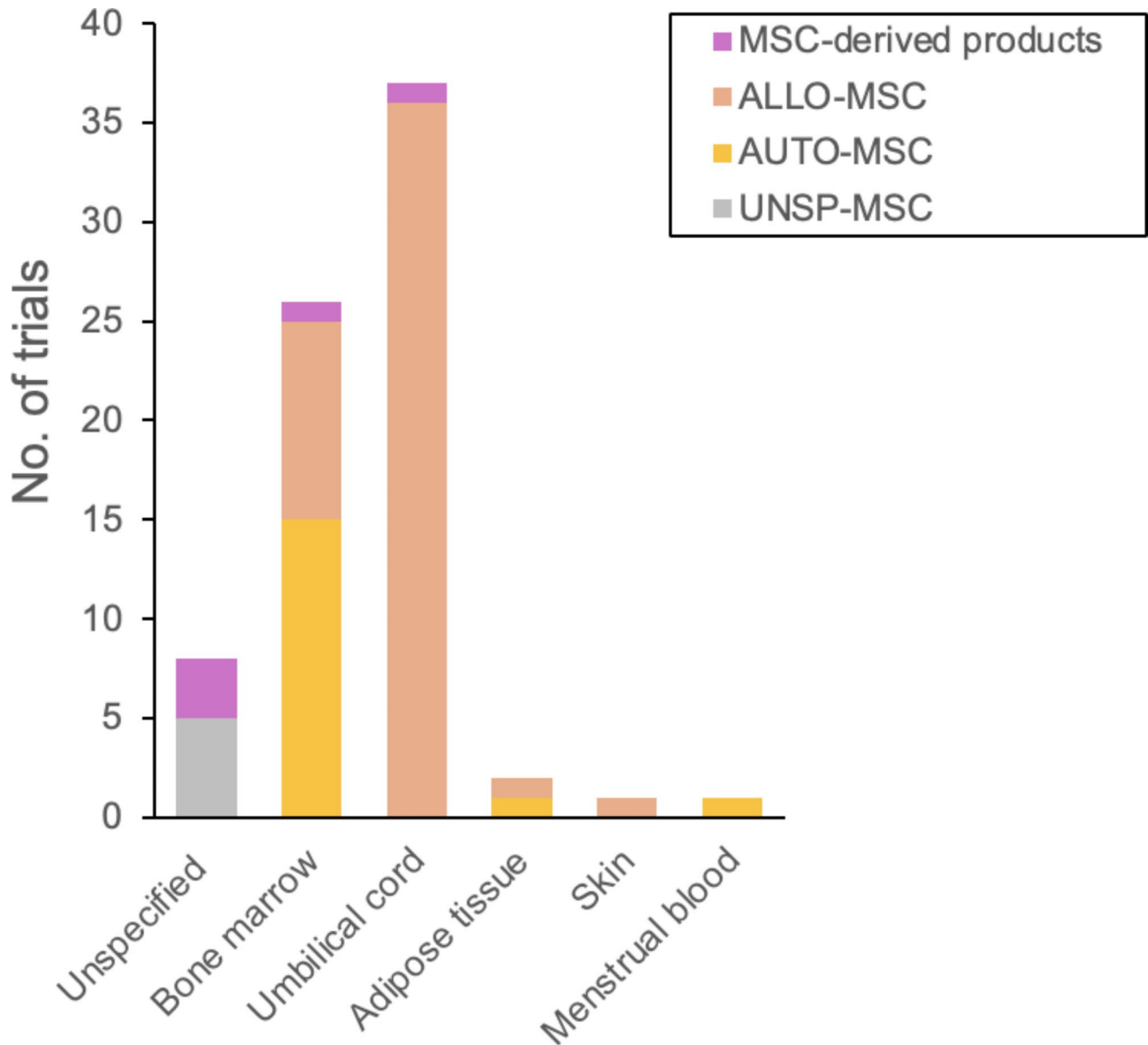
Fig. 3 Sources of human MSCs used in liver disease clinical trials. The number of trials using different sources of human MSCs is shown, categorized as autologous (AUTO-MSC), allogeneic (ALLO-MSC), unspecified (UNSP-MSC), and/or extracellular vesicles (EVs)/exosomes (MSC-derived products). Data accessed from the NIH Clinical Trial website (https://ClinicalTrials.gov/) in August 2024

Table 1 Cell sources and trial phases of MSC clinical trials for liver diseases

MSC source	Total %	Total no.	N/A	1	1 and 2	2	2 and 3	3	4
Unspecified	6.7%	5	3	0	2	0	0	0	0
Bone marrow	33.3%	25	4	6	4[a]	8	0	2	1
Adipose tissue	2.7%	2	0	1	1	0	0	0	0
Umbilical cord	48.0%	36	3	8	18[a]	6	1	0	0
Skin	1.3%	1	0	0	1	0	0	0	0
Menstrual blood	1.3%	1	0	0	1	0	0	0	0
MSC-derived product	6.7%	5	0	1[A]	3[A, B]	1[A]	0	0	0
Total no. of clinical trial phases		73	10	16	28	15	1	2	1
Total % of clinical trial phases			13.7%	21.9%	38.4%	20.5%	1.4%	2.7%	1.4%

Note: [a]Two trials using two sources of MSCs: BM and UC; [A]One trial using extracellular vesicles including exosomes; [B]Two trials using MSC-derived hepatocyte progenitors or hepatocytes

Table 2 Participants recruited MSC clinical trials for liver diseases

MSC enrollment	Total %	Total no.	N/A	1	1 and 2	2	2 and 3	3	4
Unspecified	9.9%	615	540	0	75	0	0	0	0
Bone marrow	32.0%	2000	473	73	290[a]	429	0	730	5
Adipose tissue	0.1%	5	0	0	5	0	0	0	0
Umbilical cord	55.8%	3483	144	188	1856[a]	1229	66	0	0
Skin	0.1%	5	0	0	5	0	0	0	0
Menstrual blood	0.8%	50	0	0	50	0	0	0	0
MSC-derived product	1.4%	85	0	0	70[A, B]	15[A]	0	0	0
Total no. of clinical trial phases		6013	1157	261	2121	1673	66	730	5
Total % of clinical trial phases			19.2%	4.3%	35.3%	27.8%	1.1%	12.1%	0.1%

Note: [a]Two trials using two sources of MSCs: BM and UC; [A]One trial using extracellular vesicles including exosomes; [B]Two trials using MSC-derived hepatocyte progenitors or hepatocytes

Table 3 Specific chronic liver disease

Indication	NCT number	Title	Delivery	Auto/Allo	MSC source	Age (Years)	Phase	Enrollment
Wilson's Disease	NCT01378182	Efficacy of Invitro Expanded Bone Marrow Derived Allogeneic Mesenchymal Stem Cell Transplantation Via Portal Vein or Hepatic Artery or Peripheral Vein in Patients With Wilson Cirrhosis	IV + hepatic artery	Allo	BMMSCs	18 to 65	NA	10
Autoimmune Hepatitis	NCT01661842	Umbilical Cord Mesenchymal Stem Cells for Patients With Autoimmune Hepatitis	IV	Allo	UCMSCs	18 to 65	1/2	100
Biliary Atresia	NCT04522869	Umbilical Cord Derived Mesenchymal Stem Cell (UC -MSC) Transplantation for Children Suffering From Biliary Atresia	hepatic artery	Allo	UCMSCs	0.4 to 2	1/2	20

atresia, with specific dosing strategies tailored to each condition (Table 3). In patients with Wilson's disease-related liver injury or cirrhosis, MSCs derived from healthy donor BM are infused into patients at a dose of 1 million cells per kg of body weight, with 50 million cells delivered via the hepatic artery and the remaining cells via a peripheral vein. This approach aims to promote liver regeneration, thereby reducing fibrosis, decreasing the need for chelating agents, and potentially delaying or avoiding liver transplantation. In autoimmune hepatitis, an immune-mediated liver disease traditionally treated with corticosteroids and/or immunosuppressants, a clinical trial is testing UCMSCs. Participants are randomly assigned to receive either conventional treatment combined with UCMSC infusions with 1 million cells per kg of body weight intravenously every four weeks for 12 weeks, or conventional treatment with a placebo. The study monitors liver enzyme levels, histology, and relapse rates to assess safety and efficacy. Biliary atresia, the leading cause of pediatric liver transplantation, is being addressed in another trial where Kasai-operated patients receive two UCMSC transplants via the hepatic artery, with a dosage of 1 million MSCs per kg of body weight per transplant. Safety is evaluated by monitoring adverse events post-injection, while efficacy is measured using the Pediatric End-Stage Liver Disease (PELD) score, liver function tests, and liver biopsy results. These trials demonstrate the scope of MSC therapy, with specific dosages and delivering strategies, to address the complex challenges of chronic liver diseases, offering new, regenerative treatment options.

