Trends of Stem Cell-Based Clinical Trials in Gastrointestinal Tract Diseases

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Abstract: Stem cells have great potential to be applied as a treatment for various types of disorders. These cells exert therapeutic effects by modulating the immune system with the capability to secrete cytokines and chemokines. Previous studies have indicated that stem cells could be used as a therapeutic agent for different complaints, such as gastrointestinal diseases. For a long time now, researchers have moved toward stem cells' clinical application in this context. With the increasing number of trials in stem cell therapy of gastrointestinal disease, it is now time to evaluate these clinical trials' status. This paper reviews clinical trials that have used stem cells for the treatment of gastrointestinal tract diseases.

Keywords: Gastrointestinal disease, Stem cell, Clinical trial, Cell therapy, Mesenchymal stem cell.

INTRODUCTION

The human digestive system is made up of the gastrointestinal (GI) tract and other digestive organs. Several diseases, including inflammatory conditions, infections, stones, ulcers, and malignancies, are GI tract disorders [1]. Stem cells are described as undifferentiated cells in embryonic and adult tissues that can differentiate into other cell types. These cells are obtained from different origins, including bone marrow [2], adipose tissue [3], umbilical cord blood [4], placenta [5], and other sources. Stem cells can be used for diverse therapeutic utilization. Several studies have illustrated the safety and efficacy of stem cells for the treatment of various diseases, such as lung [6] and kidney injuries [7], neurodegenerative diseases [8], stroke [9], diabetes [10], heart [11] and GI tract disorders [12-14].

Stem cells through paracrine effects, immunomodulation, and differentiation into many different cells can be appropriate choices for treating various diseases [15, 16]. Stem cells can also be applied as a vehicle for delivering therapeutic factors for targeted therapy in different conditions like GI cancers [17, 18]. The first known use of peripheral stem cell transplantation to treat liver cancer patients was performed in 1995 (NCT00007813). Hematopoietic stem cells (HSCs) transplantation is commonly used in the treatment of hematologic malignancies. Transplantation of these cells restores the immune system. Studies have shown that this treatment can help strengthen the immune system against various GI diseases with the dysfunctional immune system, such as cancers and inflammatory diseases [19, 20].

Promising preclinical studies have led to an increased number of trials investigating the effects of stem cells on the treatment of GI tract disease. In this regard, after more than 20 years from the beginning of stem cell therapies in GI diseases and an increasing number of trials, this therapy's effectiveness is still contradictory. Therefore, it is time for the comprehensive evaluation of trials in this field. To determine the trend of trials in recent years, in this review, we focus on the clinical trials that employed different types of stem cells in GI tract diseases.

Search Strategies

Related clinical trials for all types of stem cells applied in GI tract disease were searched in ClinicalTrial.gov, Irct.ir, clinicaltrialsregister.eu, and Pubmed. The terms used to search clinical trials databases are as follows; “Mesenchymal stem cell(s),”

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"Stem cell," "Stromal cell," "Embryonic stem cell," "Hematopoietic stem cell," "Mononuclear cell," "Unrestricted somatic stem cells," "Hepatocyte," "Fibroblast," AND "Gastrointestinal disease."

Clinical trials with the following criteria were included in this review; 1) Trials relevant to GI disease condition, 2) Studies designed with stem cell therapy intervention. However, the trials with other cell interventions, such as immune cells and trials related to other disease conditions, were considered exclusion criteria.

After collecting trials, the following characteristics of studies were extracted; NCT numbers of trials, trials' disease condition (cancer or non-cancerous), organs involved in the disease, source and type of stem cells used, autologous or allogeneic stem cell transplantation, route of stem cell administration, trials' phases, trials' start years, locations where trials were conducted, use of biomaterial and tissue engineering. In total, 164 unique clinical trials were included (Figure **1**). After reading various parts of the trials, the desired data were extracted.

