REVIEW

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Clinical applications of mesenchymal stem cells

Nayoun Kim[1] and Seok-Goo Cho[1,2]

[1]Laboratory of Immune Regulation, Convergent Research Consortium for Immunologic Disease, [2]Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, Seoul, Korea

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Correspondence to
Seok-Goo Cho, M.D.
Laboratory of Immune Regulation, Convergent Research Consortium for Immunologic Disease, and Department of Hematology, Catholic Blood and Marrow Transplantation Center, Seoul St. Mary's Hospital, The Catholic University of Korea College of Medicine, 222 Banpo-daero, Seocho-gu, Seoul 137-701, Korea
Tel: +82-2-2258-6052
Fax: +82-2-599-3589
E-mail: chosg@catholic.ac.kr

Mesenchymal stem cells (MSCs) are self-renewing, multipotent progenitor cells with multilineage potential to differentiate into cell types of mesodermal origin, such as adipocytes, osteocytes, and chondrocytes. In addition, MSCs can migrate to sites of inflammation and exert potent immunosuppressive and anti-inflammatory effects through interactions between lymphocytes associated with both the innate and adaptive immune system. Along with these unique therapeutic properties, their ease of accessibility and expansion suggest that use of MSCs may be a useful therapeutic approach for various disorders. In the clinical setting, MSCs are being explored in trials of various conditions, including orthopedic injuries, graft versus host disease following bone marrow transplantation, cardiovascular diseases, autoimmune diseases, and liver diseases. Furthermore, genetic modification of MSCs to overexpress antitumor genes has provided prospects for clinical use as anticancer therapy. Here, we highlight the currently reported uses of MSCs in clinical trials and discuss their efficacy as well as their limitations.

Keywords: Clinical trial; Tissue therapy; Graft vs host disease; Mesenchymal stromal cells

INTRODUCTION

Mesenchymal stem cells (MSCs) are self-renewing, multipotent progenitor cells with multilineage potential to differentiate into cell types of mesodermal origin, such as adipocytes, osteocytes, and chondrocytes [1]. While MSCs are most commonly isolated from bone marrow [2], they are also isolated from other tissues including adipose tissue [3,4], placenta [5], amniotic fluid [6], and umbilical cord blood [7,8]. Due to their accessibility and convenient expansion protocols, MSCs have been recognized as promising candidates for cellular therapy. However, growing interest in MSCs has led to questioning the equivalence of MSCs isolated from different sources and expanded from various protocols. To address this issue, the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy developed the minimal criteria to universally define human MSCs [9]. The criteria include adherence to plastic, specific surface antigen expression ($CD73^+$ $CD90^+$ $CD105^+$ $CD34^-$ $CD45^-$ $CD11b^-$ $CD14^-$ $CD19^-$ $CD79a^-$ HLA-DR^-) as well as multipotent differential potential under standard *in vitro* differentiation conditions (Table 1).

In addition to their ease of isolation and *ex vivo* expansion, MSCs possess unique characteristics that

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Table 1. Minimal criteria of mesenchymal stem cells

Surface markers	Differentiation potential	Other characteristics
$CD73^+$	Osteogenic	Adherence to plastic
$CD90^+$	Adipogenic	Spindle-shape morphology
$CD105^+$	Chondrogenic	
$CD34^-$		
$CD45^-$		
$CD11b^-$		
$CD14^-$		
$CD19^-$		
$CD79a^-$		
HLA-DR^-		

make them attractive therapeutic agents for treatment of various diseases. First, MSCs have the ability to differentiate across various lineages beyond the conventional mesodermal lineages. The multipotency of MSCs has led to their application in regenerative medicine and tissue repair. Second, recent studies have indicated that MSCs can provide therapeutic benefit through the secretion of soluble factors to induce an immunomodulatory environment. Third, MSCs have the capacity to migrate toward sites of injury and tumor microenvironments. Although the mechanisms are not fully understood, this unique tropism has allowed MSCs to serve as delivery vehicles for targeted therapy.

The potential of MSC therapy involving their unique characteristics has been demonstrated in various *in vivo* disease models and has shown encouraging results for possible clinical use. In a clinical setting, MSCs are now being explored in trials for various conditions, including orthopedic injuries, graft versus host disease (GVHD) following bone marrow transplantation (BMT), cardiovascular diseases, autoimmune diseases, and liver diseases. Furthermore, genetic modification of MSCs to overexpress antitumor genes has provided prospects for use as anticancer therapy in clinical settings. This review focuses on the currently reported uses of MSC therapy in clinical settings and highlights their therapeutic potential and limitations.

