Clinical trials using mesenchymal stem cells in liver diseases and inflammatory bowel diseases

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Abstract
Mesenchymal stem cell (MSC) therapies have been used in clinical trials in various fields. These cells are easily expanded, show low immunogenicity, can be acquired from medical waste, and have multiple functions, suggesting their potential applications in a variety of diseases, including liver disease and inflammatory bowel disease. MSCs help prepare the microenvironment, in response to inflammatory cytokines, by producing immunoregulatory factors that modulate the progression of inflammation by affecting dendritic cells, B cells, T cells, and macrophages. MSCs also produce a large amount of cytokines, chemokines, and growth factors, including exosomes that stimulate angiogenesis, prevent apoptosis, block oxidation reactions, promote remodeling of the extracellular matrix, and induce differentiation of tissue stem cells. According to ClinicalTrials.gov, more than 680 clinical trials using MSCs are registered for cell therapy of many fields including liver diseases (more than 40 trials) and inflammatory bowel diseases (more than 20 trials). In this report, we introduce background and clinical studies of MSCs in liver disease and inflammatory bowel diseases.

Keywords: Mesenchymal stem cell, Liver disease, Inflammatory bowel disease, Cell therapy

Background
The digestive system, which consists of the gastrointestinal tract, liver, pancreas, and biliary tree, functions in digestion, absorption, and metabolism and affects the basis of life. Various diseases, including cancer, inflammatory disease, infection, stones, and ulcers, are studied under the context of gastroenterology. While innovative drugs against Helicobacter pylori [1], hepatitis C virus [2], and inflammatory bowel disease (IBD) [3] have recently been developed, there are still unmet needs in this field, including in acute and chronic liver failure and refractory IBDs. Cell therapy may fulfill these unmet needs, and cell therapies using mesenchymal stem cells (MSCs) have become a major focus in many fields [4]. MSCs are reported to have multiple functions, especially anti-fibrosis and anti-inflammatory effects are focused in acute and chronic liver failure and refractory IBDs. Furthermore, MSCs have low immunogenicity, can expand easily, and can be obtained from medical waste, suggesting their potential to expand regenerative medicine for the treatment of liver diseases and IBDs.

In this paper, we review the current status of clinical trials using autologous/allogeneic MSCs in liver diseases and IBDs.

Characteristics of MSCs
MSCs have recently received attention as potential cell sources for cell therapy due to their ease of expansion and wide range of functions. MSCs can be obtained from not only bone marrow but also medical wastes, such as adipose tissue, umbilical tissue, and dental pulp. MSCs are positive for the common markers CD73, CD90, and CD105; however, they are negative for the endothelial marker CD31 and hematopoietic marker CD45 [4–7]. The expansion of MSCs in culture is relatively easy, and under appropriate conditions, MSCs have trilineage differentiation (osteogenic, chondrogenic, and adipogenic) potential. The effects of MSCs are broadly divided into two mechanisms: (1) recruited MSCs differentiate into functional cells to replace damaged cells, permitting the treatment of bone and cartilage damage; and (2) in response to inflammatory cytokines, MSCs help prepare the microenvironment by producing
immunoregulatory factors that modulate the progression of inflammation by affecting dendritic cells, B cells, T cells, and macrophages. MSCs also produce a large amount of cytokines, chemokines, and growth factors, including exosomes, which stimulate angiogenesis, prevent apoptosis, block oxidation reactions, promote remodeling of the extracellular matrix (ECM), and induce the differentiation of tissue stem cells [4, 7, 8]. These latter mechanisms can be applied for many diseases, including liver disease and IBDs. Some studies have reported that the effects of MSCs are determined by host conditions, such as inflammation stage and the use of immunosuppressants.

Although the behaviors of MSCs after administration have been analyzed, and some studies have shown that MSCs migrate to the injured site, MSC behaviors in humans have not been fully elucidated. Some studies have reported that MSCs disappear within a few weeks and do not remain long in the target tissue [5]. Recent studies have reported that only culture-conditioned medium or exosomes induce treatment effects, suggesting that the trophic effect is the most important effect of MSCs [9–11]. Another important characteristic of MSCs is that they generally have low immunogenicity. MSCs have no antigen-presenting properties and do not express major histocompatibility complex class II or costimulatory molecules; thus, injection of autologous or allogeneic MSCs has been employed in clinical studies. Allogeneic MSC therapy has the potential to expand MSC therapy to many patients [4, 7].

Clinical trials using MSCs
Since MSCs can be obtained relatively easily and have multiple functions, more than 680 clinical trials are ongoing according to ClinicalTrials.gov (https://clinicaltrials.gov/); most of these studies are phase I or II trials evaluating the use of MSCs in bone/cartilage, heart, neuron, immune/autoimmune, diabetes/kidney, lung, liver, and gastrointestinal fields. These studies aim to elucidate the safety/effectiveness of MSCs in the treatment of various diseases. In liver diseases, 40 trials are registered, most of which target liver cirrhosis or acute liver diseases (Table 1) [12–21]. The MSCs used in clinical trials of the liver are derived from the bone marrow (55%), umbilical cord tissue (35%), and adipose tissue (8%). Approximately 50% of MSCs are allogeneic. Additionally, while the major administration route is the peripheral blood, approximately 40% of cases are treated via the hepatic artery, reflecting the fact that hepatologists and radiologists often use catheters to treat hepatocellular carcinoma through the hepatic artery [22, 23] (Fig. 1).