According to disease condition, the retrieved trials were stratified, organs involved in the disease, source, and type of stem cells, etc. Since some of the trials involved more than one strata, for instance, several organs or countries together, the sum of these parts in the stratified analysis is more than the total number of trials included.

Conditions and Organs Involved in the GI Diseases

The bone marrow, adipose tissue, and medical waste such as the umbilical cord are rich sources of various types of stem cells. Generally, stem cells in GI diseases are primarily used for tissue regeneration upon injury, but after that, they are applied for different purposes in other types of digestive disorders. Studies have indicated that mesenchymal stem cells (MSCs) can differentiate into functional hepatocyte-like cells and improve liver regeneration in cirrhosis [21-23].

Besides, MSCs with anti-inflammatory effects ameliorate inflammatory diseases such as inflammatory bowel disease (IBD) [24-26]. Based on disease etiology, included clinical trials were categorized into two groups, containing cancer or non-cancerous condition. According to this category, non-cancerous conditions include diseases such as cirrhosis, fibrosis, hepatitis, metabolic disorder, ulcerative colitis, and Crohn's disease. Similarly, cancerous conditions include various types of GI tract malignancies.

Based on our data, non-cancerous conditions occupied a more considerable number of trials, 150 studies out of 164. In another category, these trials based on organs involved in the disease were categorized into five groups as follows; the liver, intestine, pancreas, gastric, esophagus. Our analysis showed that among all organs involved in the GI tract disease, the largest proportion of trials is assigned to liver diseases (Figure **2A**).

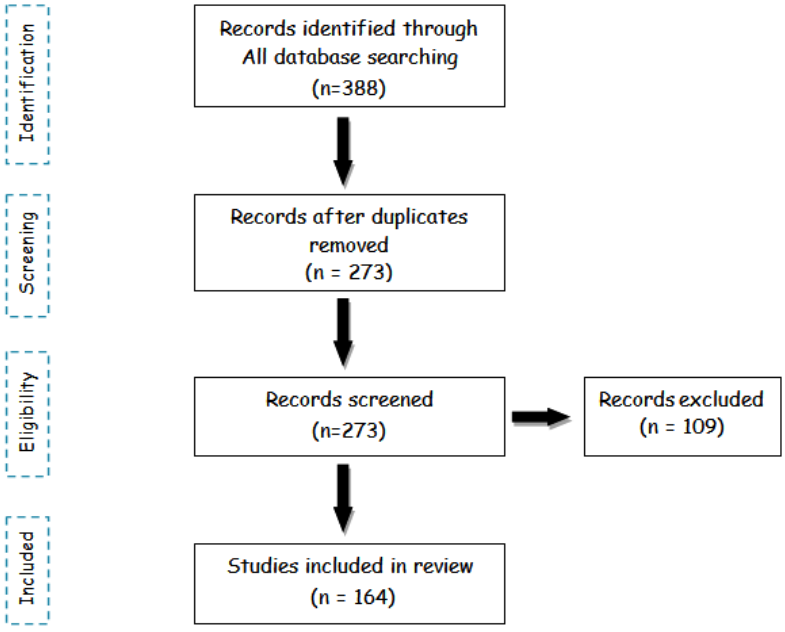

Figure 1: Search results for clinical trials of stem cells for the treatment of GI diseases.

Type of Interventions and Cell Sources

Our data analysis indicated that various types of stem cells used in clinical trials were included. Autologous HSCs were the first type of stem cells used in combination with chemotherapy to treat patients with GI tumors. HPSCs transplantation and chemotherapy aimed to restore immune cells that were destroyed by chemotherapy (NCT0000781). Subsequently, autologous MSCs from various origins were applied for the treatment of GI disease. MSCs with immunomodulatory effects and the ability to differentiate into various types of cells can be used in the regeneration of tissue in digestive diseases. In one of the newest approaches, a research group with a commercial collaborator used genetically modified autologous mesenchymal stromal cells to express HSV-Tk (TREAT-ME1) to treat advanced GI tumors. MSCs were used as carriers for the transfer of therapeutic agents to the tumor site [27]. Recently, the aqueous lipoaspirate fraction known as the stromal vascular fraction (SVF) was used in GI disease cell therapy.