THERAPEUTIC PROPERTIES OF MSCs

Recent studies involving MSC therapy have focused on their unique biological properties and functions, which may contribute to their therapeutic potential in clinic settings.

Differentiation and regenerative potential

MSCs are characterized by their ability to self-renew and to differentiate into cells of the mesenchymal lineage, including adipocytes, osteoblasts, chondrocytes, tenocytes, skeletal myocytes, and cells of the visceral mesoderm [2,10,11]. In addition, some studies suggested that the differentiation potential of MSCs extends beyond the conventional mesodermal lineage and that they can also differentiate into cells of ectodermal and endodermal origin, such as hepatocytes [12,13], neurons [14,15], and cardiomyocytes [16,17]. The multilineage differential potential of MSCs is commonly examined by *in vitro* functional assays using specific differentiation media, and these *in vitro* data encouraged further investigation of MSCs as a potential source of tissue repair. However, due to the lack of specific MSC markers, there is little information on the *in vivo* differentiation of MSCs, as compared to *in vitro* characterization. Studies have suggested MSC engraftment and transdifferentiation *in vivo* in various models of damaged or mutated bone, cartilage [18], myocardial [19,20], neural [21,22], and hepatic tissues [13], but whether the observed therapeutic effects are due to paracrine interactions or true differentiation capacity remains to be elucidated. In one study, MSCs labeled with green fluorescent protein (GFP) were injected intravenously and examined for engraftment and differentiation potential [23]. GFP-labeled MSCs were initially located in the lungs and, subsequently, MSCs were detected in other tissues at low frequencies, such as bronchiolar epithelial cells, hepatocytes, and renal tubular cells. Importantly, there was no evidence of clonal expansion and the mechanism of differentiation was not determined, suggesting that the observation of MSCs in various tissues could have been due to simple fusion events. Overall, the therapeutic potential of MSCs has been observed in various injury models, but *in vivo* data supporting the true differentiation and regenerative potential of MSCs are still lacking.

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Immune modulation

MSCs have significant clinical implications as they exert potent immunosuppressive and anti-inflammatory effects through the interactions between the lymphocytes associated with both the innate and adaptive immune systems. MSCs suppress T cell proliferation [24-26], B cell functions [25,27,28], natural killer cell proliferation and cytokine production [29], and prevent the differentiation, maturation, and activation of dendritic cells [30-37]. Importantly, MSCs can suppress cells independently of the major histocompatibility complex (MHC) identity between donor and recipient due to their low expression of MHC-II and other costimulatory molecules [38]. While MSCs can exert immunosuppressive effects by direct cell to cell contact, their primary mechanism is production of soluble factors, including transforming growth factor-β [39], hepatocyte growth factor (HGF) [26], nitric oxide [40], and indoleamine 2,3-dioxygenase (IDO) [41]. Furthermore, through cell to cell contact and the production of soluble factors, MSCs induce an immunosuppressive environment by generating regulatory T cells (Tregs). The ability of MSCs to induce Tregs has been observed both *in vitro* [42,43] and *in vivo* in various models [44-49]. In addition, MSCs can induce plasmacytoid dendritic cells to produce interleukin (IL)-10 [50], which may also support the development of Tregs *in vivo*. These observations suggest that MSCs are key regulators of immune modulation by directly suppressing activated immune cells and indirectly recruiting Tregs.

However, MSCs are not constitutively inhibitory. MSCs are highly dependent on environmental inflammatory conditions. Under acute inflammatory conditions polarized by M1 macrophages and helper T lymphocyte (Th)-type-1 cytokines, especially the proinflammatory cytokine interferon (IFN)-γ, the immunosuppressive capacity of MSCs is enhanced through increased production of ICAM-1, CXCL-10, CCL-8, and IDO [51-53]. On the other hand, under chronic inflammatory conditions when MSCs are polarized by M2 macrophages and Th2 cytokines, MSCs can be recruited into the fibrotic process [51]. Thus, the therapeutic effects of MSCs depend on the inflammatory microenvironment, which should be taken into consideration when used for therapy.