In IBDs, 26 trials are registered (Table 2), 23 of which are investigating the use of MSCs in Crohn’s disease (CD), and 3 of which are investigating the use of MSCs in ulcerative colitis (UC) [24–33]. More than 60% of trials are employing allogeneic MSCs, and in CD, more than 40% of the trials are evaluating intrallesional injection into the fistula, which is the major and refractory complication of CD (Fig. 2).

Clinical trials in liver diseases
Background of liver diseases
Although the liver has high regenerative capacity, acute liver damage caused by viruses, drugs, alcohol, and autoimmune diseases, or chronic liver damage caused by hepatitis B or C virus, alcohol, non-alcoholic steatohepatitis (NASH), autoimmune hepatitis, and primary biliary cholangitis often cause liver failure [34]. The liver has a variety of functions, including metabolism of protein, sugar, and fat; detoxification; production of coagulation factors; and production of bile. Thus, during liver failure, several symptoms, including jaundice, edema, ascites, hepatic encephalopathy, and increased bleeding, can appear at the same time, resulting in life-threatening disease. In addition, during liver failure caused by chronic liver disease, accumulated liver fibrosis (i.e., liver cirrhosis) can cause portal hypertension, which often induces the varices, and long-term liver damage can cause gene abnormalities, leading to liver cancers. The ultimate therapy for liver failure is liver transplantation; however, only a small portion of patients with liver failure can receive liver transplantation due to the shortage of donor organs, invasiveness of operations, and economic reasons [35]. Revolutionary treatments, such as interferon-free treatment for hepatitis C and providing information regarding the importance of the daily lifestyle to prevent alcoholic liver disease and NASH, can potentially decrease the liver diseases; however, unmet needs to treat advanced liver failure will continue.

Advanced acute liver failure and chronic liver failure (liver cirrhosis) can be good targets for cell therapy. Since 2003, Terai et al. initiated autologous bone marrow cell infusion (ABMI) therapy against decompenated liver cirrhosis and confirmed the improvement of liver fibrosis and liver function [36–38]. However, due to the invasiveness of liver transplantation in patients with liver failure, minimally invasive procedures using specific cells, such as MSCs and macrophages [39–41], are now being developed, with a focus on MSCs. In the next section, we will describe recent reported results using MSCs registered at ClinicalTrials.gov.