Indeed, SVF is a combination of heterogeneous cells such as MSCs, preadipocytes, endothelial progenitor cells, macrophages, and lymphocytes. The benefits of using SVF over other types of cell sources are as follows; heterogeneous cellular composition, easily obtained without the need for any cell isolation or culture, and minimal manipulation [28]. Accordingly, in the recent GI disease trials, SVF has been considered a novel approach in this context. Our data analysis indicated that the MSCs have the most outstanding interventions in these trials (Figure **2B**). Other kinds of stem cells, such as endothelial progenitor cells and adipose-derived regenerative cells, have been applied in three trials, which are uncounted in our analysis.

Several studies also did not specify the type of cell used, which was not included in our analysis. Most studies have used autologous stem cells, while the first clinical trial of GI diseases, which used allogeneic stem cells, was conducted in 2005. Based on our data, MSCs used in these trials were derived from various sources, which in order of frequency include bone marrow, umbilical cord, adipose tissue, and menstrual blood. Also, mononuclear cells (MNCs) applied in studies were derived from bone marrow and umbilical cord. Besides, HSCs, hepatocytes, and SVF were isolated from the bone marrow, liver, and adipose tissue (Figure **2B**).

Routes of Administration

Finding the best route of administration is a critical issue for stem cell therapy. The availability of the stem cells to digestive organs in disease conditions is related to the administration route. Generally, routes of administration based on the application site are categorized into intravenous (I.V), portal vein (P.V), hepatic artery (H.A), intraparenchymal (I.P) and intraarterial (I.A). The I.V injection is the oldest and most common method for stem cell delivery among available injection methods. First, passing pulmonary effect by lung trapping of stem cells is the main problem in I.V injection for GI diseases treatment.

Hence, to reduce this problem and increase access to stem cells, other administration routes were used in the trials. Studies have indicated that alternative routes such as H.A, P.V, and I.P and biomaterials as scaffolds

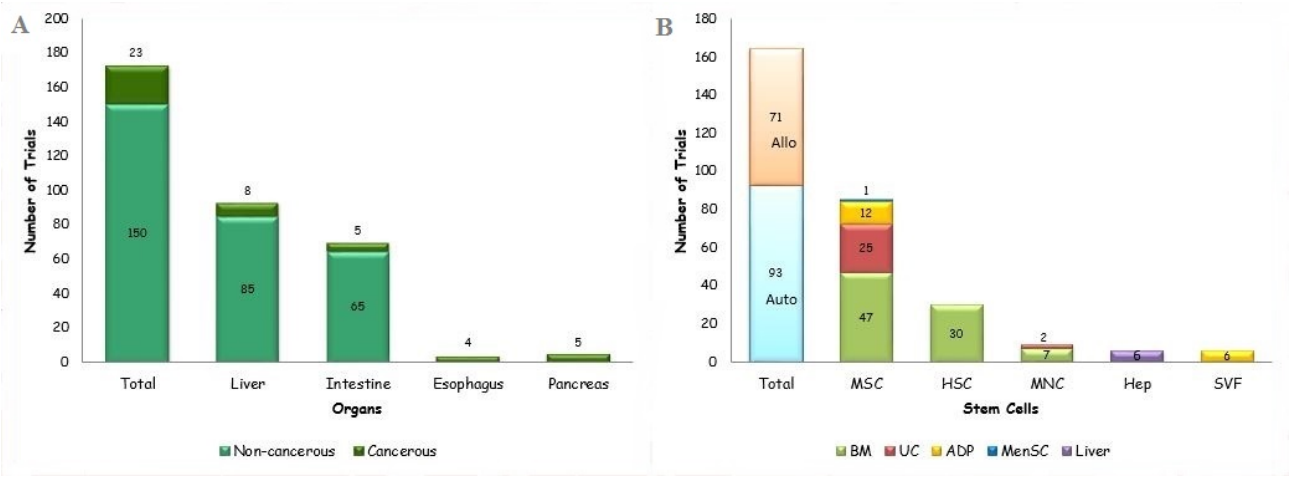

Figure 2: A. Most clinical trials have been done on the liver. **B**. The majority of clinical trials have used mesenchymal stem cells for the treatment of GI disease.