End-stage liver disease (liver cirrhosis)

Clinical trials of MSC therapy for end-stage liver disease (liver cirrhosis)

Cirrhosis is a severe condition resulting from prolonged liver damage caused by alcohol or other toxins, viral hepatitis, autoimmune hepatitis, metabolic diseases, and certain medications, to name a few. This damage leads to progressive scarring, which gradually replaces normal liver cells, causing distortion of the parenchyma architecture and the formation of regenerative nodules. Liver cirrhosis represents a late stage of hepatic fibrosis and often progresses to liver failure. Currently, liver transplantation is one of the few effective treatments available for cirrhosis, but it is associated with significant challenges, including a shortage of donors, surgical complications, graft rejection, and high costs. To address these challenges, MSC therapy has emerged as an optional treatment. There are currently 31 clinical trials investigating MSC therapy for cirrhosis (Table 4). One trial involves autologous AdMSC therapy for Hepatitis C virus (HCV)-related cirrhosis, where one million cells per kg are injected via the peripheral vein and three million cells per kg are administered into the right hepatic artery. Another trial explores allogeneic BMMSC therapy for Hepatitis B

Table 4 End-stage liver disease or liver cirrhosis

NCT number	Title	Delivery	Auto/Allo	MSC source	Age (Years)	Phase	Enrollment	Publication
NCT02705742	Mesenchymal Stem Cells Transplantation for Liver Cirrhosis Due to HCV Hepatitis	IV and hepatic artery	Auto	AdMSCs	18 to 70	1/2	5	
NCT01440309	Efficacy and Safety Study of Allogenic Mesenchymal Stem Cells for Patients With Refractory Primary Biliary Cirrhosis	IV	Allo	BMMSCs	18 to 60	1	20	
NCT01223664	Allogenic Bone Marrow Stem Cells Transplantation in Patients With Liver Cirrhosis	portal vein or hepatic artery	Allo	BMMSCs	16 to 65	2	60	
NCT03838250	Study to Evaluate Hepatic Artery Injection of Autologous Human Bone Marrow-Derived MSCs in Patients With Alcoholic LC	hepatic artery	Auto	BMMSCs	18 to 70	1	10	
NCT00976287	Autologous Bone Marrow Mesenchymal Stem Cells Transplantation Via Hepatic Artery in Patients With Liver Cirrhosis	hepatic artery	Auto	BMMSCs	18 to 70	2	50	
NCT00993941	Bone Mesenchymal Stem Cell (BMSC) Transplantation in Liver Cirrhosis Via Portal Vein	IV	Auto	BMMSCs	18 to 60	2	60	
NCT01591200	Dose Finding Study to Assess Safety and Efficacy of Stem Cells in Liver Cirrhosis	hepatic artery	Auto	BMMSCs	18 to 65	2	40	
NCT01741090	The Effectiveness and Safety for Mesenchymal Stem Cell for Alcoholic Liver Cirrhosis	hepatic artery	Auto	BMMSCs	20 to 60	2	12	Jang YO 2014
NCT01854125	Autologous Mesenchymal Stem Cell Transplantation in Cirrhosis Patients With Refractory Ascites	hepatic artery	Auto	BMMSCs	18 to 65	3	30	
NCT05080465	Long Term Follow up Mesenchymal Stem Cell Therapy for Patients Virus-related Liver Cirrhosis	IV	Auto	BMMSCs	18 to 69	3	700	
NCT03626090	Mesenchymal Stem Cell Therapy for Liver Cirrhosis	IV	Auto	BMMSCs	21 to 69	1/2	20	
NCT01729221	Application of the Stem Cell Therapy in the End Stage Liver Disease and Assessment Its Consequences in the Quality of Live Style as Well as Development of HCC.	UNS	Auto	BMMSCs	20 to 65	NA	280	Salama H 2014
NCT01877759	A Clinical Study to Evaluate the Safety and Efficacy of Mesenchymal Stem Cells in Liver Cirrhosis	IV	Auto and Allo	BMMSCs and UCMSCs	25 to 65	1/2	20	
NCT01483248	Human Menstrual Blood-derived Mesenchymal Stem Cells for Patients With Liver Cirrhosis	IV	Auto	MenSCs	20 to 50	1/2	50	
NCT02652351	Human Umbilical Cord-Mesenchymal Stem Cells for Hepatic Cirrhosis	IV or hepatic artery	Allo	UCMSCs	18 to 80	1	20	
NCT05331872	Umbilical Cord-derived Mesenchymal Stem Cell Infusion in the Management of Adult Liver Cirrhosis	UNS	Allo	UCMSCs	18 to 70	1	20	
NCT01220492	Umbilical Cord Mesenchymal Stem Cells for Patients With Liver Cirrhosis	IV	Allo	UCMSCs	18 to 65	1/2	266	
NCT01224327	Umbilical Cord Mesenchymal Stem Cells Infusion Via Hepatic Artery in Cirrhosis Patients	hepatic artery	Allo	UCMSCs	18 to 70	1/2	50	
NCT01233102	Mesenchymal Stem Cells Treat Liver Cirrhosis	IV or hepatic artery	Allo	UCMSCs	18 to 70	1/2	200	
NCT01573923	Safety and Efficacy Study of Umbilical Mesenchymal Stem Cells for Liver Cirrhosis	IV	Allo	UCMSCs	30 to 60	1/2	320	
NCT01662973	Umbilical Cord Mesenchymal Stem Cells for Patients With Primary Biliary Cirrhosis	IV	Allo	UCMSCs	18 to 65	1/2	100	

Table 4 (continued)

NCT number	Title	Delivery	Auto/Allo	MSC source	Age (Years)	Phase	Enrollment	Publication
NCT01728727	Safety and Efficacy of Human Umbilical Cord Derived Mesenchymal Stem Cells for Treatment of HBV-related Liver Cirrhosis	hepatic artery	Allo	UCMSCs	18 to 65	1/2	240	
NCT04357600	Umbilical Cord Mesenchymal Stem Cell for Liver Cirrhosis Patient Caused by Hepatitis B	IV	Allo	UCMSCs	18 to 65	1/2	12	
NCT05507762	Study of Human Umbilical Cord Mesenchymal Stem Cell in Patients With Cirrhosis Due to Hepatitis B (Compensation Stage)	IV	Allo	UCMSCs	18 to 65	1/2	20	
NCT06167473	Effect of Different Dosage of Umbilical Cord-mesenchymal Stem Cells Through Peripheral Vein in Patients With ESLD	IV	Allo	UCMSCs	18 to 80	NA	22	
NCT06242405	Effect of Different Frequencies of Umbilical Cord-mesenchymal Stem Cells Through Peripheral Vein in Patients With ESLD	IV	Allo	UCMSCs	18 to 80	NA	92	
NCT03460795	Safety and Efficacy Study of Co-transfering of Mesenchymal Stem Cell and Regulatory T Cells in Treating End-stage Liver Disease	UNS	UNS	UNS (combined with Treg transplantation)	18 to 65	1/2	30	
NCT01499459	Autologous Mesenchymal Stem Cell Transplantation in Liver Cirrhosis	IV	UNS	UNS	18 to 80	NA	25	
NCT03668145	Mesenchymal Stem Cell Transplantation for Refractory Primary Biliary Cholangitis	IV	UNS	UNS	18 to 70	NA	140	
NCT02943889	Stem Cell Transplantation in Cirrhotic Patients	portal vein	Auto	BMMSCs (defferentiated hepatocytes)	(Child, Adult, Older Adult)	1/2	40	
NCT00420134	Improvement of Liver Function in Liver Cirrhosis Patients After Autologous Mesenchymal Stem Cell Injection: a Phase I-II Clinical Trial	portal vein	Auto	UNS (differentiated hepotocyte progenitors)	≥18	1/2	30	

virus (HBV)-related cirrhosis, with cells delivered via the portal vein or hepatic artery, alongside standard antiviral treatment. A third trial involves intravenous infusion of allogeneic BMMSCs for primary biliary cholangitis, a biliary-specific inflammatory disease that leads to liver cirrhosis and eventually failure. Additionally, nine clinical trials are using autologous BMMSCs, and 12 trials are using UCMSCs, typically administered at a dose of approximately one million cells per kg via peripheral vein or hepatic artery. One trial combines autologous BMMSC therapy with allogeneic UCMSCs administered weekly for six weeks. One trial uses autologous MSCs harvested from menstrual blood at a dose of one million cells per kg via intravenous infusions twice per week for two weeks, in combination with conventional treatment like antiviral drugs. Three trials use MSCs from unspecified donation and tissue sources with one of these combining regulatory T cell transplantation, while one trial employs autologous BMMSC-derived hepatocytes and another one uses unspecified MSC-derived hepatocyte progenitors. In most trials, liver function is monitored by analyzing serum levels of alanine aminotransferase (ALT), total bilirubin, prothrombin time, prealbumin and albumin from pre-transfusion and post-transfusion. Improvements are also evaluated using the Model for End-Stage Liver Disease (MELD) score, the Child-Pugh score, or assessment of patients' quality of life.

