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REVIEW ARTICLE

Mesenchymal stem cells for the treatment and prevention of graft-versus-host disease: experiments and practice

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Abstract Mesenchymal stem cells (MSCs) have emerged as a therapeutic approach in a range of medical fields, including regenerative medicine, cancer, autoimmune diseases, and inflammatory diseases, because of their unique properties of tissue repair and major histocompatibility complex-unmatched immunosuppression. Because both in vitro and in vivo findings demonstrate that MSCs possess potent immunoregulatory functions, there has been increasing interest in the role of MSCs in allogeneic hematopoietic stem cell transplantation, especially in the prevention and treatment of graft-versus-host disease (GVHD). GVHD is a major cause of transplantation-related mortality, and conventional immunosuppressants frequently fail to treat patients suffering from GVHD. Following Ringden's pilot study that used third-party MSCs to treat a steroid-refractory GVHD patient, MSCs have created growing interest as a therapeutic agent for GVHD. There have been further studies which demonstrated the potentials of MSC treatment in steroid-refractory GVHD, de novo GVHD, and also GVHD prevention. However, MSCs still present limitations. The need for MSCs to be "licensed" in a pro-inflammatory environment, especially in the presence of interferon gamma, allows only a narrow window for their administration. Thus, their effects have been less clear as a preventive measure before the inflammatory environment of GVHD is established and also when administered during a chronic setting where MSCs may be alternatively licensed. In this review, we focus on the immunomodulatory properties of MSCs and their effects in relation to GVHD. Given the efficacy of MSCs in murine models of GVHD and their safety in clinical trials, it is crucial that larger clinical trials are conducted and further modifications are investigated.

Keywords Clinical trial · Graft-versus-host disease · Hematopoietic stem cell transplantation · Immunomodulatory therapy · Mesenchymal stem cells

Abbreviations

aGVHD	Acute graft-versus-host disease
CFU-F	Colony-forming unit fibroblast
cGVHD	Chronic graft-versus-host disease
CIA	Collagen-induced arthritis
DC	Dendritic cell
EGFP	Enhanced green fluorescent protein
GVHD	Graft-versus-host disease
GVL	Graft-versus-leukemia
HSCT	Allogeneic hematopoietic stem cell transplantation
IL-10	Interleukin-10
MSC	Mesenchymal stem cell
MHC	Major histocompatibility complex
NK	Natural killer
RFP	Red fluorescent protein
Treg	Regulatory T cell

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Introduction

Mesenchymal stem cells (MSCs) are defined as self-renewing, multipotent progenitor cells with multilineage potential to differentiate into other cell types of mesodermal origin, such as adipocytes, osteocytes, and chondrocytes [1–4]. The history of MSCs began in the 1970s when Alexander Friedenstein first isolated and cultured in vitro adherent, fibroblast-like clonogenic stromal cells with multilineage potential from whole bone marrow [5]. Currently, the minimal criteria for definition of MSCs developed by the Mesenchymal and Tissue Stem Cell Committee of the International Society for Cellular Therapy are as follows: first, adherence to plastic; second, positivity for the cell-surface molecules CD105, CD73, and CD90 and negativity for CD45, CD34, CD14 or CD11b, CD79a or CD19, and human leukocyte antigen (HLA)-DR; and third, the ability to differentiate into osteoblasts, adipocytes, and chondroblasts under standard in vitro differentiation conditions [6].

Graft-versus-host disease (GVHD) is a severe inflammatory condition that results from immune-mediated attack of recipient tissues by donor T cells during transplantation. Without intervention before and after allogeneic hematopoietic stem cell transplantation (HSCT), almost all allotransplant recipients develop significant GVHD. While immunosuppressive drugs have improved the survival rates of patients who have undergone HSCT, severe cases of GVHD are not easily reversed by high doses of steroids. The clinical outcomes of patients with severe GVHD are generally poor, with a high mortality rate due to infectious complications and sustained GVHD-related cytopenia and multiorgan failure [7]. Recently, MSCs have emerged as an alternative to current pharmacologic immunosuppressive drugs in the field of transplantation because they have potent immunomodulatory effects on various cell types, regulating both adaptive and innate immune responses. The immunomodulatory properties of MSCs have led to clinical trials of treatment of GVHD after HSCT. Many phase I/II trials worldwide have described the clinical benefits of MSC therapy in GVHD since Le Blanc et al. first reported successful treatment of a patient with severe acute GVHD (aGVHD) using third-party haploidentical MSCs [8]. In this review, we focus on the use of MSCs as a potent cell-therapy approach to controlling GVHD after HSCT. We discuss the recent advances in MSC cell therapy as well as current limitations and highlight considerations that should be made when using MSCs to treat GVHD.