Effects of MSC therapy in liver disease from published papers
Animal experiments have shown that MSCs can have anti-apoptotic [42] and antioxidant effects in hepatocytes [43], and antifibrotic [44, 45], angiogenic [46], and immunosuppressive effects in T cells, macrophages, and dendritic cells [8]. In human clinical trials, all reports have shown that MSC injection is safe. Although the effects of cell therapy
| No. | Start year | Cell source | Autologous/ allogeneic | Administration route | Number of cells infused | Etiology | Number of patients | Follow-up period | Phase | Study design | ClinicalTrials.gov identifier | Status | Result | References |
|-----|------------|-------------|------------------------|----------------------|------------------------|----------|-------------------|-----------------|-------|-------------|-----------------------------|--------|--------|------------|
| 1   | 2013       | Bone marrow | Autologous             | Peripheral vein      | Unknown                | LC       | 20                | 48 weeks         | Phase 1–2 | Non-randomized, single group assignment, open label | NCT01877759 | Unknown |            |            |
| 2   | 2009       | Bone marrow | Autologous             | Hepatic artery       | 5 x 10^6 cells/patient, 2 times | LC (alcohol) | 11 | 24 weeks | Phase 2 | Non-randomized, single group assignment, open label | NCT01741090 | Unknown | Histological improvement, Improvement in Child- Pugh score. Decrease in TGFβ1, collagen type I, and α-SMA |            |        |
| 3   | 2009       | Bone marrow | Autologous             | Peripheral vein      | 1.0 x 10^6/kg         | LC       | 25                | 24 weeks         | Unknown | Non-randomized, single group assignment, open label | NCT01499459 | Unknown | Improvement in Alb and MELD scores. | 13 |
| 4   | 2014       | Umbilical cord | Allogeneic             | Peripheral vein      | 4.0 x 10^7/patient, 4 times | LC       | 320               | 144 weeks         | Phase 1–2 | Non-randomized, parallel assignment, open label | NCT01573923 | Unknown |            |            |
| 5   | 2016       | Adipose tissue | Autologous             | Portal vein or hepatic artery | 1.0 x 10^6/kg via peripheral vein, 3 times or 3.0 x 10^6/kg via hepatic artery, 3 times | LC (HCV) | 5 | 48 weeks | Phase 1–2 | Non-randomized, single group assignment, open label | NCT02705742 | Recruiting |            |            |
| 6   | 2007       | Bone marrow | Autologous             | Peripheral or portal vein | 30–50 x 10^6/patient | LC       | 8                 | 24 weeks | Phase 1–2 | Randomized, single group assignment, single blind | NCT00420134 | Completed | Improvement in liver function and MELD scores. | 14 |
| 7   | 2016       | Bone marrow | Allogeneic             | Peripheral vein      | 2.0 x 10^6/kg, 4 times | ACLF     | 30                | 96 weeks          | Phase 1 | Randomized, parallel assignment, double blind (subject, caregiver, investigator) | NCT02857010 | Recruiting |            |            |
| 8   | 2009       | Umbilical cord | Allogeneic             | Peripheral vein      | 5.0 x 10^5/kg, 3 times | ACLF (HBA) | 43               | 96 weeks          | Phase 1–2 | Randomized, parallel assignment, double blind (subject, caregiver) | NCT01218464 | Unknown | Improvement in liver function and MELD scores. | 15 |
| 9   | 2011       | Bone marrow | Allogeneic             | Peripheral vein      | 2.0 x 10^5/kg, 4 times or | 120 | 48 weeks | Phase 2 | Randomized, parallel | NCT01322906 | Unknown |            |            |
| No. | Start year | Cell source | Autologous/ allogeneic | Administration route | Number of cells infused | Etiology | Number of patients | Follow-up period | Phase | Study design | ClinicalTrials.gov identifier | Status | Result | References |
|-----|------------|-------------|------------------------|----------------------|------------------------|----------|-------------------|-----------------|--------|-------------|-------------------------------|--------|--------|------------|
| 10  | 2010       | Umbilical cord | Allogeneic             | Unknown              | 1.0 × 10^6/kg, 4 times or 5.0 × 10^6/kg, 4 times | Liver failure (HBV) | Unknown | Unknown | 48 weeks | Phase 1–2 | Randomized, parallel assignment, open label | NCT01342250 | Completed |
| 11  | 2012       | Bone marrow   | Allogeneic             | Hepatic artery       | 1.0 × 10^6/kg, 4 times | Liver failure (Alcohol) | 40      | 96 weeks | Phase 2     | Randomized, parallel assignment, open label | NCT01591200 | Completed |
| 12  | 2012       | Umbilical cord | Allogeneic             | Peripheral vein      | 1.0 × 10^6/kg, 4 times | Liver failure (HBV) | 120     | 48 weeks | Phase 1–2 | Randomized, parallel assignment, open label | NCT01724398 | Unknown |
| 13  | 2016       | Bone marrow   | Autologous             | Portal vein          | 2.0 × 10^6/kg         | Liver failure (HBV) | 40      | 24 weeks | Phase 1–2 | Non-randomized, parallel assignment, open label | NCT02943889 | Not yet recruiting |
| 14  | 2009       | Umbilical cord | Allogeneic             | Portal vein or hepatic artery | 1.0 × 10^5/kg, 1.0 × 10^6/kg | Liver failure (HBV) | 200     | 48 weeks | Phase 1–2 | Randomized, parallel assignment, single blind (subject) | NCT01233102 | Suspended |
| 15  | 2009       | Bone marrow   | Autologous             | Portal vein          | 2.0 × 10^6/kg         | Liver failure (HBV) | 60      | 48 weeks | Phase 2     | Non-randomized, parallel assignment, open label | NCT00993941 | Unknown |
| 16  | 2010       | Umbilical cord | Allogeneic             | Hepatic artery       | 1.0 × 10^6/kg         | Liver failure (HBV) | 50      | 4 weeks   | Phase 1–2 | Randomized, parallel assignment, open label | NCT01224327 | Unknown |
| 17  | 2013       | Bone marrow   | Autologous             | Hepatic artery       | 1.0 × 10^6/kg         | Liver failure (HBV) | 30      | 12 weeks | Phase 3     | Non-randomized, single group assignment, open label | NCT01854125 | Enrolling by invitation |
| 18  | 2012       | Umbilical cord | Allogeneic             | Hepatic artery       | 1.0 × 10^6/kg         | Liver failure (HBV) | 240     | 48 weeks | Phase 1–2 | Randomized, parallel assignment, open label | NCT01728727 | Unknown |
| 19  | 2013       | Umbilical cord | Allogeneic             | Peripheral vein      | 1.0 × 10^5/kg, 1.0 × 10^6/kg | Liver failure (HBV) | 210     | 72 weeks | Phase 1–2 | Randomized, parallel assignment, open label | NCT01844063 | Recruiting |
| No. | Start year | Cell source | Autologous/ allogeneic | Administration route | Number of cells infused | Etiology | Number of patients | Follow-up period | Phase | Study design | ClinicalTrials.gov identifier | Status | Result | References |
|-----|------------|-------------|-----------------------|----------------------|------------------------|----------|--------------------|------------------|-------|-------------|-----------------------------|--------|--------|------------|
| 20  | 2016       | Umbilical cord | Allogeneic             | Peripheral vein      | 4 or 8 times           | ACLF (HBV) | 261                | 52 weeks         | Phase 2 | Randomized, parallel assignment, open label | NCT02812121 | Not yet recruiting |            |
| 21  | 2010       | Menstrual blood | Allogeneic             | Peripheral vein      | 1.0 x 10^6/kg, 4 times | LC        | 50                 | 48 weeks         | Phase 1–2 | Randomized, single group assignment, open label | NCT01483248 | Enrolling by invitation |            |
| 22  | 2008       | Bone marrow   | Autologous             | Hepatic artery       | Unknown                | LC        | 50                 | 96 weeks         | Phase 2 | Randomized, parallel assignment, single blind (subject) | NCT00976287 | Unknown |            |
| 23  | 2012       | Bone marrow   | Autologous             | Hepatic artery       | 5 x 10^7/patient, 1 time or 2 times | LC (alcohol) | 72                 | 24 weeks         | Phase 2 | Randomized, parallel assignment, open label | NCT01875081 | Completed | Histological improvement. Improvement in AST, ALT, ALP, γ-GTP, Child-Pugh score, and MELD score. | 16     |
| 24  | 2014       | Bone marrow   | Autologous             | Peripheral vein      | Unknown                | LC        | 10                 | 24 weeks         | Phase 1 | Non-randomized, single group assignment, open label | NCT02327832 | Recruiting |            |
| 25  | 2005       | Bone marrow   | Autologous             | Hepatic artery       | 3.4 x 10^6/patient    | Liver failure (HBV) | 158                | 192 weeks        | Phase 1–2 | Case control, retrospective | NCT009565891 | Completed | Improvement in Alb, T-Bil, PT, and MELD score. | 17     |
| 26  | 2009       | Umbilical cord | Allogeneic             | Peripheral vein      | 5.0 x 10^5/kg, 3 times | LC        | 45                 | 48 weeks         | Phase 1–2 | Randomized, parallel assignment, open label | NCT01220492 | Unknown |            |
| 27  | 2010       | Bone marrow   | Autologous             | Portal vein          | 1.4–2.5 x 10^8/patient, 2 times | LC        | 2                  | 48 weeks         | Phase 1 | Non-randomized, single group assignment, open label | NCT01454336 | Completed | Transient improvement in MELD scores. | 18     |
| 28  | 2007       | Bone marrow   | Autologous             | Peripheral vein      | (1.2–2.95 x 10^8) 1.95 x 10^8/patient | LC        | 27                 | 48 weeks         | Unknown | Randomized, parallel assignment, double | NCT00476060 | Unknown | No beneficial effect. | 19     |
Table 1 Clinical trials in liver diseases (Continued)