Results of clinical trials evaluating MSC therapy for end-stage liver disease (liver cirrhosis)

For end-stage liver diseases or liver cirrhosis, two clinical trials have published results. In a trial registered under NCT01741090, twelve patients (11 males, 1 female) with biopsy-proven alcoholic cirrhosis, who had been abstinent from alcohol for at least six months, were enrolled to evaluate the efficacy of autologous BMMSCs [101]. BMMSCs were isolated from BM of each patient, cultured for one month, and then administered at a dose of fifty million cells twice at weeks 4 and 8 via the hepatic artery. One patient was withdrawn from the trial due to alcohol consumption, leaving 11 patients who completed follow-up biopsies and laboratory tests 12 weeks after the second injection. The primary outcome was the improvement of liver histology in 6 patients (54.5%) following BMMSC therapy according to the Laennec fibrosis scoring system. Regarding the secondary outcome, 10 patients of the 11 patients (90.9%) experienced an improvement in liver function, as indicated by their Child-Pugh scores following BMMSC therapy. Additionally, significant reductions were observed in levels of transforming growth factor-β1, type 1 collagen, and α-smooth muscle actin following BMMSC therapy. The study also reported no significant complications or side effects. In another trial registered under NCT01729221,

forty patients with HCV-related liver cirrhosis were randomized into the control group with standard liver-supportive treatment and the MSC-treated group, each with 20 patients [102]. In the MSC-treated group, patients received granulocyte colony-stimulating factor for 5 days followed by autologous BMMSC infusion via the peripheral vein. Among the MSC-infused patients, 54% showed near normalization of liver enzymes and improvement in liver synthetic function. Significant changes were reported in albumin, bilirubin, prothrombin concentration, and ALT levels. Therefore, autologous BMMSC therapy in patients with alcoholic cirrhosis or end-stage liver disease demonstrated histological and quantitative improvements in liver synthetic functions and hepatic fibrosis.

Liver failure (liver decompensation)
Clinical trials of MSC therapy for liver failure (liver decompensation)

The leading cause of death in patients with cirrhosis is the development of acute-on chronic liver failure (ACLF), a syndrome associated with high mortality. Currently, liver transplantation is the only effective treatment for ACLF or decompensated liver diseases, but the availability of donor organs is severely limited. Other treatments, including artificial liver support systems, have not shown an improvement in survival rates. ACLF is characterized by an increased systemic inflammatory state, coupled with impaired liver regeneration, leading to multiorgan failure. MSC therapy is a promising strategy for treating ACLF, as well as chronic or acute liver failure, due to the immunomodulatory and regenerative properties of these cells. To date, 34 clinical trials are investigating MSC-based therapies, including two utilizing cell-free products, for the treatment of liver failure or liver decompensation (Table 5). Among these, five trials involve autologous BMMSC infusion. Two trials focus on treating decompensated liver through peripheral blood injection, with one of them involving a one-time infusion of 300 million cells. Another trial targets HBV-related liver failure, a critical condition of extensive liver cell necrosis, with follow-up monitoring for the incidence of hepatocellular carcinoma and mortality. One trial is exploring the use of portal vein infusion combined with Pioglitazone, which has shown benefits in ameliorating liver dysfunction in type 2 diabetic (T2D) patients with non-alcoholic fatty liver disease. Additionally, another trial focuses on decompensated cirrhosis by co-infusing autologous hematopoietic stem cells (HSCs) and BMMSCs via the hepatic artery, as autologous HSCs have demonstrated the capability to improve liver function. In addition to autologous therapies, 27 trials are investigating the use of allogeneic MSC sources. These include 18 trials using UCMSCs, 3 using BMMSCs, 1

Table 5 Liver failure or liver decompensation

NCT number	Title	Delivery	Auto/Allo	MSC source	Age (Years)	Phase	Enrollment	Publication
NCT03629015	Safety Study of Stemchymal® in Acute Liver Failure	IV	Allo	AdMSCs	20 to 70	1	0	
NCT02857010	Allogeneic Bone Marrow Mesenchymal Stem Cell Therapy in Acute-on-chronic Liver Failure	IV	Allo	BMMSCs	18 to 79	1	23	
NCT01221454	Allogenic Bone Marrow Stem Cell Transplantation in Liver Failure	portal vein or hepatic artery	Allo	BMMSCs	16 to 65	2	60	Lin BM 2017
NCT01322906	Allogeneic Bone Marrow Mesenchymal Stem Cells Transplantation in Patients With Liver Failure Caused by Hepatitis B Virus (HBV)	IV	Allo	BMMSCs	16 to 65	2	120	
NCT01454336	Transplantation of Autologous Mesenchymal Stem Cell in Decompensate Cirrhotic Patients With Pioglitazone	portal vein	Auto	BMMSCs	18 to 65	1	3	
NCT02327832	Safety Study of Liver Regeneration Therapy Using Cultured Autologous BMSCs	IV	Auto	BMMSCs	20 to 75	1	10	
NCT00476060	Mesenchymal Stem Cell Transplantation in Decompensated Cirrhosis	IV	Auto	BMMSCs	18 to 65	2	27	
NCT00956891	Therapeutic Effects of Liver Failure Patients Caused by Chronic Hepatitis B After Autologous MSCs Transplantation	hepatic artery	Auto	BMMSCs	15 to 70	NA	158	Peng L 2011
NCT04243681	Combination of Autologous MSC and HSC Infusion in Patients With Decompensated Cirrhosis	hepatic artery	Auto	BMMSCs (combined with HSCs)	20 to 70	4	5	Sharma M 2021
NCT01844063	Safety and Efficacy of Diverse Mesenchymal Stem Cells Transplantation for Liver Failure	IV	Allo	BMMSCs and UCMSCs	18 to 65	1/2	210	
NCT03860155	Allogeneic ABCB5-positive Stem Cells for Treatment of Acute-on-Chronic Liver Failure	IV	Allo	SKIN-MSCs	20 to 75	1/2	5	
NCT03826433	hUC Mesenchymal Stem Cells (19#ISCLife®-LC) in the Treatment of Decompensated Hepatitis b Cirrhosis	IV	Allo	UCMSCs	18 to 60	1	20	
NCT05155657	Study of Decompensated Alcoholic Cirrhosis Treatment by Stem Cells	UNS	Allo	UCMSCs	18 to 60	1	36	
NCT05227846	Human Umbilical Cord-derived Mesenchymal Stem Cells for Decompensated Cirrhosis (MSC-DLC-1)	IV	Allo	UCMSCs	18 to 75	1	12	Wang Z 2023
NCT05442437	Clinical Study of hUC-MSCs Treating Decompensated Liver Cirrhosis With HBV	IV	Allo	UCMSCs	18 to 65	1	24	
NCT05984303	Human Umbilical Cord-derived Mesenchymal Stem Cells for Decompensated Cirrhosis (MSC-DLC-1b)	IV	Allo	UCMSCs	18 to 75	1	6	
NCT02812121	UC-MSC Infusion for HBV-Related Acute-on-Chronic Liver Failure	IV	Allo	UCMSCs	18 to 65	2	261	
NCT03529136	Clinical Trial of Umbilical Cord Mesenchymal Stem Cell Transfusion in Decompensated Liver Cirrhosis	IV	Allo	UCMSCs	18 to 65	2	252	
NCT03945487	Mesenchymal Stem Cells Treatment for Decompensated Liver Cirrhosis	IV	Allo	UCMSCs	18 to 69	2	200	
NCT04822922	Safety of UC-MSC Transfusion for ACLF Patients	IV	Allo	UCMSCs	18 to 70	2	16	
NCT05121870	Treatment With Human Umbilical Cord-derived Mesenchymal Stem Cells for Decompensated Cirrhosis	IV	Allo	UCMSCs	18 to 75	2	240	
NCT05224960	Human Umbilical Cord-derived Mesenchymal Stem Cells for Decompensated Cirrhosis (MSC-DLC-2)	IV	Allo	UCMSCs	18 to 75	2	140	
NCT01218464	Safety and Efficacy of Human Mesenchymal Stem Cells for Treatment of Liver Failure	IV	Allo	UCMSCs	18 to 70	1/2	70	
NCT01342250	Human Umbilical Cord Mesenchymal Stem Cells Transplantation for Patients With Decompensated Liver Cirrhosis	UNS	Allo	UCMSCs	18 to 70	1/2	20	