Migratory capacity

A number of studies have suggested that MSCs have the capacity to migrate to sites of inflammation and tumor microenvironments. Although the exact mechanisms underlying MSC migration remain to be elucidated, studies have shown that MSC migration is dependent on various chemokine and receptor interactions, such as stromal cell-derived factor 1 (SDF-1)/C-X-C chemokine receptor type 4 (CXCR4) [54,55], stem cell factor/c-kit, HGF/c-Met [56], vascular endothelial growth factor (VEGF)/VEGF receptor [57], platelet-derived growth factor (PDGF)/PDGF receptor [54,58], monocyte chemoattractant protein-1 (MCP-1)/C-C chemokine receptor type 2 [59], and high mobility group box 1/receptor for advanced glycation endproducts [60,61] as well as other cell adhesion molecules [55,62]. These cytokine and chemokine receptor pairs play important roles in leukocytes that respond to injury and inflammation or hematopoietic stem cells (HSC) and are thought to function similarly in MSCs. Furthermore, the tumor microenvironment closely resembles an unhealed wound that continuously produces inflammatory mediators, including cytokines, chemokines, and other chemoattractant molecules [63]. This constant inflammatory signaling may become a target for MSC migration. Among the chemokine receptor pairs, SDF-1 and CXCR4 are important mediators of stem cell recruitment to tumors [54]. In addition, many tumor microenvironments exhibit hypoxia that results in expression of proangiogenic molecules. The hypoxia-induced transcription factor HIF-1α activates the transcription of genes, including VEGF, macrophage migration inhibitor factor, tumor necrosis factors, and numerous proinflammatory cytokines [64], inducing the generation of chemokines, such as MCP-1, involved in migration of MSCs toward tumors [59]. Many different chemokine factors and receptors have been implicated in the migration of MSCs and further studies that exploit additional chemokine/receptor interactions are needed to develop targeted MSC therapies to inflammatory and tumor sites.

CLINICAL APPLICATIONS OF MSCs

MSCs have attracted attention due to their unique ther-

apeutic properties. In this review, we summarize some of the clinical trials of MSC therapy in various fields (Table 2).

Bone and cartilage diseases

The ability of MSCs to differentiate into osteoblasts, tenocytes, and chondrocytes has attracted interest for their use in orthopedic settings. First, MSCs have been shown to be beneficial in treating bone disorders, such as osteogenesis imperfecta (OI) and hypophosphatasia. OI is characterized by skeletal fragility and connective tissue alterations caused by alteration of type I collagen production by osteoblasts. Pediatric patients with OI underwent allogeneic hematopoietic stem cell transplantation (HSCT) and the transplanted bone marrow cells engrafted and generated functional osteoblasts leading to improvement in bone structure and function [65]. Although, only a low level of engraftment was achieved, a follow-up study demonstrated continued improvements in patients for 18 to 36 months post-transplantation [66]. It is important to note that these patients were transplanted with whole bone marrow instead of MSCs alone. In another follow-up study, patients who received HSCT were infused with the same donor MSCs [67]. The additional infusion of MSCs showed further benefit, but this was limited in duration. Furthermore, a fetus diagnosed with severe OI underwent *in utero* MSC transplantation [68]. After birth, psychomotor development and growth were normal. Hypophosphatasia is a genetic disorder of mesenchymal origin with mutation in tissue nonspecific alkaline phosphatase. Although the numbers of clinical studies are limited, pediatric patients who received BMT showed significant clinical improvements [69,70]. Administration of MSCs alone in hypophosphatasia has not yet been studied; some authors have suggested that cultured MSCs may fail to engraft after intravenous infusion due to loss of adhesion molecules and loss of self-renewal ability [71,72]. However, even patients receiving whole bone marrow did not reveal significant donor MSC engraftment despite clinical improvements [69].