| No. | Start year | Cell source | Autologous/ allogeneic | Administration route | Number of cells infused | Etiology | Number of patients | Follow-up period | Phase | Study design | ClinicalTrials.gov identifier | Status | Result | References |
|-----|------------|-------------|------------------------|----------------------|------------------------|----------|-------------------|-----------------|-------|--------------|-------------------------------|--------|--------|------------|
| 29  | 2011       | Bone marrow | Allogeneic             | Hepatic artery and peripheral artery | 1.0 × 10^6/kg (5.0 × 10^7 cells via the hepatic artery and the remaining cells via the peripheral vein) | Wilson’s disease | 10               | 24 weeks       | Unknown | Non-randomized, single group assignment, open label | NCT01378182 | Completed |          | |
| 30  | 2016       | Umbilical cord or bone marrow | Allogeneic | Portal vein or hepatic artery | 2.0 × 10^7/patient, 4 times | LC | 20               | 48 weeks       | Phase 1 | Non-randomized, single group assignment, open label | NCT02652351 | Recruiting |          | |
| 31  | 2016       | Bone marrow | Autologous             | Hepatic artery | 5 × 10^7/patient, 1 time or 2 times | LC (alcohol) | 50               | 144 weeks      | Phase 2 | Randomized, parallel assignment, open label | NCT02806011 | Enrolling by invitation |          | |
| 32  | 2011       | Umbilical cord | Allogeneic | Peripheral vein | 1.0 × 10^6/kg, 3 times | Liver failure (Alk) | 100              | 96 weeks       | Phase 1–2 | Randomized, parallel assignment, open label | NCT01661842 | Unknown |          | |
| 33  | 2009       | Adipose tissue | Autologous | Unknown | Unknown | Unknown | LC | 6               | 24 weeks       | Phase 1 | Non-randomized, single group assignment, open label | NCT00913289 | Terminated |          | |
| 34  | 2012       | Adipose tissue | Autologous | Hepatic artery | Unknown | LC | 4               | 4 weeks         | Unknown | Non-randomized, single group assignment, open label | NCT01062790 | Completed |          | |
| 35  | 2016       | Umbilical cord | Allogeneic | Lobe | 5.0 × 10^8/patient | LC | 40               | 96 weeks       | Phase 1–2 | Randomized, parallel assignment, double blind (subject, outcomes assessor) | NCT02786017 | Recruiting |          | |
| 36  | 2011       | Bone marrow | Unknown | Peripheral vein | 5.0–50 × 10^6/kg | LC (PBC) | 20               | 96 weeks       | Phase 1 | Randomized, parallel assignment, open label | NCT01440309 | Unknown |          | |
| 37  | 2011       | Umbilical cord | Allogeneic | Peripheral vein | 5.0 × 10^5/kg, 3 times | LC (PBC) | 7               | 48 weeks       | Phase 1–2 | Randomized, parallel assignment, open label | NCT01662973 | Unknown | Improvement in Alb, T-Bil, and MELD score. | | | |
### Table 1 Clinical trials in liver diseases (Continued)