Table 5 (continued)

NCT number	Title	Delivery	Auto/Allo	MSC source	Age (Years)	Phase	Enrollment	Publication
NCT01724398	Umbilical Cord Mesenchymal Stem Cells Transplantation Combined With Plasma Exchange for Patients With Liver Failure	IV	Allo	UCMSCs	16 to 65	1/2	120	Xu WX 2019
NCT02786017	Injectable Collagen Scaffold Combined With HUC-MSCs Transplantation for Patients With Decompensated Cirrhosis	UNS	Allo	UCMSCs	≥18	1/2	40	
NCT05948982	Safety of Umbilical Cord Mesenchymal Stem Cells (UC-MSC) in Patients With Decompensated Hepatitis B Cirrhosis	IV	Allo	UCMSCs	18 to 75	1/2	18	
NCT05985863	Human Umbilical Cord Mesenchymal Stem Cell Transplantation for The Treatment of Acute-on-Chronic Liver Failure	IV	Allo	UCMSCs	18 to 70	1/2	150	
NCT05106972	Umbilical Cord Mesenchymal Stem Cell Transplantation for Decompensated Hepatitis B Cirrhosis	IV	Allo	UCMSCs	20 to 60	NA	30	
NCT03863002	Safety and Efficacy of Mesenchymal Stem Cell Transplantation for Acute-on-Chronic Liver Failure	IV	UNS	UNS	16 to 60	1/2	45	
NCT03209986	Trial of Mesenchymal Stem Cell Transplantation in Decompensated Liver Cirrhosis	IV	UNS	UNS	18 to 65	NA	200	
NCT03668171	Mesenchymal Stem Cell Transplantation for Acute-on-chronic Liver Failure	IV	UNS	UNS	18 to 70	NA	200	
NCT05940610	The Safety and Efficacy of MSC-EVs in Acute/Acute-on-Chronic Liver Failure	UNS	UNS	MSC-EV	18 to 65	1/2	0	
NCT05871463	Effect of Mesenchymal Stem Cells-derived Exosomes in Decompensated Liver Cirrhosis	UNS	Allo	UC-exosomes	18 to 75	2	15	

combining BMMSCs and UCMSCs, 1 using AdMSCs, 1 using skin-derived MSCs, and 3 using unspecified sources. For instance, allogeneic AdMSCs (Stemchymal®) are being tested for acute liver failure (ALF) and ACLF at doses of 0.5 million versus 2 million cells per kg via intravenous injection. Allogeneic skin-derived ABCB5-postive MSCs are being used to treat ACLF at three doses of 2 million cells per kg via intravenous injection on days 0, 5, 13. Among the three trials with allogeneic BMMSCs, one trial focuses on ACLF with 4 doses of 2 million cells per kg intravenously administered on days 1, 4, 11, and 18. Another trial addresses HBV-related liver failure with doses of 0.5, 2 or 5 million cells per kg via intravenous injection, while the third trial administers BMMSCs via the portal vein or hepatic artery in conjunction with conventional therapy. Allogeneic UCMSCs are the most commonly used in treating liver failure or liver decompensation, including HBV or alcohol-related AFLD, with doses ranging from 10 to 100 million cells via intravenous administration. Additionally, three trials using allogeneic MSCs of unspecified sources are being conducted in patients with AFLD, with treatments involving 3 or 4 doses of approximately 1 million cells per kg via peripheral vein infusion. Moreover, one trial compares the effects of allogeneic BMMSCs and UCMSCs in treating HBV-related liver failure. This trial administers weekly intravenous infusions of 0.1, 1, or 10 million cells per kg for 8 weeks. For the two cell-free therapies, one trial uses EVs for treating ALF and ACLF, with a weekly injection of 10^{10} MSC-EV particles per 100 ml for four weeks. The other trial uses UCMSC-derived exosomes for treating decompensated liver cirrhosis, with a final dose of 40 mg over three weeks. These trials typically assess liver function, as well as survival rate.

Results of clinical trials evaluating MSC therapy for liver failure (liver decompensation)

Among the clinical trials for liver failure or liver decompensation, five have published results. In a trial registered under NCT01322906, the efficacy of allogeneic BMMSCs was evaluated in 110 patients with HBV-mediated ACLF [103]. Patients were randomized into two groups: 56 received weekly infusions of 0.1-1 million cells/kg for 4 weeks, while 54 received standard medical therapy (SMT). The BMMSC group had a 24-week survival rate of 73.2% (95% CI: 61.6-84.8%) compared to 55.6% (95% CI: 42.3-68.9%) in the SMT group (*P*=0.026). In another trial registered under NCT00476060, the safety of autologous BMMSCs was assessed in 53 patients [104]. A control group of 105 patients was matched for age, sex, and biochemical indices, including ALT, albumin, total bilirubin, prothrombin time, and MELD. At 192 weeks of follow-up, there were no significant differences in the incidence of hepatocellular carcinoma or

Table 6 Liver failure or liver decompensation

NCT number	Title	Delivery	Auto/Allo	MSC source	Age (Years)	Phase	Enrollment	Publication
NCT02957552	Safety and Tolerance of Immunomodulating Therapy With Donor-specific MSC in Pediatric Living-Donor Liver Transplantation	IV and portal vein	Allo	BMMSCs	0.17 to 18	1	7	
NCT01690247	Human Mesenchymal Stem Cells Induce Liver Transplant Tolerance	IV	Allo	UCMSCs	18 to 70	1	50	
NCT02223897	Mesenchymal Stem Cells Transplantation for Ischemic-type Biliary Lesions	IV	Allo	UCMSCs	18 to 60	2/3	66	
NCT01429038	Mesenchymal Stem Cells After Renal or Liver Transplantation	UNS	Allo	BMMSCs	18 to 75	1/2	40	Detry O 2017
NCT05881668	MSC-EV in Acute-on-Chronic Liver Failure After Liver Transplantation	UNS	Allo	MSC-EV	18 to 60	1	0	

mortality between the two groups. This indicates that autologous BMMSC transplantation is safe for patients with liver failure due to chronic hepatitis B. In the trial registered under NCT04243681 assessing the safety of infusing a combination of autologous HSCs and MSCs in patients with decompensated liver cirrhosis, the cells were infused through hepatic artery [105]. The study concluded that the combination of autologous HSC and MSC infusion is a safe procedure for patients with decompensated liver cirrhosis, with further evaluation in larger studies currently ongoing. Another trial registered under NCT05227846 using UCMSCs administered a single injection of UCMSCs at predetermined doses (ranging from 5×10^7 to 2×10^8) following the '3+3' rule [106]. The primary outcomes measured were the incidence of adverse events and changes in MELD scores from baseline to the 28th day. Secondary outcomes included changes in the MELD score over time, the incidence of complications associated with decompensated cirrhosis, liver transplant-free survival, and the occurrence of liver failure. Patients in this ongoing study will be followed up to further evaluate safety and tolerability of UCMSC treatment in patients with decompensated liver cirrhosis. In the other trial registered under NCT01724398, a total of 110 patients with HBV-ACLF were enrolled and assigned to one of four treatment groups: control ($n=30$), UCMSC ($n=30$), plasma exchange (PE) ($n=30$), and UCMSC+PE ($n=20$) [107]. The endpoints were the need for liver transplantation or death. While both the UCMSCs alone and the combination of UCMSCs with PE demonstrated good safety, the UCMSC group showed similar outcomes to the control and PE groups. In contrast, the UCMSC+PE group exhibited the lowest rates of liver transplantation and mortality at 30, 60, and 90 days post-treatment compared to the other groups; however, these differences did not reach statistical significance. Though further studies are needed, with over thirty trials underway, MSC therapy offers an encouraging alternative

to liver failure or decompensation, particularly those of autologous and umbilical cord-derived sources.