Table 2. Clinical trials of mesenchymal stem cell therapy

Reference	Disease	Phase	No. of patients	MSC source	Route	Outcome
Horwitz et al. [65]	OI	I	3	Allo-BM	IV	Improved
Horwitz et al. [67]	OI	I	6	Allo-BM	IV	Improved
Le Blanc et al. [68]	OI	I	1	Allo-fetal	*In utero* transplantation	Improved
Wakitani et al. [73]	Cartilage defects	I	2	Allo-BM	Intra-articular cartilage	Improved
Wakitani et al. [74]	Cartilage defects	I	12	Allo-BM	Intra-articular cartilage	Improved
Wakitani et al. [75]	Cartilage defects	I	24	Allo-BM	Intra-articular cartilage	Improved
Kuroda et al. [76]	Cartilage defects	I	1	Allo-BM	Intra-articular cartilage	Improved
Baron et al. [78]	HSCT	I	20	Allo-BM	Cotransplantation	Improved
Lazarus et al. [79]	HSCT	I	46	Allo-BM	Cotransplantation	Improved
Ning et al. [80]	HSCT	I	10	Allo-BM	Cotransplantation	Improved but higher recurrence rate of hematologic malignancy
Bernardo et al. [82]	HSCT	I	13	Allo-BM	Cotransplantation	Did not support engraftment but abrogated GVHD
Macmillan et al. [83]	HSCT	I/II	15	Allo-BM	Cotransplantation	Improved
Le Blanc et al. [84]	aGVHD	I	1	Allo-BM	IV	Improved
Fang et al. [85]	aGVHD	I	6	Allo-adipose tissue	IV	Improved

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Table 2. Continued

Reference	Disease	Phase	No. of patients	MSC source	Route	Outcome
Le Blanc et al. [86]	aGVHD	II	55	Allo-BM	IV	Improved
Lucchini et al. [87]	aGVHD, cGVHD	I	16	Allo-BM	IV	Improved (greater in aGVHD)
Muller et al. [88]	aGVHD, cGVHD	I	5	Allo-BM	IV	Improved (greater in aGVHD)
Prasad et al. [89]	aGVHD	I	12	Allo-BM	IV	Improved
Ringden et al. [90]	aGVHD	I	8	Allo-BM	IV	Improved
von Bonin et al. [91]	aGVHD	I	13	Allo-BM	IV	Improved
Wu et al. [92]	aGVHD	I	2	Allo-UCB	IV	Improved
Zhou et al. [93]	cGVHD	I	4	Allo-BM	Intra-BM	Improved
Kebriaei et al. [94]	aGVHD	II	32	Allo-BM	IV	Improved
Weng et al. [95]	cGVHD	I	19	Allo-BM	IV	Improved
Kuzmina et al. [96]	aGVHD, cGVHD	II	37	Allo-BM	IV	Improved
Chen et al. [100]	MI	I	69	Allo-BM	Intracoronary	Improved
Chen et al. [101]	MI	I	46	Allo-BM	Intracoronary	Improved
Katritsis et al. [102]	MI	I	22	Allo-BM	Intracoronary	Improved
Katritsis et al. [103]	MI	I	5	Allo-BM	Intracoronary	Improved
Yang et al. [104]	MI	I	16	Allo-BM	Intracoronary	Improved
Zeinaloo et al. [105]	MI	I	1	Allo-BM	Intracoronary	Improved
Hare et al. [106]	MI	I	53	Allo-BM	IV	Improved
Ichim et al. [107]	MI	I	1	Allo-placental	IV	Improved
Garcia-Olmo et al. [109]	Crohn disease	I	10	Allo-BM	Intrafistula	Improved
Garcia-Olmo et al. [110]	Crohn disease	II	14	Auto adipose-tissue	Intrafistula	Improved
Mohyeddin Bonab et al. [111]	Multiple sclerosis	I	10	Allo-BM	Intrathecal	Mixed
Yamout et al. [112]	Multiple sclerosis	I	10	Allo-BM	IV	Mixed
Karussis et al. [113]	Multiple sclerosis	I/II	15	Allo-BM	Intrathecal	Mixed
Riordan et al. [114]	Multiple sclerosis	I	3	Auto/allo adipose-tissue	IV and Intrathecal	Mixed
Liang et al. [116]	SLE	I	15	Allo-BM	IV	Improved
Sun et al. [117]	SLE	I	16	Allo-UCB	IV	Improved
Liang et al. [118]	SLE	I	1	Allo-UCB	IV	Improved
Carrion et al. [119]	SLE	I	2	Allo-BM	IV	No change
Mohamadnejad et al. [125]	Liver cirrhosis	I	4	Allo-BM	IV	Improved
Kharaziha et al. [126]	Liver cirrhosis	I/II	8	Allo-BM	IV	Improved

MSC, mesenchymal stem cell; OI, osteogenesis imperfecta; Allo, allogeneic; BM, bone marrow; IV, intravenous; HSCT, hematopoietic stem cell transplantation; aGVHD, acute graft versus host disease; cGVHD, chronic graft versus host disease; UCB, umbilical cord blood; MI, myocardial infarction; Auto, autologous; SLE, systemic lupus erythematosus.