| No. | Start year | Cell source | Autologous/ allogeneic | Administration route | Number of cells infused | Etiology | Number of patients | Follow-up period | Phase | Study design | ClinicalTrials.gov identifier | Status | Result | References |
|-----|------------|-------------|------------------------|----------------------|------------------------|----------|--------------------|-----------------|-------|--------------|-----------------------------|--------|--------|------------|
| 38  | 2010       | Bone marrow | Allogeneic             | Portal vein or hepatic artery | Unknown                | Liver failure (HBV) | 60                 | 48 weeks         | Phase 2 | Non-randomized, parallel assignment, open label | NCT01221454 | Unknown | Reduction of ascites. |
| 39  | 2010       | Bone marrow | Allogeneic             | Portal vein or hepatic artery | Unknown                | LC                   | 60                 | 48 weeks         | Phase 2 | Non-randomized, parallel assignment, open label | NCT01223664 | Unknown |         |
| 40  | 2010       | Bone marrow | Autologous             | Hepatic artery          | (0.25–1.25 × 10^6)    | LC (HBV)            | 39                 | 24 weeks         | Phase 2–3 | Non-randomized, parallel assignment, open label | NCT01560845 | Unknown | Decrease in Th-17 cells, RORγt, IL-17, TNF-α, and IL-6. Increase in Tregs and Foxp3. |

LC liver cirrhosis, ACLF acute-on-chronic liver failure, HBV hepatitis B virus, HCV hepatitis C virus, AIH autoimmune hepatitis, PBC primary biliary cholangitis, MELD Model for End-Stage Liver Disease, AST aspartate transaminase, ALT alanine transaminase, ALP alkaline phosphatase, γ-GTP gamma-glutamyl transpeptidase, Alb albumin, T-bill total bilirubin, PT prothrombin time, PC protein C, ROR RAR-related orphan receptor, Foxp3 forkhead box P3, IL interleukin, Th T helper, SMA smooth muscle actin, TGF transforming growth factor, TNF tumor necrosis factor.
are not uniform, the majority of therapies have some beneficial effects; in contrast, in a few reports, treatment effects were not observed. For example, Kantarcioglu et al. [13] and Mohamadnejad et al. [19] injected bone marrow-derived MSCs into patients with liver cirrhosis and did not observe treatment effects. However, Khraziha et al. [14] reported phase I–II clinical trials using autologous bone marrow-derived MSCs against liver cirrhosis with a variety of etiologies, and improvement of liver function was confirmed. Jang et al. and Suk et al. [12, 16] reported a pilot study and a phase II study using autologous bone marrow-derived MSCs injected through the hepatic artery against alcoholic liver cirrhosis, and improvement of histological liver fibrosis and liver function was confirmed. Xu et al. [21] reported trials using autologous bone marrow-derived MSCs against hepatitis B virus-associated cirrhosis and confirmed the improvement of liver function, the decrease of Th17 cells, and the increase of regulatory T cells. Xhang et al. [17] and Wang et al. [20] reported trials using allogeneic umbilical cord-derived MSCs in patients with chronic hepatitis B having decompensated liver cirrhosis and primary biliary cirrhosis, respectively. They confirmed improvement of liver function, particularly reduced ascites and recovery of biliary enzymes, respectively. Shi et al. [15] reported a trial investigating acute or chronic liver failure associated with hepatitis B virus and confirmed that MSCs significantly increased survival rates. From these reports, MSCs appeared to improve liver function; however, additional trials are needed to confirm these effects and to elucidate the mechanisms in more detail.

Clinical trials in IBDs

Background of IBDs

IBDs are chronic inflammatory disorders, including UC and CD. The pathogenesis of IBD is thought to be highly complex due to several factors, such as environmental factors, genetic predisposition, and inflammatory abnormalities [47]. UC is characterized by inflammation of the mucosal membrane of the colon continued from the rectum. Type 2 T helper cell (Th2) cytokine profile is associated with the pathogenesis of UC. In contrast, CD is a segmental, transmural disorder that can arise within the entire gastrointestinal tract from the mouth to the anus. Th1 cells are associated with the pathogenesis of CD [48]. Furthermore, a recent report showed that Th17 cells are present in both UC and CD. Thus, mucosal CD4+ T cells are key mediators of the driving response [49]. Macrophages that produce tumor necrosis factor (TNF)-α have also been reported to be relevant in IBD. Imbalances in other cytokines, such as interleukin (IL)-1β, IL-6, IL-8, IL-10, IL-12, IL-17, IL-23, and transforming growth factor-β (TGF-β), are also detected during diseases [48]. Recent advancements in the development of drugs for IBD include drugs targeting TNF and new candidate drugs, such as antibodies against IL-6 [50] and IL-12/23 [51–53], small molecules including Janus kinase inhibitors [54], antisense oligonucleotides against SMAD7 mRNA [55], and inhibitors of leukocyte trafficking to intestinal sites of inflammation [56, 57]. However, some patients will fail to respond to current medical options, immunosuppressive agents, and anti-TNF biologics. MSCs may be an effective option in these patients [9, 49]. In the next section, we will describe recently reported results using MSCs registered in ClinicalTrials.gov.