Immunomodulatory properties of MSCs

One of the most intriguing properties of MSCs is that they exert potent immunosuppressive and anti-inflammatory effects. MSCs are known to suppress T cell proliferation [9–11] and the interactions between T cells and MSCs have significant clinical implications. Importantly, MSCs can suppress T cells independently of major histocompatibility complex (MHC) identity between donor and recipient because of their low expression of MHC-II and other costimulatory molecules [12]. In addition, MSCs can affect lymphocytes associated with both innate and adaptive immunity. They suppress the functions of B cells [10, 13, 14], inhibit natural killer (NK) cell proliferation and cytokine production [15–17], and prevent the differentiation, maturation, and activation of dendritic cells (DCs) [18–25]. While MSCs can exert immunosuppressive effects by direct cell-to-cell contact [26], the primary mechanism is production of soluble factors, including transforming growth factor (TGF)-β [27], hepatocyte growth factor [11], nitric oxide [28], HLA-G [29], and indoleamine 2,3-dioxygenase (IDO) [30]. Through cell-to-cell contact and the production of soluble factors, MSCs can induce other regulatory immune cells. When CD3+ T cells were co-cultured with MSCs, the proliferation of T cells decreased while the percentage of CD4+CD25+ regulatory T cells (Tregs) increased [31, 32]. The levels of anti-inflammatory cytokines, including TGF-β and interleukin (IL)-10, also increased in the co-cultures, suggesting that MSCs also induced the production of soluble factors. The ability of MSCs to induce Tregs has also been observed in vivo in various models, including GVHD [33], experimental autoimmune encephalomyelitis [34], experimental arthritis [35], breast cancer [36], asthma [37], and diabetes [38]. In addition, MSCs can induce plasmacytoid DCs to produce IL-10, which may support the development of Tregs in vivo [39]. Furthermore, regulatory CD4+ or CD8+ lymphocytes are generated in co-cultures of peripheral blood mononuclear cells and MSCs [40]. Table 1 summarizes the immunomodulatory properties of MSCs.

These observations identify MSCs as key regulators of immune modulation as they have the capacity to directly suppress T cells and to indirectly recruit and activate Tregs. However, MSCs are not constitutively inhibitory. MSCs are highly dependent on environmental inflammatory conditions and require "licensing" by acute inflammatory helper T lymphocyte (Th1)-type cytokines [41]. Under acute inflammatory conditions, the microenvironment contains polarized M1 macrophages and "licenses" MSCs to inhibit effector T, B, and NK cells and DCs. The immunosuppressive capacity of MSCs is notably enhanced under inflammatory conditions by the pro-inflammatory cytokine interferon gamma (IFN-γ) [16, 42]. Treatment of MSCs with IFN-γ results in secretion of ICAM-1, CXCL-10, and CCL-8 [43], as well as increased IDO production [16]. This phenomenon suggests that MSC-mediated immune regulation requires pro-inflammatory cytokines for suppressive activity. On the other hand, if MSCs are "licensed" after the polarization of M2 macrophages by Th2-type cytokines