Transplantation complications

Liver transplantation is used to restore liver function in end-stage liver diseases or liver failure; however, its complications often lead to lethality. To date, five allogenic MSC-based trials have been conducted, including two using BMMSCs, two using UCMSCs, and one using EVs to treat or prevent complications associated with liver transplantation (Table 6). The introduction of calcineurin-based immunosuppression has significantly improved patient and graft survival in pediatric liver transplantation. However, calcineurin inhibitor (CNI) toxicity reduces the quality of life for many recipients and results in significant morbidity. Moreover, CNI is unable to prevent long-term allograft inflammation and fibrosis. MSCs are believed to have potent immunomodulatory properties, potentially promoting allograft tolerance and reducing the toxicity from high-dose CNI exposure. In one trial, allograft BMMSCs were administered in two doses of one million cells, first via the portal vein and then through the peripheral vein, to evaluate their safety in pediatric living-donor liver transplantation and their effect on immunomodulation and graft survival. Despite the benefits of current immunosuppressive agents in reducing acute cellular rejection after liver transplantation, the rate remains high, reaching 20–50%. Furthermore, the long-term side effects of these treatments pose a major challenge for liver transplant recipients, increasingly being recognized as an unmet clinical need. One trial assesses the safety and tolerability of third-part BMMSC administration with a dose of 1.5 to 3 million cells per kg after liver or kidney organ transplantation. One trial is focused on assessing the impact of UCMSCs on improving conditions in liver transplant patients. In this trial, UCMSCs are administered in conjunction with 12 weeks of standard immunosuppressive agents to evaluate their safety. Another trial is investigating UCMSCs' effectiveness in treating or preventing ischemic-type

biliary lesions, a significant cause of graft loss and mortality after orthotopic liver transplantation. Patients in this trial receive UCMSCs at a dose of one million cells per kg once a week for the first month, and then once a month for six months (a total of 9 doses). In addition to BMMSC or UCMSC therapies using intravenous infusion, another trial uses MSC-derived EV from unspecified sources with a dose of 10^{10} particles per 100 ml for ACLF after liver transplantation. Among these trials, one BMMSC trial registered under NCT01429038 has published results, showing no side effects from MSC infusion at day 3 after liver transplantation, though the infusion did not promote tolerance [108]. This study showed no toxicity after a single MSC infusion, but was insufficient to allow the withdrawal of immunosuppression. It opens the path for further trials with repeated infusions or combining MSCs with other immunosuppressive cells, such as Tregs, in liver transplant recipients. Overall, the five allogeneic MSC-based trials, including two BMMSCs, two UCMSCs, and one EV trial, target complications in liver transplantation. Additionally, results from a clinical trial registered as ChiCTR2000037732 on another platform chictr.org.tw indicated that allogeneic UCMSCs are comparable to rituximab treatment for the prophylaxis of antibody-mediated rejection in ABO-incompatible liver transplantation [109]. These studies evaluate immunomodulatory properties, safety, and graft tolerance, with ongoing research needed to address remaining challenges.

Limitations and challenges

While MSC-based treatments for liver diseases have shown promise in clinical practice, several limitations and challenges remain. One significant issue is the low engraftment and retention rates of MSCs in the liver following intravenous infusion [110], which can reduce their therapeutic efficacy. Additionally, the variability in MSC sources, methods of isolation, and culture conditions may lead to inconsistent quality and functionality of the cells, complicating standardization across studies [111]. Immunogenicity is another concern, as MSCs may elicit variable immune responses in recipients, potentially resulting in adverse outcomes [112]. Furthermore, our understanding of the detailed mechanisms through which MSCs exert their effects is still limited, hindering the optimization of treatment protocols and patient selection criteria. Addressing these challenges is essential for advancing MSC therapies in the clinical management of liver diseases.

Summary

In our study, we reviewed the current clinical trials of MSC therapy for treating various liver diseases. Chronic liver diseases often progress to cirrhosis and liver failure, for which treatment options are limited. MSCs, with their immunomodulatory and regenerative properties, as well as their ability to transdifferentiate into hepatocytes, offer promising alternatives. Based on current clinical trials, According to current clinical trials, UCMSCs are the most commonly used source, offering an off-the-shelf solution. Autologous MSC-derived hepatocytes specifically target cirrhosis, while allogeneic sources are used to address complications in liver transplantation. Current clinical results indicate that MSC therapy is both safe and effective. However, further large-scale studies are necessary to confirm its broader applications.

Author contributions

W.C.H.: conception, manuscript writing, and funding; Y.C.L. & P.X.C.: data research & organization; L.T.W.: conception, manuscript writing and editing, final approval, funding.

Declarations

Competing interests
The authors declare that they have no competing financial interests.

References

1. Devarbhavi H, Asrani SK, Arab JP, Nartey YA, Pose E. Kamath P.S. global burden of liver disease: 2023 update. J Hepatol. 2023;79(2):516–37.
2. Sharma A, Nagalli S. Chronic Liver Disease. StatPearls, Treasure Island (FL) ineligible companies. Disclosure: Shivaraj Nagalli declares no relevant financial relationships with ineligible companies., 2024.
3. Sriram I, Nicklas D. Biliary atresia. Pediatr Rev. 2022;43(11):659–61.
4. Alkhouri N, Gonzalez-Peralta RP, Medici V. Wilson disease: a summary of the updated AASLD practice Guidance. Hepatol Commun. 2023;7(6).
5. Meng Z, Yang Y. Advances in the treatment of Autoimmune Hepatitis. J Clin Transl Hepatol. 2024;12(10):878–85.
6. Tapper EB, Parikh ND. Diagnosis and management of cirrhosis and its complications: a review. JAMA. 2023;329(18):1589–602.
7. Shingina A. Highlights from the ACG guidelines for Acute Liver failure. Gastroenterol Hepatol (N Y). 2024;20(1):61–3.
8. European Association for the Study of the Liver. Electronic address e.e.e., Clinical Practice Guideline Panel, Samuel C, Representative D. E.G.B., Panel m. and European Association for the Study of the L. EASL Clinical Practice Guidelines on liver transplantation. J Hepatol. 2024;81(6):1040–1086.
9. Issa DH, Alkhouri N. Long-term management of liver transplant recipients: a review for the internist. Cleve Clin J Med. 2015;82(6):361–72.
10. Alfaifi M, Eom YW, Newsome PN, Baik SK. Mesenchymal stromal cell therapy for liver diseases. J Hepatol. 2018;68(6):1272–85.
11. Wang LT, Liu KJ, Sytwu HK, Yen ML, Yen BL. Advances in mesenchymal stem cell therapy for immune and inflammatory diseases: Use of cell-free products and human pluripotent stem cell-derived mesenchymal stem cells. Stem Cells Transl Med. 2021;10(9):1288–303.

12. Yao L, Hu X, Dai K, Yuan M, Liu P, Zhang Q, Jiang Y. Mesenchymal stromal cells: promising treatment for liver cirrhosis. Stem Cell Res Ther. 2022;13(1):308.

13. Asrani SK, Devarbhavi H, Eaton J, Kamath PS. Burden of liver diseases in the world. J Hepatol. 2019;70(1):151–71.

14. Mack CL, Adams D, Assis DN, Kerkar N, Manns MP, Mayo MJ, Vierling JM, Alsawas M, Murad MH, Czaja AJ. Diagnosis and management of Autoimmune Hepatitis in adults and children: 2019 Practice Guidance and Guidelines from the American Association for the study of Liver diseases. Hepatology. 2020;72(2):671–722.

15. Czlonkowska A, Litwin T, Dusek P, Ferenci P, Lutsenko S, Medici V, Rybakowski JK, Weiss KH, Schilsky ML. Wilson disease. Nat Rev Dis Primers. 2018;4(1):21.

16. Schilsky ML. Wilson disease: new insights into pathogenesis, diagnosis, and future therapy. Curr Gastroenterol Rep. 2005;7(1):26–31.

17. Hartley JL, Davenport M, Kelly DA. Biliary atresia. Lancet. 2009;374(9702):1704–13.

18. Bezerra JA, Wells RG, Mack CL, Karpen SJ, Hoofnagle JH, Doo E, Sokol RJ. Biliary atresia: clinical and Research challenges for the twenty-First Century. Hepatology. 2018;68(3):1163–73.

19. Schuppan D, Afdhal NH. Liver cirrhosis. Lancet. 2008;371(9615):838–51.

20. Tsochatzis EA, Bosch J, Burroughs AK. Liver cirrhosis. Lancet. 2014;383(9930):1749–61.

21. Zhang CY, Yuan WG, He P, Lei JH, Wang CX. Liver fibrosis and hepatic stellate cells: etiology, pathological hallmarks and therapeutic targets. World J Gastroenterol. 2016;22(48):10512–22.

22. Bernal W, Wendon J. Acute liver failure. N Engl J Med. 2013;369(26):2525–34.

23. Stravitz RT, Lee WM. Acute liver failure. Lancet. 2019;394(10201):869–81.

24. Neuberger JM, Bechstein WO, Kuypers DR, Burra P, Citterio F, De Geest S, Duvoux C, Jardine AG, Kamar N, Kramer BK, Metselaar HJ, Nevens F, Pirenne J, Rodriguez-Peralvarez ML, Samuel D, Schneeberger S, Seron D, Trunecka P, Tisone G, van Gelder T. Practical recommendations for long-term management of modifiable risks in kidney and liver transplant recipients: a Guidance Report and Clinical Checklist by the Consensus on managing modifiable risk in transplantation (COMMIT) Group. Transplantation. 2017;101(4S Suppl 2):S1–56.