Effects of MSC therapy in IBD from published papers

Eight CD trials and one UC trial have been published in ClinicalTrials.gov. Six papers describing CD are on trials treating fistula, and two papers are trials for luminal CD. Molendijk et al. [25] reported improved healing of refractory perianal fistulas using allogeneic bone marrow-derived MSCs. They administered these allogeneic MSCs locally and confirmed the safety of the MSCs and the healing effects of MSCs on the fistula. Dijvjestek et al. [32] reported a phase I study of refractory luminal CD using autologous bone marrow-derived MSCs and confirmed the safety of the MSCs and the healing effects of MSCs on the fistula. Dijvjestek et al. [32] reported a phase I study of refractory luminal CD using autologous bone marrow-derived MSCs and confirmed the safety and feasibility of MSC therapy. Forbes et al. [24] reported a phase II study using allogeneic bone marrow-derived MSCs for luminal CD refractory to biologic therapy. They administered 2 × 10^6 cells/kg weekly for 4 weeks and found that allogeneic MSCs reduced the CD activity index (CDAI) and CD endoscopic index of severity (CDEIS) scores in patients with luminal CD refractory to biologic therapy. Hu et al. [33] reported a phase I/II study for severe UC using umbilical cord-derived allogeneic MSCs by combination injection through the peripheral blood and superior mesenteric artery with a 7-day interval. They confirmed the safety of
| No. | Start year | Cell source | Autologous/ allogeneic | Administration route | Number of cells infused | Diseases | Number of patients | Follow-up period | Phase | Study design | ClinicalTrials.gov identifier | Status | Result | References |
|-----|------------|-------------|------------------------|----------------------|------------------------|----------|-------------------|-----------------|-------|-------------|-----------------------------|--------|--------|------------|
| 1   | 2006       | Bone marrow | Allogeneic             | Peripheral vein      | 8 × 10^6 cells/kg, 2 times or 2 × 10^6 cells/kg, 2 times | Crohn's disease | 10                | 4 weeks        | Phase 2 | Randomized, parallel assignment, open label | NCT00294112 | Completed |            |            |
| 2   | 2007       | Bone marrow | Allogeneic             | Peripheral vein      | Total of 6 × 10^8 cells/patient, 4 times or total of 12 × 10^8 cells/patient, 4 times | Crohn's disease | 98                | 24 weeks       | Phase 3 | Randomized, parallel assignment, double blind | NCT00548374 | Completed |            |            |
| 3   | 2010       | Adipose tissue | Autologous             | Unknown              | Unknown | Fistulizing Crohn's disease | 15 | 3 years | Phase 1–2 | Non-randomized, single group assignment, open label | NCT01157650 | Completed |            |            |
| 4   | 2015       | Umbilical cord | Allogeneic             | Peripheral vein | Unknown | Crohn's disease | 32 | 1 year | Phase 1–2 | Randomized, parallel assignment, open label | NCT02446547 | Completed |            |            |
| 5   | 2012       | Bone marrow | Allogeneic             | Peripheral vein | 2 × 10^8 cells/patient, more than 4 times | Crohn's disease | 11 | 4 weeks | Phase 1–2 | Non-randomized, single group assignment, open label | NCT01510431 | Completed |            |            |
| 6   | 2010       | Bone marrow | Allogeneic             | Peripheral vein | 2 × 10^6 cells/kg, 4 times | Crohn's disease | 15 | 6 weeks | Phase 2 | Non-randomized, single group assignment, open label | NCT01090817 | Completed | Improvement in CDAI, AQoL score. Decrease in CRP. Endoscopic improvement | 24 |
| 7   | 2012       | Bone marrow | Autologous             | Peripheral vein | 2 × 10^6 cells/kg, 5 × 10^6 cells/kg, or 1 × 10^7 cells/kg | Crohn's disease | 16 | 1 year | Phase 1 | Non-randomized, single group assignment, open label | NCT01659762 | Completed |            |            |
| 8   | 2010       | Bone marrow | Allogeneic             | Intrallesional | 1 × 10^7 cells/patient, 3 × 10^7 cells/patient, or 9 × 10^7 cells/patient | Fistulizing Crohn's disease | 21 | 12 weeks | Phase 1–2 | Randomized, parallel assignment, double blind | NCT01144962 | Completed | Local treatment with MSCs showed promotion of fistula healing. Lower MSC dose seemed superior. | 25 |
| 9   | 2009       | Adipose tissue | Autologous             | Intrallesional | 3 × 10^7 cells/patient in the event of incomplete closure at 8 weeks, a second injection | Fistulizing Crohn's disease | 43 | 8 weeks | Phase 1 | Non-randomized, single group assignment, open label | NCT00992485 | Completed | Local treatment with MSCs showed promotion of fistula healing. | 26 |
**Table 2 Clinical trials in inflammatory bowel diseases (Continued)**