Table 1 Immunmodulatory properties of MSCs

Author(Ref.)	Lymphocyte affected	Effects of MSCs	Possible mechanisms
English et al. [9], Glennie et al. [10], Di Nicola et al. [11], Stagg et al. [12], Tse et al. [63], and Meisel et al. [30]	T cells	Suppress T cell proliferation	Production of PGE2, TGF-β, HGF, and IDO
		Alter cytokine secretion profile of T cells	Induction of division arrest energy of T cells
Glennie et al. [10], Corcione et al. [13], and Augello et al. [14]	B cells	Suppress B cell proliferation Inhibit B cell differentiation	Production of PGE2 and IDO
Spaggiari et al. [15], Krampera et al. [16], and Sotiropoulou et al. [17]	NK cells	Suppress NK cell proliferation Prevent cytotoxic activity and cytokine production	Production of PGE2, TGF-β, and IDO
Jiang et al. [18], Aggarwal et al. [19], Maccario et al. [20], Groh et al. [21], Beyth et al. [22], Zhang et al. [23], Ramasamy et al. [24], and Nauta et al. [25]	DCs	Inhibit monocyte differentiation to DCs Alter cytokine secretion Prevent DC maturation and activation	Production of PGE2, TGF-β, MCSF, IL-6, IL-10, and HGF
Ye et al. [31], Di Ianni et al. [32], Joo et al. [33], Zappia et al. [34], Gonzalez et al. [35], Patel et al. [36], Nemeth et al. [37], and Madec et al. [38]	Tregs	Induction of Treg -Recruitment of Tregs in vivo	Production of TGF-β and IL-10

Abbreviations: *DC* dendritic cell, *HGF* hepatocyte growth factor, *IDO* indoleamine 2,3-dioxygenase, *IL* interleukin, *M-CSF* macrophage colony-stimulating factor, *NK* natural killer, *PGE2* prostaglandin E2, *TGF-β* transforming growth factor-β, *Treg* regulatory T cell

during chronic inflammation, the microenvironment can provide alternative licensing and recruit MSCs to the fibrotic process [41]. MSCs in the inflammatory microenvironment depend on MSC licensing; in inflammation that is too mild or chronic, the lack of MSC licensing can result in a lack of a therapeutic effect.

Preclinical experiments using MSCs in the treatment of aGVHD

Many murine models have been used to investigate the potential of MSCs for prevention and/or treatment of aGVHD (Table 1). Preclinical studies have yielded contradictory results, with some demonstrating the therapeutic efficacy of MSCs and others not. MSCs have been considered therapeutic agents for aGVHD based on their immunomodulatory properties in vitro; however, there is an inconsistency between in vitro and in vivo studies. While MSCs inhibited T cell responses in a dose-dependent manner in vitro, the administration of MSCs did not affect the course of aGVHD, regardless of the cell dose at the time of HSCT [44]. This in vivo study of MSCs suggested that MSC therapy could not prevent aGVHD. Subsequent studies using aGVHD models suggested that increasing the number of doses may be more beneficial. aGVHD could be significantly ameliorated by multiple doses at weekly intervals prior to HSCT, which initially led to the conclusion that MSCs were useful only for prevention, but not treatment, of aGVHD when given in multiple doses [45]. Polchert et al. attributed the failure of MSC treatment to the absence of pro-inflammatory cytokines, such as IFN-γ, in the environment at the time of administration. The study showed that the survival rate of mice increased only when MSCs were administered when IFN-γ levels were highest (day +2 or +20 of HSCT) [46]. Even a single infusion, when injected at the appropriate time, was effective. The roles of IFN-γ and the inflammatory environment in activating MSCs to exhibit inhibitory activity had already been described in vitro [16]. Clearly, timing is essential because an appropriate inflammatory environment is needed to license the MSCs in vivo [42, 45]. In an inbred murine model, the infusion of MSCs 3 days after transplantation similarly delayed the development of aGVHD [47]. Interestingly, MSC infusion increased the number of T cells in secondary lymphoid organs, rather than at sites of aGVHD damage such as the intestines. Furthermore, in the presence of MSCs, T cells acquired a naïve phenotype, downregulating T cell activation while continuing to migrate to lymphoid organs.