25. Charlton M, Levitsky J, Aqel B, O'Grady J, Hemibach J, Rinella M, Fung J, Ghabril M, Thomason R, Burra P, Little EC, Berenguer M, Shaked A, Trotter J, Roberts J, Rodriguez-Davalos M, Rela M, Pomfret E, Heyrend C, Gallegos-Orozco J, Saliba F. International Liver Transplantation Society Consensus Statement on Immunosuppression in Liver Transplant recipients. Transplantation. 2018;102(5):727–43.

26. Kuo A, Terrault NA. Management of hepatitis C in liver transplant recipients. Am J Transpl. 2006;6(3):449–58.

27. Koyama Y, Brenner DA. Liver inflammation and fibrosis. J Clin Invest. 2017;127(1):55–64.

28. Papaioannou S, See JX, Jeong M, De La Torre C, Ast V, Reiners-Koch PS, Sati A, Mogler C, Platten M, Cerwenka A, Stojanovic A. Liver sinusoidal endothelial cells orchestrate NK cell recruitment and activation in acute inflammatory liver injury. Cell Rep. 2023;42(8):112836.

29. Wang LT, Ting CH, Yen ML, Liu KJ, Sytwu HK, Wu KK, Yen BL. Human mesenchymal stem cells (MSCs) for treatment towards immune- and inflammation-mediated diseases: review of current clinical trials. J Biomed Sci. 2016;23(1):76.

30. Kharaziha P, Hellstrom 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(10):1199–205.

31. Shi M, Zhang Z, Xu R, Lin H, Fu J, Zou Z, Zhang A, Shi J, Chen L, Lv S, He W, Geng H, Jin L, Liu Z, Wang FS. Human mesenchymal stem cell transfusion is safe and improves liver function in acute-on-chronic liver failure patients. Stem Cells Transl Med. 2012;1(10):725–31.

32. Lu W, Qu J, Yan L, Tang X, Wang X, Ye A, Zou Z, Li L, Ye J, Zhou L. Efficacy and safety of mesenchymal stem cell therapy in liver cirrhosis: a systematic review and meta-analysis. Stem Cell Res Ther. 2023;14(1):301.

33. Liu P, Qian Y, Liu X, Zhu X, Zhang X, Lv Y, Xiang J. Immunomodulatory role of mesenchymal stem cell therapy in liver fibrosis. Front Immunol. 2022;13:1096402.

34. Sioud M, Mobergslien A, Boudabous A, Floisand Y. Mesenchymal stem cell-mediated T cell suppression occurs through secreted galectins. Int J Oncol. 2011;38(2):385–90.

35. Fan J, Tang X, Wang Q, Zhang Z, Wu S, Li W, Liu S, Yao G, Chen H, Sun L. Mesenchymal stem cells alleviate experimental autoimmune cholangitis through immunosuppression and cytoprotective function mediated by galectin-9. Stem Cell Res Ther. 2018;9(1):237.

36. Zafranskaya M, Nizheharodava D, Yurkevich M, Ivanchik G, Demidchik Y, Kozhukh H, Fedulov A. PGE2 contributes to in vitro MSC-mediated inhibition of non-specific and antigen-specific T cell proliferation in MS patients. Scand J Immunol. 2013;78(5):455–62.

37. Yang SH, Park MJ, Yoon IH, Kim SY, Hong SH, Shin JY, Nam HY, Kim YH, Kim B, Park CG. Soluble mediators from mesenchymal stem cells suppress T cell proliferation by inducing IL-10. Exp Mol Med. 2009;41(5):315–24.

38. Cho WJ, Pulimamidi VK, Mittal SK, Chauhan SK. Mesenchymal stromal cells protect tissues from Th1 immune responses via IL-11 secretion. FASEB J. 2024;38(10):e23683.

39. Wang WB, Yen ML, Liu KJ, Hsu PJ, Lin MH, Chen PM, Sudhir PR, Chen CH, Chen CH, Sytwu HK, Yen BL. Interleukin-25 mediates Transcriptional Control of PD-L1 via STAT3 in Multipotent Human mesenchymal stromal cells (hMSCs) to suppress Th17 responses. Stem Cell Rep. 2015;5(3):392–404.

40. Lee K, Park N, Jung H, Rim YA, Nam Y, Lee J, Park SH, Ju JH. Mesenchymal stem cells ameliorate experimental arthritis via expression of interleukin-1 receptor antagonist. PLoS ONE. 2018;13(2):e0193086.

41. Ren G, Zhang L, Zhao X, Xu G, Zhang Y, Roberts AI, Zhao RC, Shi Y. Mesenchymal stem cell-mediated immunosuppression occurs via concerted action of chemokines and nitric oxide. Cell Stem Cell. 2008;2(2):141–50.

42. Su J, Chen X, Huang Y, Li W, Li J, Cao K, Cao G, Zhang L, Li F, Roberts AI, Kang H, Yu P, Ren G, Ji W, Wang Y, Shi Y. Phylogenetic distinction of iNOS and IDO function in mesenchymal stem cell-mediated immunosuppression in mammalian species. Cell Death Differ. 2014;21(3):388–96.

43. Mougiakakos D, Jitschin R, Johansson CC, Okita R, Kiessling R, Le Blanc K. The impact of inflammatory licensing on heme oxygenase-1-mediated induction of regulatory T cells by human mesenchymal stem cells. Blood. 2011;117(18):4826–35.

44. Morandi F, Raffaghello L, Bianchi G, Meloni F, Salis A, Millo E, Ferrone S, Barnaba V. and, Pistoia V. Immunogenicity of human mesenchymal stem cells in HLA-class I-restricted T-cell responses against viral or tumor-associated antigens. Stem Cells. 2008;26(5):1275–87.

45. Selmani Z, Naji A, Zidi I, Favier B, Gaiffe E, Obert L, Borg C, Saas P, Tiberghien P, Rouas-Freiss N, Carosella ED, Deschaseaux F. Human leukocyte antigen-G5 secretion by human mesenchymal stem cells is required to suppress T lymphocyte and natural killer function and to induce CD4 + CD25highFOXP3 + regulatory T cells. Stem Cells. 2008;26(1):212–22.

46. Yen BL, Hwa HL, Hsu PJ, Chen PM, Wang LT, Jiang SS, Liu KJ, Sytwu HK, Yen M. L. HLA-G expression in human mesenchymal stem cells (MSCs) is related to unique methylation pattern in the proximal promoter as well as Gene body DNA. Int J Mol Sci. 2020;21(14).

47. Chen QH, Wu F, Liu L, Chen HB, Zheng RQ, Wang HL, Yu LN. Mesenchymal stem cells regulate the Th17/Treg cell balance partly through hepatocyte growth factor in vitro. Stem Cell Res Ther. 2020;11(1):91.

48. Xue M, Zhang X, Chen J, Liu F, Xu J, Xie J, Yang Y, Yu W, Qiu H. Mesenchymal stem cell-secreted TGF-beta1 restores Treg/Th17 Skewing Induced by Lipopolysaccharide and Hypoxia Challenge via miR-155 suppression. Stem Cells Int. 2022;2022:5522828.

49. Davies LC, Heldring N, Kadri N, Le Blanc K. Mesenchymal stromal cell secretion of programmed Death-1 Ligands regulates T cell mediated Immunosuppression. Stem Cells. 2017;35(3):766–76.

50. Cahill EF, Tobin LM, Carty F, Mahon BP, English K. Jagged-1 is required for the expansion of CD4 + CD25 + FoxP3 + regulatory T cells and tolerogenic dendritic cells by murine mesenchymal stromal cells. Stem Cell Res Ther. 2015;6(1):19.

51. Akiyama K, Chen C, Wang D, Xu X, Qu C, Yamaza T, Cai T, Chen W, Sun L. and, Shi S. Mesenchymal-stem-cell-induced immunoregulation involves FAS-ligand-/FAS-mediated T cell apoptosis. Cell Stem Cell. 2012;10(5):544–55.

52. Augello A, Tasso R, Negrini SM, Amateis A, Indiveri F, Cancedda R, Pennesi G. Bone marrow mesenchymal progenitor cells inhibit lymphocyte proliferation by activation of the programmed death 1 pathway. Eur J Immunol. 2005;35(5):1482–90.

53. Bai X, Chen T, Li Y, Ge X, Qiu C, Gou H, Wei S, Liu T, Yang W, Yang L, Liang Y, Jia Z, Lv L, Li T. PD-L1 expression levels in mesenchymal stromal cells predict their therapeutic values for autoimmune hepatitis. Stem Cell Res Ther. 2023;14(1):370.

54. Ren G, Zhao X, Zhang L, Zhang J, L'Huillier A, Ling W, Roberts AI, Le AD, Shi S, Shao C, Shi Y. Inflammatory cytokine-induced intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 in mesenchymal stem cells are critical for immunosuppression. J Immunol. 2010;184(5):2321–8.

