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**Stem cell transplantation for treatment of end-stage liver disease**

Wu DB *et al*. Stem cell for ESLD therapy

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**Abstract**

The past two decades have witnessed an explosion of research and clinical application of stem cells, transforming the field of regenerative medicine. Stem cell transplantation has already been performed to treat patients with cancer, liver diseases, and various kinds of chronic diseases. Indeed, stem cell-based therapies are effective for many diseases, including providing novel insights into the treatment of end-stage liver disease. Several clinical trials have indicated the efficacy profiles of stem cell transplantation for patients with end-stage liver disease, including liver cirrhosis, liver failure, and liver tumors. Animal models of acute liver failure have also provided important insights into the safety, mechanisms, and efficacy of stem cell therapies. Nevertheless, excitement of this promising field must be tempered with careful and calculated research. In particular, studies on the quality, safety, and efficacy of stem cell transplantation are needed so that qualified products are tested in well-designed clinical trials and approved by governments. Therefore, there is much more work required to effectively balance the safety with the innovation of stem cell transplantation research toward the effective treatment of end-stage liver disease.

**Key words:** Stem cell transplantation; End-stage liver disease; Clinical treatment; Efficacy; Safety

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**Core tips**: Stem cells have the capacity for multiple rounds of self-renewal and differentiation, and play important roles in numerous biological functions. Treatment of end-stage liver disease *via* stem cell transplantation has emerged as an effective therapeutic alternative in clinical practice. However, caution should be paid to ensuring the safety and efficacy of stem cell transplantation in cases to avoid the use of products that are not rigorously tested that may put patients at risk.

Wu DB, Chen EQ, Tang H. Stem cell transplantation for treatment of end-stage liver disease. *World J Hepatol* 2018; In press

**INTRODUCTION**

Owing to their capacity for multiple rounds of self-renewal and differentiation, stem cells play roles in numerous biological phenomena including immunomodulation, anti-inflammation, anti-apoptosis regulation, angiogenesis, promotion of tissue repair, and production of growth factors[[1-3](#_ENREF_1)]. The term “stem cells” represents cells of various origins, including mesenchymal stem cells (MSCs), adipose-derived mesenchymal stem cells, embryonic stem cells, induced pluripotent stem cells, hepatic progenitor cells, and hematopoietic stem cells[[1](#_ENREF_1),[4-8](#_ENREF_4)]. However, MSCs are the most common stem cell source for basic and clinical research given the lack of ethical constraints regarding their usage and their availability[[4](#_ENREF_4),[8](#_ENREF_8)].

In the past few decades, stem cell transplantation has emerged as a novel and promising therapy for the treatment of patients with cancer, nervous system diseases, eye diseases, orthopedic disorders, diabetes mellitus, and liver diseases. Moreover, advances in stem cell transplantation from basic and translational clinical research have yielded improvements in the survival of patients with benign and malignant hematologic disorders[[9](#_ENREF_9)] and stem cell transplantation has proven to be an effective therapeutic alternative for central nervous system diseases, including Alzheimer’s disease[[10](#_ENREF_10)]. Moreover, stem cell therapy has been shown to delay or suppress the progression of end-stage liver disease[[4](#_ENREF_4),[8](#_ENREF_8),[11](#_ENREF_11)].

**TREATMENT OF END-STAGE LIVER DISEASE VIA STEM CELL TRANSPLANTATION**

To date, there have been numerous clinical studies on stem cell transplantation for treating end-stage liver disease, demonstrating its side effects and efficacy profiles. Furthermore, there were 139 clinical trials registered, including 27 ongoing clinical trials, on the association between stem cell transplantation and liver disease in accordance with the guidelines outlined in ClinicalTrials.gov on July 01, 2018 (http://www.clinicaltrials.gov). Of these, 52 clinical trials were focused on liver cirrhosis (LC), nine on liver failure, and six on liver cancer.