Another suggested role of the inflammatory environment is to attract MSCs to the area since MSCs can home to sites of inflammation and tissue injury [48]. In addition to their immunomodulatory effects, MSCs can increase tissue repair at the site of injury by providing soluble factors, transdifferentiation, and cell fusion. In one study, bioimaging was used to track the biodistribution of MSCs in a murine model of aGVHD [49]. The donor C57BL/6 splenocytes that were used to induce aGVHD expressed enhanced green fluorescent protein (EGFP). MSCs were generated from C57BL/6 donor mice expressing red fluorescent

protein (RFP). RFP-MSCs were injected and both fluorescent protein signals were consistently detected. EGFP was first detected in the lungs, and its levels increased in the gastrointestinal (GI) tract, liver, skin, and lymph nodes, all of which known to be major clinical targets of aGVHD. After administration of MSCs, RFP and EGFP signals co-localized at the aGVHD target sites, proving that MSCs can be home to sites of aGVHD and potentially exert direct cell-to-cell contact-mediated effects and paracrine tissue repair effects.

Preclinical experiments using MSCs in the treatment of chronic graft-versus-host disease

The effects of MSCs for the treatment of chronic graft-versus-host disease (cGVHD) remain unclear. There is a lack of preclinical studies on cGVHD in general because the immune mechanisms that cause the development of cGVHD are not completely understood. Furthermore, in contrast to aGVHD where murine models of MHC-mismatched models exist, there is absence of an animal model that includes all of the clinical features of cGVHD [50]. Despite these limitations, there are few available models of cGVHD [51–54]; however, the use of MSC for the treatment of these cGVHD models has not yet been reported. It is likely that the development of novel murine models of cGVHD will lead to opportunities to examine the efficacy of MSCs cGVHD and will provide new insights into MSC therapy. Pre-clinical experiments of MSC treatment for GVHD are summarized in Table 2.

Clinical trials of MSCs in patients with aGVHD

The clinical efficacy of MSCs in aGVHD was first observed in a 9-year-old boy suffering from steroid-resistant grade IV aGVHD, who received haploidentical third-party MSCs [8]. MSCs were administered after the patient showed severe resistance to steroid treatments. The patient, who was unresponsive to almost all therapy, showed a complete response after MSC treatment. This report exemplifies the potential of MSCs in the treatment of GVHD and became a cornerstone for further clinical studies.

MSC treatment has been most extensively studied in steroid-refractory GVHD [8, 55–62]. Following Ringden's pilot study in 2006, six of eight patients with steroid-resistant grades III–IV GVHD who were administered MSCs showed complete remission [60]. Their overall survival rate was significantly better than those not treated with MSCs during the same period. Similar results were obtained using adipose-derived MSCs from both related haploidentical family donors and unrelated mismatched donors [55]. These encouraging results led to a multicenter phase II study by the European Group for Blood and Marrow Transplantation [56]. Twenty-five pediatric and 30 adult patients with steroid-resistant GVHD were treated with MSCs derived from HLA-identical and HLA-haplo-identical sibling donor bone marrow or third-party mismatched bone marrow. Sixty-eight percent of the patients who showed complete responses had a significantly reduced level of transplantation-related mortality. Not only did this demonstrate the efficacy of MSC treatment, but it also reduced concerns regarding HLA disparity between the MSC donor and recipient. MSCs have been considered a powerful therapeutic tool because of their absent or low expression of MHC-II and other costimulatory molecules [11, 63]. This suggested that MSCs could modulate immune responses in an HLA-unmatched recipient. The first clinical trial [8] as well as the following multicenter trial [56] which used third-party MSCs demonstrated their safety as well as efficacy. In fact, because of these properties, MSCs have the potential to be used as "off-the-shelf" products. Prochymal® (Osiris Therapeutics, Inc.), an FDA-approved commercialized MSC product, is derived from the bone marrow of healthy adult donors and is being evaluated in numerous clinical trials, including against aGVHD, Crohn's disease, and acute myocardial infarction trials [64]. In relation to GVHD, Prochymal® was first used to treat patients with de novo aGVHD [65]. Whereas most studies discussed thus far involved steroid-resistant GVHD patients who failed initial treatment lines, this was the first randomized prospective study to use MSCs to treat GVHD directly after diagnosis. Patients received GVHD prophylaxis, such as tacrolimus, cyclosporine, and/or mycophenolate mofetil before HSCT and received a combination of MSCs plus corticosteroids after diagnosis of GVHD. Ninety-four percent of the patients had an initial response, and no infusional toxicities or ectopic tissue formation were reported. Prochymal® was then used to specifically treat pediatric patients aged under 18 years [59], who had severe steroid-resistant grades III and IV aGVHD and were treated with MSCs twice per week for 4 weeks. Overall, 7 of 12 patients showed complete responses while the remainder showed partial or mixed responses. The complete responders showed significantly increased survival, suggesting that pediatric patients may respond better to MSC treatment. This finding is supported by Ringden's phase II trial which reported a higher response rate in children (84 %) than in adults (60 %) [56]. The studies on the use of MSCs for the treatment of aGVHD patients have been promising and encouraging; however, further large-scare randomized clinical trials are still needed.