55. Piekarska K, Urban-Wojciuk Z, Kurkowiak M, Pelikant-Malecka I, Schumacher A, Sakowska J, Spodnik JH, Arcimowicz L, Zielinska H, Tymoniuk B, Renkielska A, Slominska SJ, Trzonkowski E P., Hupp T. and, Marek-Trzonkowska. N.M. Mesenchymal stem cells transfer mitochondria to allogeneic Tregs in an HLA-dependent manner improving their immunosuppressive activity. Nat Commun. 2022;13(1):856.

56. Akhter W, Nakhle J, Vaillant L, Garcin G, Le Saout C, Simon M, Crozet C, Djouad F, Jorgensen C, Vignais ML, Hernandez J. Transfer of mesenchymal stem cell mitochondria to CD4(+) T cells contributes to repress Th1 differentiation by downregulating T-bet expression. Stem Cell Res Ther. 2023;14(1):12.

57. Luz-Crawford P, Hernandez J, Djouad F, Luque-Campos N, Caicedo A, Carrere-Kremer S, Brondello JM, Vignais ML, Pene J, Jorgensen C. Mesenchymal stem cell repression of Th17 cells is triggered by mitochondrial transfer. Stem Cell Res Ther. 2019;10(1):232.

58. Luz-Crawford P, Djouad F, Toupet K, Bony C, Franquesa M, Hoogduijn MJ, Jorgensen C, Noel D. Mesenchymal stem cell-derived interleukin 1 receptor antagonist promotes macrophage polarization and inhibits B cell differentiation. Stem Cells. 2016;34(2):483–92.

59. Hermankova B, Zajicova A, Javorkova E, Chudickova M, Trosan P, Hajkova M, Krulova M, Holan V. Suppression of IL-10 production by activated B cells via a cell contact-dependent cyclooxygenase-2 pathway upregulated in IFN-gamma-treated mesenchymal stem cells. Immunobiology. 2016;221(2):129–36.

60. Cho KA, Lee JK, Kim YH, Park M, Woo SY, Ryu KH. Mesenchymal stem cells ameliorate B-cell-mediated immune responses and increase IL-10-expressing regulatory B cells in an EBI3-dependent manner. Cell Mol Immunol. 2017;14(11):895–908.

61. Li H, Deng Y, Liang J, Huang F, Qiu W, Zhang M, Long Y, Hu X, Lu Z, Liu W, Zheng SG. Mesenchymal stromal cells attenuate multiple sclerosis via IDO-dependent increasing the suppressive proportion of CD5 + IL-10 + B cells. Am J Transl Res. 2019;11(9):5673–88.

62. Che N, Li X, Zhang L, Liu R, Chen H, Gao X, Shi S, Chen W, Sun L. Impaired B cell inhibition by lupus bone marrow mesenchymal stem cells is caused by reduced CCL2 expression. J Immunol. 2014;193(10):5306–14.

63. Spaggiari GM, Capobianco A, Abdelrazik H, Becchetti F, Mingari MC, Moretta L. Mesenchymal stem cells inhibit natural killer-cell proliferation, cytotoxicity, and cytokine production: role of indoleamine 2,3-dioxygenase and prostaglandin E2. Blood. 2008;111(3):1327–33.

64. Sotiropoulou PA, Perez SA, Gritzapis AD, Baxevanis CN, Papamichail M. Interactions between human mesenchymal stem cells and natural killer cells. Stem Cells. 2006;24(1):74–85.

65. Liu KJ, Wang CJ, Chang CJ, Hu HI, Hsu PJ, Wu YC, Bai CH, Sytwu HK, Yen BL. Surface expression of HLA-G is involved in mediating immunomodulatory effects of placenta-derived multipotent cells (PDMCs) towards natural killer lymphocytes. Cell Transpl. 2011;20(11–12):1721–30.

66. Djouad F, Charbonnier LM, Bouffi C, Louis-Plence P, Bony C, Apparailly F, Cantos C, Jorgensen C, Noel D. Mesenchymal stem cells inhibit the differentiation of dendritic cells through an interleukin-6-dependent mechanism. Stem Cells. 2007;25(8):2025–32.

67. Spaggiari GM, Abdelrazik H, Becchetti F, Moretta L. MSCs inhibit monocyte-derived DC maturation and function by selectively interfering with the generation of immature DCs: central role of MSC-derived prostaglandin E2. Blood. 2009;113(26):6576–83.

68. Wu L, Cao H, Tian X, Zheng W, Yuan M, Li X, Tian X, Wang Y, Song H. Bone marrow mesenchymal stem cells modified with heme oxygenase-1 alleviate rejection of donation after circulatory death liver transplantation by inhibiting dendritic cell maturation in rats. Int Immunopharmacol. 2022;107:108643.

69. Chen HW, Chen HY, Wang LT, Wang FH, Fang LW, Lai HY, Chen HH, Lu J, Hung MS, Cheng Y, Chen MY, Liu SJ, Chong P, Lee OK, Hsu SC. Mesenchymal stem cells tune the development of monocyte-derived dendritic cells toward a myeloid-derived suppressive phenotype through growth-regulated oncogene chemokines. J Immunol. 2013;190(10):5065–77.

70. Zhang B, Liu R, Shi D, Liu X, Chen Y, Dou X, Zhu X, Lu C, Liang W, Liao L, Zenke M, Zhao RC. Mesenchymal stem cells induce mature dendritic cells into a novel jagged-2-dependent regulatory dendritic cell population. Blood. 2009;113(1):46–57.

71. Whelan DS, Caplice NM, Clover AJP. Mesenchymal stromal cell derived CCL2 is required for accelerated wound healing. Sci Rep. 2020;10(1):2642.

72. Liu F, Qiu H, Xue M, Zhang S, Zhang X, Xu J, Chen J, Yang Y, Xie J. MSC-secreted TGF-beta regulates lipopolysaccharide-stimulated macrophage M2-like polarization via the Akt/FoxO1 pathway. Stem Cell Res Ther. 2019;10(1):345.

73. Wang J, Liu Y, Ding H, Shi X, Ren H. Mesenchymal stem cell-secreted prostaglandin E(2) ameliorates acute liver failure via attenuation of cell death and regulation of macrophage polarization. Stem Cell Res Ther. 2021;12(1):15.

74. Choi H, Lee RH, Bazhanov N, Oh JY, Prockop DJ. Anti-inflammatory protein TSG-6 secreted by activated MSCs attenuates zymosan-induced mouse peritonitis by decreasing TLR2/NF-kappaB signaling in resident macrophages. Blood. 2011;118(2):330–8.

75. Xia TT, Hu R, Shao CJ, Feng Y, Yang XL, Xie YP, Shi JX, Li JS, Li XM. Stannio-calcin-1 secreted by human umbilical mesenchymal stem cells regulates interleukin-10 expression via the PI3K/AKT/mTOR pathway in alveolar macrophages. Cytokine. 2023;162:156114.

76. Lv H, Liu Q, Sun Y, Yi X, Wei X, Liu W, Zhang Q, Yi H, Chen G. Mesenchymal stromal cells ameliorate acute lung injury induced by LPS mainly through stanniocalcin-2 mediating macrophage polarization. Ann Transl Med. 2020;8(6):334.

77. Du L, Lin L, Li Q, Liu K, Huang Y, Wang X, Cao K, Chen X, Cao W, Li F, Shao C, Wang Y, Shi Y. IGF-2 Preprograms Maturing macrophages to acquire oxidative phosphorylation-dependent anti-inflammatory properties. Cell Metab. 2019;29(6):1363–e13751368.

78. Lee JW, Krasnodembskaya A, McKenna DH, Song Y, Abbott J, Matthay MA. Therapeutic effects of human mesenchymal stem cells in ex vivo human lungs injured with live bacteria. Am J Respir Crit Care Med. 2013;187(7):751–60.

79. Li H, Yuan Y, Chen H, Dai H, Li J. Indoleamine 2,3-dioxygenase mediates the therapeutic effects of adipose-derived stromal/stem cells in experimental periodontitis by modulating macrophages through the kynurenine-AhR-NRF2 pathway. Mol Metab. 2022;66:101617.

80. Jiang D, Muschhammer J, Qi Y, Kugler A, de Vries JC, Saffarzadeh M, Sindrilaru A, Beken SV, Wlaschek M, Kluth MA, Ganss C, Frank NY, Frank MH, Preissner KT, Scharffetter-Kochanek K. Suppression of neutrophil-mediated tissue Damage-A novel skill of mesenchymal stem cells. Stem Cells. 2016;34(9):2393–406.