combined with stem cells increase cell availability [29, 30]. Based on our data, included trials were typically classified into two categories; 1) trials where stem cells have been used alone (cell therapy) and 2) studies that have utilized the cells along with biomaterials such as fibrin and collagen (tissue Engineering) (Figure **3A**).

The use of biomaterials as a scaffold for cell therapy has been done in organs such as the liver and intestine. Fibrin and collagen were used in this category of trials. Among these clinical trials, 150 cases out of 164 have used stem cells to treat of GI diseases. The main routes of cell administration into the liver were as follows; I.V, H.A, P.V, I.P and, I.A of which administration from I.V has the largest number of delivery methods. Administration routes in the intestine include I.P and I.V. Moreover, I.V and I.P were major administration routes in the esophagus (Figure **3B**).

The Phase and Start Year of Clinical Trials

Overall clinical trials are conducted in four main phases. These phases aim to determine whether the new interventions would be useful as a treatment for patients. Indeed, the progression of trial phases indicates the effectiveness of these interventions. After two decades of stem cell therapy in GI disease, and despite the promising results of pre-clinical studies and an increasing number of trials, clinical trials have not reached completed phases. Trials phases were evaluated for all studies, which are included in our review.

Data analysis of these trials indicated that most trials in all organs were in phases 1and 1, 2. However, clinical trials in liver and intestinal diseases such as cirrhosis and Crohn's disease have reached phase 3. Most of the trials in phase 3 are related to intestinal disease. Also, our data analysis showed that no clinical trial had been registered in phase 4. Moreover, for 27 of these studies, the trial phase was not provided.

Also, in this review, the trial phase and start year were assessed for included studies. Our data analysis showed that the largest number of trials registered in recent years were in phases 1 and 2 (Figure **4A**). Also after a long time of the first trial in this field, the number of phases 3 and 4 studies have not increased yet. Phases 1 and 1,2 clinical trials in various GI tract disease types started from 1995 till now, whereas phase 3 trials started in 2005 and are still ongoing (Figure **4B**).

Location and Start Year of Trials

Our data demonstrated how different countries had registered many trials based on stem cell therapy in GI tract disease. Information on these trials showed that the largest proportion of studies is registered in China. Most contributions to trials in China are dedicated to liver disease. The United States of America had the largest number of clinical trials after China. The greatest number of registered trials in the USA is related to intestinal diseases. Information on trials in other countries is shown in Figure **5A**. The number of trials conducted in collaboration between several countries and their data counted separately. Countries with less than four trials, such as Switzerland, Turkey, Jordan, India, Saudi Arabia, Russian, Hungary, Denmark, Indonesia, Sweden, Singapore, and Slovakia, were not included in our analysis.

Regarding the start year of trials, the first study that employed stem cells to treat GI tract diseases was