Similar to studies on genetic bone disorders, there have been limited reports demonstrating the efficacy of MSCs in promoting cartilage repair in which MSCs embedded in collagen gel were transplanted into the knee joints of patients with articular cartilage defects [73-76]. MSC transplantation has been shown to produce significant clinical improvements with cartilage repair; however, the mechanisms underlying cartilage regeneration are still unknown. The transplanted MSCs may have differentiated into chondrocytes, but it is also possible that MSCs produce soluble factors to induce other cells of the microenvironment to differentiate into cartilage.

BMT and GVHD

HSCT has been widely used over the past several decades to treat patients with various malignant and non-malignant diseases. However, the procedure remains complicated by regimen-related toxicity, engraftment failure, and GVHD [77]. Preconditioning regimens, such as chemotherapy and/or radiotherapy, may damage the bone marrow and lead to a diminished engraftment of stem cells. MSCs are an attractive therapeutic approach during or after transplantation as their transplantation can minimize the toxicity of the conditioning regimens while inducing hematopoietic engraftment and decrease the incidence and severity of GHVD. In several studies, MSCs were cotransplanted with HSCs to facilitate engraftment [78-83] but their efficacy remains unclear. Similarly, the infusion of third-party haploidentical MSCs during pediatric umbilical cord blood transplantation was shown to induce prompt hematopoietic recovery [83]. On the other hand, some studies have suggested that cotransplantation of MSCs does not affect the kinetics of engraftment [82]. While there have been no trials of MSCs for hematopoiesis, the best studied therapeutic application of MSC is GVHD.

GVHD is a severe inflammatory condition that results from immune-mediated attack of recipient tissues by donor T cells during BMT. The clinical efficacy of MSCs in acute GVHD (aGVHD) was first observed in a 9-year-old boy with steroid-resistant grade IV aGVHD [84]. The patient, who was unresponsive to other therapies, showed a complete response after receiving haploidentical third-party MSCs. Following this pilot study, MSC treatment has been studied extensively in steroid-refractory GVHD [84-92]. In 2006, six of eight patients with steroid-resistant grade III to IV GVHD showed complete remission to MSC treatment [90]. The European Group for Blood and Marrow Transplantation then led a multicenter phase II study in which both pediatric and adult patients with steroid-resistant GVHD were treated with MSCs derived from various sources, including HLA-identical and haploidentical sibling donor bone marrow or third-party mismatched donor bone marrow [86]. Sixty-eight percent of these patients showed complete responses with a significantly reduced transplantation-related mortality rate. Not only did this multicenter study confirm that MSCs are a powerful therapeutic tool it also reduced concerns regarding HLA disparity between the MSC donor and recipient through extensive use of third-party-derived MSCs. Based on these properties, MSCs have been further developed into an FDA-approved commercialized "off-the-shelf" product known as Prochymal (Osiris Therapeutics Inc., Columbia, MD, USA), which is derived from the bone marrow of healthy adult donors [93]. Prochymal was used in a randomized prospective study to treat patients directly after diagnosis of GVHD [94]. Ninety-four percent of the patients had an initial response and showed no infusional toxicities or ectopic tissue formation. In a multicenter trial, a higher response rate was seen in children (84%), as compared to adults (60%) [86]. Therefore, Prochymal was used to specifically treat pediatric patients less than 18 years old with severe steroid-resistant grade III and IV aGVHD [89]. Overall, seven of 12 patients showed complete responses suggesting that pediatric patients may respond better to MSC treatment.

While studies on the use of MSCs for treatment of aGVHD have yielded promising results, the therapeutic efficacy of MSCs in chronic GVHD (cGVHD) is less clear because of the paucity of studies. While some studies indicated efficacy of MSCs, even in cGVHD [93], others suggested that MSCs are less effective in cGVHD than aGVHD [87,88,95]. In studies of MSC therapy in both aGVHD and cGVHD patients, the response rates were higher in aGVHD than cGVHD patients [96]. In addition, the infusion of MSCs following HSCT could prevent the development of aGVHD, while the development cGVHD remained unaffected. Thus, specific pa-

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tient recruitment and study designs may allow critical analysis of the effects of MSC treatment in GVHD patients in the future.