| No. | Start year | Cell source | Autologous/ allogeneic | Administration route | Number of cells infused | Diseases | Number of patients | Follow-up period | Phase | Study design | ClinicalTrials.gov identifier | Status | Result | References |
|-----|------------|-------------|------------------------|----------------------|------------------------|----------|-------------------|-----------------|-------|--------------|-------------------------------|--------|--------|------------|
| 10  | 2010       | Adipose tissue | Allogeneic | Intralesional | 2 × 10^7 cells/patient (in the event of incomplete closure at 12 weeks, an additional 4 × 10^7 cells were administered) | Fistulizing Crohn’s disease | 24 | 24 weeks | Phase 1–2 | Non-randomized, single group assignment, open label | NCT01372969 | Completed | Local treatment with MSCs showed promotion of fistula healing. | 27 |
| 11  | 2009       | Adipose tissue | Autologous | Intralesional | 1 × 10^7 cells/patient, 2 × 10^7 cells/patient, or 4 × 10^7 cells/patient | Fistulizing Crohn’s disease | 10 | 4 weeks | Phase 1 | Non-randomized, single group assignment, open label | NCT00992485 | Completed | Local treatment with MSCs showed promotion of fistula healing. All patients with complete healing showed a sustained effect. | 28 |
| 12  | 2009       | Adipose tissue | Allogeneic | Intralesional | 2 × 10^7 cell/s/patient (in the event of incomplete closure at 12 weeks, an additional 4 × 10^7 cells were administered) | Fistulizing Crohn’s disease | 10 | 12 weeks | Phase 1–2 | Non-randomized, single group assignment, open label | NCT00999115 | Completed | Local treatment with MSCs showed promotion of fistula healing; 60% of patients achieved complete healing. | 29 |
| 13  | 2009       | Adipose tissue | Autologous | Intralesional | 1 × 10^7 cells/cm^2 | Fistulizing Crohn’s disease | 43 | 8 weeks | Phase 2 | Non-randomized, single group assignment, open label | NCT01011244 | Completed | In most cases, complete closure after initial treatment was well-sustained over a 24-month period. | 30 |
| 14  | 2007       | Bone marrow | Allogeneic | Peripheral vein | Total of 6 × 10^8 cells/patient, 4 times or total of 1.2 × 10^9 cells/patient, 4 times | Crohn’s disease | 330 | 4 weeks | Phase 3 | Randomized, parallel assignment, double blind | NCT00482092 | Active | | |
| 15  | 2012       | Adipose tissue | Allogeneic | Intralesional | 1.2 × 10^8 cells/patient | Fistulizing Crohn’s disease | 212 | 24 weeks | Phase 3 | Randomized, parallel assignment, double blind | NCT01541579 | Active | Local treatment with MSCs showed promotion of fistula healing. | 31 |
Table 2: Clinical trials in inflammatory bowel diseases (Continued)

| No. | Start year | Cell source | Autologous/ allogeneic | Administration route | Number of cells infused | Diseases | Number of patients | Follow-up period | Phase | Study design | ClinicalTrials.gov identifier | Status | Result | References |
|-----|-------------|-------------|------------------------|----------------------|------------------------|---------|-------------------|-----------------|-------|--------------|-------------------------------|--------|--------|------------|
| 16  | 2010        | Bone marrow | Allogeneic             | Peripheral vein       | 2 × 10^8 cells/patient, 3 times | Crohn's disease | 120               | 180 days        | Phase 3 | Non-randomized, single group assignment, open label | NCT01233960 | Active |            |
| 17  | 2015        | Adipose tissue | Autologous             | Intralesional         | Unknown                 | Fistulizing Crohn's disease | 10                | 62 weeks        | Phase 2 | Non-randomized, single group assignment, open label | NCT02403232 | Recruiting |            |
| 18  | 2013        | Bone marrow  | Autologous             | Intralesional         | Unknown                 | Fistulizing Crohn's disease | 10                | 16 weeks        | Phase 1 | Randomized, parallel assignment, single blind | NCT01874015 | Recruiting |            |
| 19  | 2015        | Adipose tissue | Allogeneic             | Peripheral vein       | 5 × 10^7 cells/patient, 7.5 × 10^7 cells/patient, or 1 × 10^8 cells/patient | Crohn's disease | 9                 | 4 weeks         | Phase 1 | Non-randomized, single group assignment, open label | NCT02580617 | Recruiting |            |
| 20  | 2013        | Umbilical cord | Allogeneic             | Peripheral vein       | 5 × 10^7 cells/patient or 1 × 10^8 cells/patient | Crohn's disease | 24                | 12 weeks        | Phase 1–2 | Non-randomized, single group assignment, open label | NCT02000362 | Recruiting |            |
| 21  | 2013        | Adipose tissue | Autologous             | Intralesional         | 2 × 10^7 cells/patient | Fistulizing Crohn's disease | 20                | 2–24 months    | Phase 1 | Non-randomized, single group assignment, open label | NCT01915927 | Recruiting |            |
| 22  | Unknown     | Bone marrow  | Autologous             | Peripheral vein       | 1–2 × 10^6 cells/kg | Crohn's disease | 10                | 6 weeks         | Phase 1 | Unknown | – | – | Three patients showed clinical response (decrease in CDAI). Three patients required surgery due to disease worsening. |
| 23  | 2016        | Bone marrow  | Allogeneic             | Intralesional         | 2 × 10^7 cells/patient | Fistulizing Crohn's disease | 20                | 7, 10, 16 months | Phase 1 | Non-randomized, single group assignment, open label | NCT02677350 | Not yet recruiting |            |
| 24  | 2015        | Umbilical cord | Allogeneic             | Peripheral vein       | 1 × 10^6 cells/kg, 3 times | Ulcerative colitis | 30                | 24 weeks | Phase 1–2 | Randomized, parallel | NCT02442037 | Recruiting |            |
| No. | Start year | Cell source | Autologous/ allogeneic | Administration route | Number of cells infused | Diseases | Number of patients | Follow-up period | Phase | Study design | ClinicalTrials.gov identifier | Status | Result | References |
|-----|------------|-------------|------------------------|---------------------|-----------------------|---------|-------------------|-----------------|-------|-------------|-----------------------------|--------|--------|------------|
| 25  | 2015       | Adipose tissue | Allogeneic            | Through a colonoscope | $6 \times 10^7$ cells/patient | Ulcerative colitis | 8      | 12 weeks          | Phase 1–2 | Non-randomized, single group assignment, single blind | NCT01914887 | Unknown | Decrease in the median Mayo score and histology score. Improvement in IBDQ scores. | 33     |
| 26  | 2015       | Umbilical cord | Allogeneic            | First peripheral vein, second: superior mesenteric artery | First: $3.8 \pm 1.6 \times 10^7$ cells/patient, second: $1.5 \times 10^7$ cells/patient | Ulcerative colitis | 80     | 12 weeks          | Phase 1–2 | Non-randomized, single group assignment, open label | NCT01221428 | Unknown | | 33     |