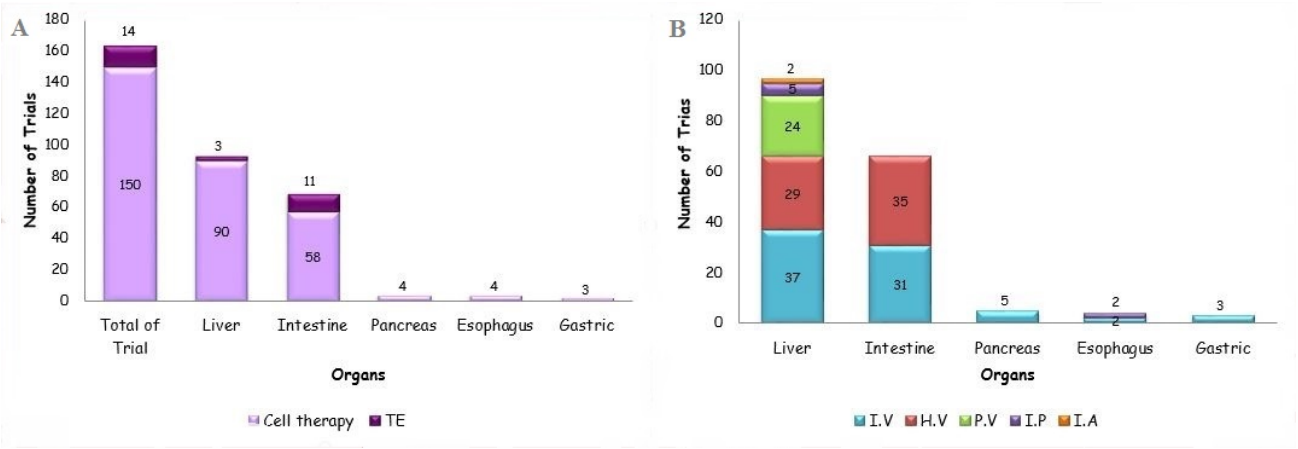

Figure 3: A. Interventions in GI clinical trials are divided into two categories, including: cell therapy and tissue engineering. **B**. Intravenous injection is the most frequently used route of stem cell administration in GI disease.

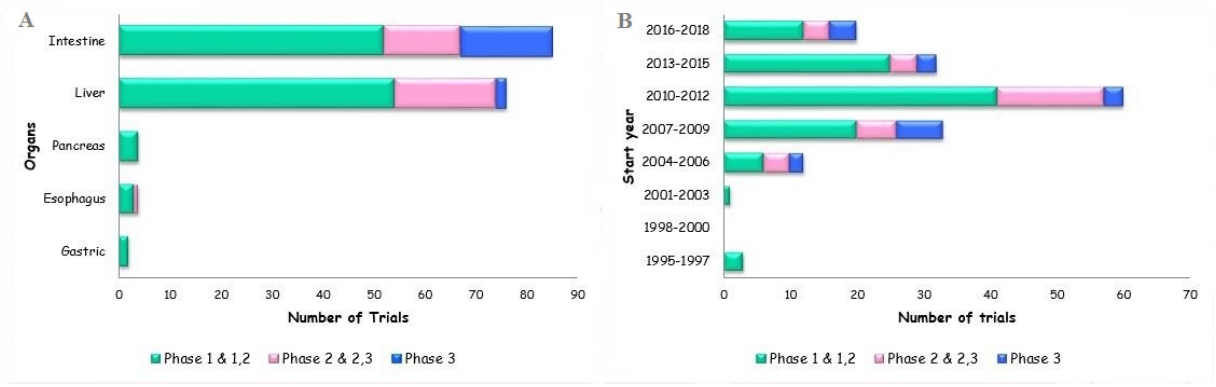

Figure 4: A. Most clinical trials are in phases 1 and 1, 2, phase 3 trials are related to intestinal diseases. **B**. The percentage of phases 2, 3, and 3 have not increased in trials.