81. Yen BL, Yen ML, Hsu PJ, Liu KJ, Wang CJ, Bai CH, Sytwu HK. Multipotent human mesenchymal stromal cells mediate expansion of myeloid-derived suppressor cells via hepatocyte growth factor/c-met and STAT3. Stem Cell Reports. 2013;1(2):139–151.

82. Lee HJ, Ko JH, Kim HJ, Jeong HJ, Oh JY. Mesenchymal stromal cells induce distinct myeloid-derived suppressor cells in inflammation. JCI Insight. 2020;5(12).

83. Lee HJ, Ko JH, Jeong HJ, Ko AY, Kim MK, Wee WR, Yoon SO, Oh JY. Mesenchymal stem/stromal cells protect against autoimmunity via CCL2-dependent recruitment of myeloid-derived suppressor cells. J Immunol. 2015;194(8):3634–45.

84. Yang S, Wei Y, Sun R, Lu W, Lv H, Xiao X, Cao Y, Jin X, Zhao M. Umbilical cord blood-derived mesenchymal stromal cells promote myeloid-derived suppressor cell proliferation by secreting HLA-G to reduce acute graft-versus-host disease after hematopoietic stem cell transplantation. Cytotherapy. 2020;22(12):718–33.

85. Lee C, Kim M, Han J, Yoon M, Jung Y. Mesenchymal stem cells influence activation of hepatic stellate cells, and constitute a Promising Therapy for Liver Fibrosis. Biomedicines. 2021;9(11).

86. Hazrati A, Malekpour K, Soudi S, Hashemi SM. Mesenchymal Stromal/Stem cells and their extracellular vesicles application in Acute and Chronic Inflammatory Liver diseases: emphasizing on the anti-fibrotic and immunomodulatory mechanisms. Front Immunol. 2022;13:865888.

87. Nazarie Ignat SR, Gharbia S, Hermenean A, Dinescu S, Costache M. Regenerative Potential of Mesenchymal Stem Cells' (MSCs) Secretome for Liver Fibrosis Therapies. Int J Mol Sci. 2021;22(24).

88. Parekkadan B, van Poll D, Suganuma K, Carter EA, Berthiaume F, Tilles AW, Yarmush ML. Mesenchymal stem cell-derived molecules reverse fulminant hepatic failure. PLoS ONE. 2007;2(9):e941.

89. Kisseleva T, Brenner DA. Anti-fibrogenic strategies and the regression of fibrosis. Best Pract Res Clin Gastroenterol. 2011;25(2):305–17.

90. Lee KD, Kuo TK, Whang-Peng J, Chung YF, Lin CT, Chou SH, Chen JR, Chen YP, Lee OK. In vitro hepatic differentiation of human mesenchymal stem cells. Hepatology. 2004;40(6):1275–84.

91. Lee HJ, Jung J, Cho KJ, Lee CK, Hwang SG, Kim GJ. Comparison of in vitro hepatogenic differentiation potential between various placenta-derived stem cells and other adult stem cells as an alternative source of functional hepatocytes. Differentiation. 2012;84(3):223–31.

92. Meirelles Lda S, Fontes AM, Covas DT, Caplan AI. Mechanisms involved in the therapeutic properties of mesenchymal stem cells. Cytokine Growth Factor Rev. 2009;20(5–6):419–27.

93. Han Y, Yang J, Fang J, Zhou Y, Candi E, Wang J, Hua D, Shao C, Shi Y. The secretion profile of mesenchymal stem cells and potential applications in treating human diseases. Signal Transduct Target Ther. 2022;7(1):92.
94. Ryan JM, Barry FP, Murphy JM, Mahon BP. Mesenchymal stem cells avoid allogeneic rejection. J Inflamm (Lond). 2005;2:8.
95. Ankrum JA, Ong JF, Karp JM. Mesenchymal stem cells: immune evasive, not immune privileged. Nat Biotechnol. 2014;32(3):252–60.
96. Barbash IM, Chouraqui P, Baron J, Feinberg MS, Etzion S, Tessone A, Miller L, Guetta E, Zipori D, Kedes LH, Kloner RA, Leor J. Systemic delivery of bone marrow-derived mesenchymal stem cells to the infarcted myocardium: feasibility, cell migration, and body distribution. Circulation. 2003;108(7):863–8.
97. Tsuchiya A, Takeuchi S, Watanabe T, Yoshida T, Nojiri S, Ogawa M, Terai S. Mesenchymal stem cell therapies for liver cirrhosis: MSCs as conducting cells for improvement of liver fibrosis and regeneration. Inflamm Regen. 2019;39:18.
98. Eom YW, Kang SH, Kim MY, Lee JI, Baik SK. Mesenchymal stem cells to treat liver diseases. Ann Transl Med. 2020;8(8):563.
99. Zhang S, Yang Y, Fan L, Zhang F, Li L. The clinical application of mesenchymal stem cells in liver disease: the current situation and potential future. Ann Transl Med. 2020;8(8):565.
100. Han HT, Jin WL, Li X. Mesenchymal stem cells-based therapy in liver diseases. Mol Biomed. 2022;3(1):23.
101. Jang YO, Kim YJ, Baik SK, Kim MY, Eom YW, Cho MY, Park HJ, Park SY, Kim BR, Kim JW, Soo Kim H, Kwon SO, Choi EH, Kim YM. Histological improvement following administration of autologous bone marrow-derived mesenchymal stem cells for alcoholic cirrhosis: a pilot study. Liver Int. 2014;34(1):33–41.
102. Salama H, Zekri AR, Medhat E, Al Alim SA, Ahmed OS, Bahnassy AA, Lotfy MM, Ahmed R, Musa S. Peripheral vein infusion of autologous mesenchymal stem cells in Egyptian HCV-positive patients with end-stage liver disease. Stem Cell Res Ther. 2014;5(3):70.
103. Lin BL, Chen JF, Qiu WH, Wang KW, Xie DY, Chen XY, Liu QL, Peng L, Li JG, Mei YY, Weng WZ, Peng YW, Cao HJ, Xie JQ, Xie SB, Xiang AP, Gao ZL. Allogeneic bone marrow-derived mesenchymal stromal cells for hepatitis B virus-related acute-on-chronic liver failure: a randomized controlled trial. Hepatology. 2017;66(1):209–19.
104. 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(3):820–8.
105. Sharma M, Pondugala PK, Jaggaihgari S, Mitnala S, Krishna VV, Jaishetwar G, Naik P, Kumar P, Kulkarni A, Gupta R, Singh JR, Darisetty S, Sekharan A, Reddy DN, Rao GV, Syeda F. Jagtap N. and Rao P.N. Safety Assessment of autologous stem cell combination therapy in patients with decompensated liver cirrhosis: a pilot study. J Clin Exp Hepatol. 2022;12(1):80–8.
106. Wang Z, Li T, Zhang Z, Yuan M, Shi M, Wang FS, Linghu EQ, Shi L. Human umbilical cord-derived mesenchymal stem cells for the treatment of decompensated cirrhosis (MSC-DLC-1): a dose-escalation, phase I trial protocol. BMJ Open. 2023;13(12):e078362.
107. Xu WX, He HL, Pan SW, Chen YL, Zhang ML, Zhu S, Gao ZL, Peng L, Li JG. Combination treatments of plasma exchange and umbilical cord-derived mesenchymal stem cell transplantation for patients with Hepatitis B Virus-related Acute-on-chronic liver failure: a clinical trial in China. Stem Cells Int. 2019;2019:4130757.
108. Detry O, Vandermeulen M, Delbouille MH, Somja J, Bletard N, Briquet A, Lechanteur C, Giet O, Baudoux E, Hannon M, Baron F, Beguin Y. Infusion of mesenchymal stromal cells after deceased liver transplantation: a phase I-II, open-label, clinical study. J Hepatol. 2017;67(1):47–55.
109. Zhang Y, Zhang J, Yi H, Zheng J, Cai J, Chen W, Lu T, Chen L, Du C, Liu J, Yao J, Zhao H, Wang G, Fu B, Zhang T, Zhang J, Wang G, Li H, Xiang AP, Chen G, Yi S, Zhang Q, Yang Y. A novel MSC-based immune induction strategy for ABO-incompatible liver transplantation: a phase I/II randomized, open-label, controlled trial. Stem Cell Res Ther. 2021;12(1):244.
110. Parekkadan B, Milwid JM. Mesenchymal stem cells as therapeutics. Annu Rev Biomed Eng. 2010;12:87–117.
111. Mushahary D, Spittler A, Kasper C, Weber V. and, Charwat V. Isolation, cultivation, and characterization of human mesenchymal stem cells. Cytometry A. 2018;93(1):19–31.
112. Chen W, Lv L, Chen N, Cui E. Immunogenicity of mesenchymal stromal/stem cells. Scand J Immunol. 2023;97(6):e13267.

Publisher's note