Cardiovascular diseases

Despite improvements in medical and surgical therapies, heart disease and heart failure continue to show high morbidity and mortality rates. MSC therapy is an attractive candidate for cardiovascular repair due to its regenerative and immunomodulatory properties. In preclinical studies, MSCs were shown to engraft and improve cardiac repair after administration [97-99]. Clinical trials using MSCs to improve cardiac function have also yielded encouraging results. In a pilot study, 69 patients with acute myocardial infarction received percutaneous coronary injection, and were randomized to receive intracoronary injection of autologous MSCs or standard saline as controls [100]. There were no serious adverse events following MSC administration and the MSC-treated group showed significant improvements in cardiac function, as compared to the control group. This was also the first study to follow and detect the viability of MSCs and cardiac function with cardiac electromechanical mapping. The results indicated that MSCs were still viable 3 months after transplantation. Following this study, MSCs have been used to treat acute and chronic myocardial infarction patients, with significant improvements in heart functions [101-105]. In addition to autologous MSCs, the efficacy of allogeneic MSCs has also been reported. The commercial bone marrow-derived MSC product Prochymal was administered to reperfused myocardial infarction patients in a double blind, placebo-controlled dose-range safety trial [106]. Allogeneic MSCs were well tolerated with a significant increase in left ventricular ejection fraction and lower incidences of arrhythmia and chest pain, as compared to the placebo group. Allogeneic MSCs derived from the placenta also resulted in significant clinical improvements [107]. Thus, the availability of an off-the-shelf MSC product shows promise with regard to the development of cardiac therapy.

Autoimmune diseases

Autoimmune diseases result from an inappropriate immune response of the body against normal cells and tissues. Based on their ability to modulate immune responses, MSCs have also been proposed as a treatment for autoimmune diseases. Patients suffering from severe autoimmune diseases do not respond to standard therapy and often require autologous or allogeneic HSCT [108]. However, HSCT presents many additional complications as well as risks such as toxicity and the incidence of GVHD. Autologous HSCT has often been criticized as identical autoimmune immune cells are being returned back to the patient. Thus, the administration of MSCs may be a safer and more feasible method of treatment. First, the therapeutic role of MSCs has been investigated in patients with Crohn disease. Crohn disease, also known as inflammatory bowel disease, is a chronic inflammatory disorder in which the immune system attacks the gastrointestinal tract. Five patients with Crohn disease were treated with autologous adipose tissue-derived MSCs [109]. The patients were given intralesional treatment of MSCs mixed with fibrin glue. Two patients showed normal healing of the infiltrated area and 75% of treated fistulas had closed and showed signs of significant repair 8 weeks after treatment. These promising results led to a phase II clinical trial [110]. Second, on the basis of preclinical studies, there have been clinical reports on the therapeutic role of MSCs in multiple sclerosis, a chronic inflammatory demyelinating disease of the central nervous system that leads to irreversible damage. Therapeutic approaches have aimed to control the immune response; however, there are still no effective treatments available. In a pilot study, 10 patients with multiple sclerosis received intrathecal injection of culture-expanded MSCs [111]. While administration of MSCs is feasible and safe, the clinical improvements are less clear. During functional assessments, six patients showed some degree of improvement in their sensory, pyramidal, and cerebellar functions, while others showed no improvement or deterioration. Furthermore, the majority of patients showed no differences in MRI assessments after 12 months, indicating that MSC therapy may have less efficacy in multiple sclerosis. Subsequent trials similarly showed mixed results [112-114]. Third, the role of MSCs has also been documented in systemic lupus erythematosus (SLE), an autoimmune inflammatory disease with multiorgan involvement including the kidney, brain, lung, and hematopoietic systems. The most widely

used immunosuppressive therapy is corticosteroid administration; however, steroid-based therapies are associated with significant side effects. While MSCs seem to be an attractive therapeutic approach, a recent study suggested that MSCs derived from SLE patients show functional abnormalities [115] and, thus, MSC transplantation may be more effective, as compared to autologous MSCs. In a pilot study determining the safety and efficacy of MSC transplantation in refractory SLE patients, allogeneic MSC transplantation ameliorated disease activity, improved serological markers, and stabilized renal functions [116]. Umbilical cord-derived MSCs have also shown therapeutic potential in SLE patients [117,118]. On the other hand, the use of autologous MSCs was safe, but did not induce significant changes in disease activity [119].