Clinical trials of MSCs in patients with cGVHD

Similar to preclinical experiments, the therapeutic efficacy of MSCs in patients with cGVHD is less clear. While some cases demonstrated successful improvement in rates of

Table 2 Preclinical studies of MSC therapy for GVHD

Author (references)	Host	Donor	MSC source	Route	Dose	Time	Observations
Sudres et al. [44]	BALB/c	C57BL/6	Donor BM	I.V.	5×10^5, 3×10^6, and 4×10^6	D+0	MSCs showed no clinical benefit on the incidence or severity of GVHD. MSCs could be detected in recipients after injection, but there was an absence of suppressive effect in vivo
Tisato et al. [45]	NOD/SCID	Human PBMC	Human UCB	I.V.	3×10^6	D-5,-4,-3,-2,-1	A single dose of MSCs could not treat GVHD. There was a decrease in GVHD development only when given at weekly intervals. Also, no therapeutic effect was obtained if MSCs were administered at onset of GVHD
Polchert et al. [46]	C57BL6	BALB/c	Donor BM	I.V.	1×10^5 and 5×10^5	D+2, D+2, D+20, and D+30	MSCs had no significant efficacy when given at the time of transplant, D+0, or during severe GVHD, D+30, which could be associated with insufficient levels of IFN-γ. MSCs could significantly improve mortality given during ongoing GVHD, D+2 and D+20; however, there was no dose–response effect at higher dose
Joo et al. [33]	BALB/c	C3H/he	Donor BM	I.V.	5×10^5, 1×10^6, and 2×10^6	D+0 and D+0	MSCs inhibit GVHD in a dose-dependent manner where no therapeutic effect was obtained at a low dose
Min et al. [96]	B6D2F1	C57BL/6	Donor BM and IL-10 transduced donor MSC	I.V.	1×10^6, 2×10^6, and 2×10^6	D+1, D+1,3,5, and D+1	The early injection of nontransduced MSCs did not attenuate the severity of aGVHD in a dose-dependent manner
Li et al. [47]	CB6F1	C57BL/6	Donor BM	I.V.	2×10^4, 2×105^5, 1×10^6, and 2×10^6	D+3	The infusion of MSCs could significantly delay the development of aGVHD in a dose-dependent manner
Badillo et al. [68]	CB6F1	C57BL/6	Donor BM	I.V.	5×10^4, 1×10^5, and 1×10^6	D+0, D+2, D+0,7,14, D+10, and D+21	MSCs administered using various dose and timing protocols could neither prevent nor treat GVHD
Prigozhina et al. [69]	CB6F1	C57BL/6	Donor and recipient BM	I.V.	5×10^4 and 5×10^5	D+0,7,14	The injection of MSCs could not control GVHD suggested that MSCs lose their immunosuppressive potential in mismatched settings
Chung et al. [70]	BALB/c	C3H/he	Donor BM	I.V.	1×10^5	D+0	Cotransplantation of MSCs could prevent GVHD by immune modulation