CD Crohn's disease, CDAI Crohn's Disease Activity Index, AQoL The Assessment of Quality of Life, CRP C-reactive protein, IBDQ Inflammatory Bowel Disease Questionnaire
MSCs and alleviation of diffuse and deep ulcer formation and severe inflammatory mucosa by MSCs.

Safety of the MSC therapy
MSC therapy is associated with some concerns, such as adverse events related to infusion, tumor formation during the treatment of liver cirrhosis, and long-term observations of tumor formation. Regarding adverse events related to the infusion, Lalu et al. performed a meta-analysis of the safety of MSCs in clinical trials and showed that autologous and allogeneic MSC therapies were related to transient fever but not infusion toxicity, organ system complications, infection, death, and malignancies (Table 2) [5]. Regarding tumor formation during the treatment of liver cirrhosis, Peng et al. reported that no severe adverse events or no significant differences in tumor formation were detected compared with those in the control group during autologous bone marrow-derived MSC therapy for liver cirrhosis [58]. Regarding long-term observations of tumor formation derived from MSCs, Bahr et al. reported recent autopsy data from patients in a clinical trial of graft-versus-host disease (GvHD) who received MSC therapy between 2002 and 2007 and revealed no ectopic tissues, neoplasms, or donor-derived DNA [6].

Conclusions
Many clinical trials of autologous and allogeneic MSCs have aimed to elucidate the effects and mechanisms of MSCs. MSCs can expand easily and can be obtained from medical waste, suggesting their applications in regenerative medicine for the treatment of liver diseases and IBDs. Recently, limitations of MSCs have been reported. For example, therapeutic effects were not long term and were affected by inflammatory condition [59, 60]. Thus, the results of ongoing clinical studies will be expected to provide further insights.

Abbreviations
ABM: Autologous bone marrow cell infusion; CD: Crohn’s disease; CD CDEIS: Endoscopic index of severity; CDAI: CD activity index; ECM: Extracellular matrix; GvHD: Graft-versus-host disease; IBD: Inflammatory bowel disease; IL: Interleukin; MSCs: Mesenchymal stem cells; NASH: Non-alcoholic steatohepatitis; TGF-B: Transforming growth factor; TNF: Tumor necrosis factor; UC: Ulcerative colitis

Acknowledgements
The authors thank Dr. Takayuki Watanabe and Dr. Suguru Takeuchi for their cooperation.

Funding
This work was supported by a Grant-in-Aid for Scientific Research (B) (26293175) from the Ministry of Education, Science, Technology, Sports, and Culture of Japan and by Highway Program for Realization of Regenerative Medicine from Japan Agency for Medical Research and Development, AMED.

Availability of data and materials
There is no available data except the manuscript and tables.

Author’s contributions
AY and ST wrote the paper. YK, SI, SS, YW, and YK prepared the data and made the tables. All authors read and approved the final manuscript.

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

Consent for publication
All authors agreed to publish this work.

Ethics approval and consent to participate
There is no ethics approval and consent to participate due to review.

Publisher’s Note
Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

Received: 30 January 2017 Accepted: 13 April 2017
Published online: 03 July 2017

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