Finally, rheumatoid arthritis (RA) is a T cell-mediated autoimmune disease characterized by cartilage and bone destruction. Their anti-inflammatory properties and regenerative potential indicate that MSCs could offer a novel therapeutic approach to treat RA. However, the role of MSCs in RA has not yet been reported in clinical trials. The therapeutic potential of MSCs is controversial in preclinical studies, which may have delayed their application in clinical trials. While some studies have suggested the efficacy of MSC therapy in collagen-induced arthritis (CIA) models [120,121], many others have suggested that MSCs alone do not suppress the development of Th17-mediated joint inflammation [122,123]. We have also observed that MSCs are ineffective for treatment of CIA [124]. Thus, MSCs have attracted attention as a therapeutic approach for rheumatic diseases, but the immunomodulatory mechanisms must be clarified to ensure further applications in autoimmune diseases.

Liver diseases

MSCs have been used to treat cirrhosis in a limited number of trials. Cirrhosis is a chronic liver disease characterized by progressive hepatic fibrosis and loss of hepatic structure with formation of regenerative nodules. Liver transplantation is often the only option in advanced stage patients; however, it is limited by lack of donors, surgical complications, and rejection. MSCs have the potential to be used for the treatment of liver diseases due to their regenerative potential and immunomodulatory properties. Furthermore, MSC therapy could provide minimally invasive procedures with relatively few complications, as compared to liver transplantation. In a phase I trial, four patients suffering from end-stage liver cirrhosis were treated with autologous MSCs and showed improved quality of life with no side effects during follow-up [125]. In another phase I to II clinical trial, eight patients with end-stage liver diseases received autologous MSCs. MSC administration was well tolerated and improved liver functions [126]. Thus, MSC therapy is safe, feasible, and applicable in end-stage liver disease.

Cancer

MSCs are emerging as vehicles for cancer gene therapy due to their inherent migratory abilities toward tumors [127]. Whether MSCs themselves have antitumor effects is still controversial as some studies have suggested that even unmodified MSCs inhibit tumor growth and angiogenesis [128-130], while others report that MSCs promote tumorigenesis and metastasis [131-133]. Nonetheless, MSCs have been genetically modified to overexpress various anticancer genes, such as ILs [134-138], IFNs [139-141], prodrugs [142,143], oncolytic viruses [144-147], antiangiogenic agents [148], proapoptotic proteins [149,150], and growth factor antagonists [151], for targeted treatment of different cancer types. While preclinical models using gene-modified MSCs for the treatment of cancer have been well studied, clinical trials utilizing engineered MSCs for cancer therapy have not yet been reported. The safety of MSC administration remains a concern even though MSC administration has not yet shown any major adverse events. Their potential to transform malignantly [152,153] and weaken graft versus leukemia effects following HSCT [80] are major issues with regard to guaranteeing the safety of MSC therapy. Engineered MSCs that overexpress potentially hostile molecules may pose serious problems in addition to these concerns. The lack of safety mechanisms following MSC administration has delayed the application of engineered MSCs in clinical settings. Recently, a safety system to allow control of the growth and survival of MSCs has been developed. The safety mechanism is a suicide system based on an inducible caspase-9 protein that is activated using a specific chemical inducer of dimerization (CID) [154]. Exposure

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to CID induced directed MSC killing within 24 hours. The development of such safety mechanisms and their incorporation into MSC therapy may allow extensive use of genetically engineered MSCs to treat cancer patients in clinical settings.

CONCLUSIONS

With their ability to differentiate into multiple lineages, secrete factors related to immune regulation, and migrate toward sites of inflammation, MSCs have many clinical implications. The results of multiple clinical trials using MSCs have been promising but also highlight the critical challenges that must be addressed in the future. More research is needed to determine the mechanisms and biological properties of MSCs to enhance their therapeutic efficacy in various diseases. Furthermore, the heterogeneity of the MSC population presents a challenge for generalized findings. Therefore, it is important to standardize the generation protocols, including cell culture conditions, source, passage, and cell density, as they may impact MSC phenotype as well as functions. Further randomized, controlled, multicenter clinical trials are necessary to determine the optimal conditions for MSC therapy. With further advances, MSCs will play an important role in managing many disorders that lack effective standard treatment.

Conflict of interest

No potential conflict of interest relevant to this article is reported.

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