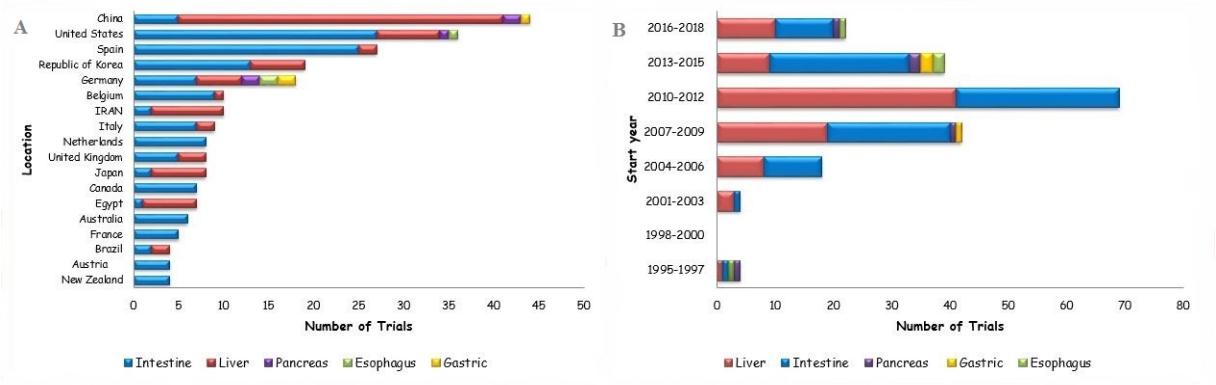

Figure 5: A. Most clinical trials have been conducted in China. **B**. The largest number of trials was registered between 2010 and 2012.

done in 1995. Also, no trials have been registered between 1998 and 2000. Generally, the number of trials significantly increased between 2007 and 2015, especially in 2010-2012. Besides, the number of studies has declined since 2013. Indeed, this decrease is probably due to the low efficacy of these cells in GI disease treatment. Based on our data, trials initially focused on liver and intestinal disease. However, in recent years, diseases in other organs such as the esophagus, gastric, and pancreas have also been considered (Figure **5B**).

Commercialization and Marketing

To produce a new drug, pharmaceutical companies must complete four phases of clinical research. Given that the phases of clinical trials in stem cell therapy of GI diseases have not been completed, there is no FDA approved product in the market. However, many companies have been producing stem cell-based products that are approved by local regulatory agencies. Several examples of stem cell products that are used for the treatment of GI diseases are as follows; Prochymal (NCT00294112), (NCT00543374), (NCT01510431), (NCT01233960), (NCT00482092), Furestem (CD) (NCT02000362), (NCT02926300), Livercellgram (NCT01875081), (NCT02806011), Multistem (NCT01240915), etc. As mentioned earlier, all of these products are stem cell-based.

CONCLUSION

Despite the promising results for using stem cells in treating different diseases, lower effectiveness was observed in the treatment of GI tract diseases. For this reason, the number of trials in this field has declined over time. According to the results of previous studies, stem cells can be used for cell-based regenerative medicine in the various types of GI diseases such as cirrhosis, hepatitis, and Crohn's disease. Among GI diseases, the application of stem cells showed promising results in treating Crohn's disease. Studies show that the administration of MSCs can improve the healing of the fistula in Crohn's disease. Reports demonstrate that MSCs can repair liver damages caused by diseases by modulating immune responses with several mechanisms. According to the results of studies in this field, the cellular products related to

Crohn's disease enter the market more quickly. This review provides an overview of the clinical trials based on stem cell therapy in GI diseases. In this context, gene manipulation of stem cells and biomaterials as a scaffold are new approaches in cell therapy. Our data analysis of these trials indicates interesting stem cell therapy trends and focused approaches in GI disease.

ABBREVIATIONS

GI = Gastrointestinal

MSC = Mesenchymal stem cell

HSC = Hematopoietic stem cell

MNC = Mononuclear cell

Hep = Hepatocyte

SVF = Stromal vascular fraction

Auto = Autologous

Allo = Allogeneic

BM = Bone marrow

UC = Umbilical cord

ADP = Adipose tissue

MenSC = Menstrual stem cells

TE = Tissue engineering

I.V = Intravenous

P.V = Portal vein

H.A = Hepatic artery

I.P = Intraparenchymal

I.A = Intraarterial

AUTHORS' CONTRIBUTIONS

NA and MHG contributed to conception and design. ZJ contributed to data acquisition, statistical analysis, and interpretation of data and drafted the manuscript, which was revised by MS and JK. All authors read and approved the final manuscript.

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CONFLICT OF INTEREST

The authors notify that they have no conflicts of interest.

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