Previous studies indicated that MSC transplantation could constitute an effective treatment of liver cirrhosis. In a multicenter, randomized, open-label, phase 2 trial, autologous bone marrow-derived transplantation of mesenchymal stem cells safely improved liver function and facilitated the quantification of fibrosis upon liver biopsy in patients with alcoholic cirrhosis[[7](#_ENREF_7)]. Another open-labeled, paired, controlled study from China demonstrated that transplantation of umbilical cord-derived MSCs (UC-MSCs) also improved liver function and reduced ascites in patients with chronic hepatitis B (CHB) and in decompensated LC[[1](#_ENREF_1)]. MSC transplantation was also shown to improved liver function in LC patients with autoimmune diseases[[12](#_ENREF_12)]. However, another randomized, controlled phase 2 trial yielded no evidence in support of the benefits of administration of granulocyte colony-stimulating factor (G-CSF) alone or supplementation of G-CSF with stem-cell transplantation, with no significant diﬀerences in improved liver dysfunction or decreased fibrosis in LC patients after stem cell transplantation[[3](#_ENREF_3)]. This conflicting result may be associated with differences in LC etiology, an increased frequency of adverse events, and differences in stem cell types used among the studies.

Moreover, studies with animal models of acute liver failure have shown strong evidence pointing to the success of MSC transplantation in improving liver function, inhibiting hepatocyte apoptosis, and promoting hepatocyte proliferation in animal models of acute liver failure[[6](#_ENREF_6)], suggesting that MSC transplantation may be used to treat liver failure. In 2012, Shi *et al*[[5](#_ENREF_5)] performed a case-control study to evaluate the safety and efficacy of UC-MSC transplantation in CHB patients with acute-on-chronic liver failure (ACLF); and found increased survival rates, accompanied by reduced the end-stage liver disease scores and enhanced liver function. Another study on MSC transplantation for treating ACLF patients also achieved similar results, in which the treatment increased the 24-wk survival rate, improved liver function, and decreased the incidence of severe infections[[11](#_ENREF_11)]. Moreover, we recently conducted a systematic review and meta-analysis of MSC transplantation in ACLF patients, which showed that the treatment significantly reduced mortality rates, without increasing the incidence of severe complications[[13](#_ENREF_13)]. There were also no differences in the incidences of severe complications (*e.g.*, encephalopathy, hepatorenal syndrome, gastrointestinal bleeding) between the stand medicine treatment and the MSC treatment group in ACLF patients[[5](#_ENREF_5)]. Nevertheless, long-term follow-up is needed to confirm the safety of MSC transplantation therapy.

**FUTURE PERSPECTIVES**

Studies on stem cells and regenerative medicine have received increasing attention in the life sciences in the past 20 years. Stem cells are undifferentiated cells that undergo both self-renewal through symmetric cell division and differentiate into specialized cells, tissues, and organs through asymmetric cell division. Stem cell-based therapies have proven to be effective for many diseases, providing novel insights into the treatment of end-stage liver disease. Indeed, in recent years, numerous studies have reported stem cell-based “cures” for an extraordinary and implausible range of medical conditions.

However, research on the safety and innovation of stem cell transplantation for end-stage liver disease must be well-balanced. Some risky procedures performed without substantial evidence have led to medical accidents, leading to blindness, paralysis, or even death[[14](#_ENREF_14)].

Moreover, both the administration and the government must be involved in regulations and advisement to ensure the quality, safety, and efficacy of stem cell transplantation. Two finalized tenders regarding guidelines to establish a more stringent policy framework were issued by the Food and Drug Administration (FDA), which included the requirement of sponsors to document a biological license application, request permission from the agency before proceeding to FDA-supervised clinical trials, and obtain agency approval before marketing[[15](#_ENREF_15)]. To promote rapid yet responsible advancements in the fundamental knowledge and clinical application of stem cells and regenerative medicine, the International Society for Stem Cell Research (ISSCR) has issued three guidelines[[2](#_ENREF_2)]. The 2016 guidelines revise and extend two prior sets of guidelines (ISSCR, 2006; ISSCR, 2008) and address an integrated set of principles and best practices for ensuring progress in basic, translational, and clinical trials[[2](#_ENREF_2)]. Overall, safe and effective stem cell transplantation for treating end-stage liver disease will only be achieved from well-designed clinical trials and qualified products approved by the FDA or the government, while avoiding the high risks of unproven cell therapy products.

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