Abbreviations: *BM* bone marrow, *I.V.* intravenous, *PBMC* peripheral blood mononuclear cells, *UCB* umbilical cord blood

cGVHD after MSC treatment [66], most cGVHD-related studies suggest MSCs to be less effective in cGVHD than in aGVHD [57, 58, 67]. In one study, the infusion of culture-expanded MSCs was investigated as a therapeutic approach for patients with steroid-resistant cGVHD. Although 14 of 19 patients (73.7 %) were reported to respond to MSC treatment, only four showed complete remission [67]. The majority of patients showed a partial or mixed response, suggesting that MSCs may not be a potent immunomodulator in the cGVHD environment. Furthermore, cGVHD patients studied in steroid-resistant aGVHD trials exhibited mixed responses to MSCs [57, 58]. Too few cGVHD studies have investigated the effectiveness of MSC. It is apparent that MSC treatment is safe, without infusion-related toxicity, in all GVHD patients; however, the therapeutic effect seems limited. Additional studies are needed to confirm the effectiveness of MSCs for treatment of cGVHD patients and to address their limitations in the chronic setting.

Clinical trials of MSCs for GVHD prophylaxis

Although reports have suggested that MSCs are not effective for GVHD prophylaxis [44, 45, 68, 69], beneficial effects have also been demonstrated [32, 70]. Clinical trials of MSCs for GVHD prophylaxis have been based on positive results showing efficacy. Although trials of MSCs for GVHD prevention are lacking, several studies have co-transplanted MSCs with hematopoietic stem cells (HSCs) to prevent GVHD development and facilitate engraftment. The studies involved co-transplantation of culture-expanded third-party MSCs with either HLA-mismatched HSCs [71] or HLA-matched HSCs [72, 73]. The primary end point of these studies was the safety and feasibility of MSC co-transplantation. The results showed the absence of infusion-related adverse events and other late-term MSC-associated toxicities [71–73]. After co-infusion of MSCs, only 28 % of patients who received HLA-matched sibling allografts developed grades II to IV aGVHD [72]. While these results may seem encouraging, the small number of subjects and lack of control cohort groups are limitations. In a study that included a historic control group, the 100-day cumulative incidence of aGVHD in patients who received MSCs was 45 % and the 1-year incidence of death from GVHD or infection with GVHD was 10 %. In contrast, in the historic group of patients who received only HSCT, 56 % developed grades II to IV aGVHD, and the 1-year incidence of death from GVHD was 31 % [71]. Furthermore, in an open-label randomized clinical trial, HSCs were transplanted alone or co-transplanted with MSCs into patients with hematologic malignancies. Only 11 % of patients who were co-transplanted with MSCs developed grades II to IV aGVHD, while 53 % of the patients who did not receive MSCs developed GVHD [73]. The outcomes were not statistically significant due to the small number of subjects; however, these results suggest that MSCs play a role in GVHD prophylaxis in an allogeneic HSCT setting. In the most recent prophylaxis phase II study, 37 patients were randomly divided into two groups receiving either standard GVHD prophylaxis alone or GVHD prophylaxis combined with MSC treatment. Only one of the 19 patients assigned to the MSC treatment group developed aGVHD, while 6 of 18 patients who did not receive MSCs developed aGVHD [74]. It is important to note that in this study MSCs were not co-transplanted with HSCs but instead infused at the time of blood count recovery. Although there seems to be a significant difference between the two groups, the authors noted that the number of patients included in the trial was limited. The use of MSCs to prevent GVHD should be evaluated in additional phase II clinical trials.

Clinical trials of MSC treatment for aGVHD, cGVHD, and GVHD prophylaxis are summarized in Table 3.

Characteristics of complete responders to MSC treatment

While the guidelines for grading GVHD and evaluating the response rate differ from case to case, patients were generally graded according to internationally accepted criteria prior to MSC therapy, at the start of MSC treatment, and after completion of treatment [75]. Responses were evaluated as follows: complete response, loss of all symptoms of GVHD; partial response, improvement of at least one grade; stable disease, no change in GVHD grade; progressive disease, worsening of GVHD; or mixed response, improvement in one organ but worsening in another. Depending on the clinical trial, no response was defined as either no change in GVHD grade or worsening of GVHD [56, 59]. Responders were defined as temporary if they showed an improved GVHD score after MSC therapy but then flared earlier than 28 days after MSC therapy. Definitive complete responders were patients with a stable response for more than 28 days after MSC therapy [57].

Due to the small sample size and heterogeneous sample group in each study, it is difficult to characterize the complete responders of MSC treatment in clinical trials. However, a general trend exists for certain characteristics of patients who showed complete response to MSC treatment. MSC treatment appears to be more effective in pediatric patients. In a large-scale, multicenter trial, a greater proportion of pediatric patients responded to MSCs than adults [56]. Subsequently, other studies aimed to specifically investigate the effects of MSCs in pediatric patients [57–59]. Furthermore, the majority of patients who participated in the

Table 3 Clinical trials of MSC therapy for GVHD

Author (references)	Phase	Patient	Grade	MSC source	Results	Comments
Le Blanc et al. [8]	I	1	IV	BM	CR (100 %)	Pilot study to use third-party MSCs to treat steroid refractory GVHD patients
Lazarus et al. [72]	I	46	Prophylaxis	BM	13 developed aGVHD (28 %)	Cotransplantation of HLA-identical sibling culture expanded MSCs is safe and feasible for the prevention of GVHD
Ringden et al. [60]	I	8	III–IV	BM	6 CR (75 %)	MSC donor DNA was detected in the colon and lymph node in 1 patient
						The overall survival rate was significantly better than those not treated with MSCs
Le Blanc et al. [56]	II	55	II–IV	BM	30 CR (54 %)	Complete responders had lower transpalntation-related mortality and higher 2-year overall survival
					9 PR (16 %)	A greater proportion of pediatric patients responded than adults
Fang et al. [55]	I	6	III–IV	Adipose	5 CR (83 %)	Adipose tissue-derived MSCs were evaluated for safety and efficacy as salvage therapy for steroid-refractory acute GVHD and showed promising results for MSCs derived from a source other than bone marrow
Muller et al. [58]	I	2	III–IV	BM	1 CR (50 %)	First study to target pediatric patients undergoing allogeneic transplantation with MSCs treatment
		3	Chronic	BM	1 improvement (33 %)	
Ning et al. [73]	I	10	Prophylaxis	BM	1 developed	The cotransplantation of MSCs during HSCT prevented GVHD development, but the relapse rate was higher than the control group
Kebriaei et al. [65]	II	32	II–IV	BM (Prochymal)	24 CR (77 %) 5 PR (16 %)	Third-party off-the-shelf MSC products were used to treat de novo GVHD in combination with corticosteroids and induced a response in majority of patients
Von Bonin et al. [61]	I	13	III–IV	BM	1 CR (7 %)	MSCs were expanded in platelet containing medium from HLA-mismatched donors
					1 PR (7 %)	The efficacy in this study was lower than other reported studies
Osiris Therapeutics, Inc [77]	III	192	II–IV	BM (Prochymal)	86 CR (45 %)–MSC group	There was no significant difference between MSCs and placebo group for steroid refractory and de novo GVHD
					88 CR (45 %)–placebo group	MSCs significantly improved patients with steroid refractor liver and GI GVHD
						MSCs showed a trend of improvement in response rates in pediatric patients
Baron et al. [71]	I	20	Prophylaxis	BM	9 developed aGVHD (45 %)	MSCs are well tolerated in patients with hematologic malignancies undergoing HLA-mismatched nonmyeloablative HSCT without preventing GVL effect
Lucchini et al. [57]	I	11	I–IV	BM	2 CR (23.8 %) 5 PR (47.6 %)	MSCs expanded in platelet containing medium could be safely infused in pediatric patients
		5	Chronic	BM	1 CR (20 %) 2 PR (40 %)	MSC efficacy was greater in aGVHD than in cGVHD
Prasad et al. [59]	I	12	III–IV	BM (Prochymal)	7 CR (58 %)	First study using premanufactured, universal donor MSC product in pediatric patients
					2 PR (17 %)	Clinical responses were seen especially in the Gl system
Zhou et al. [66]	I	4	Chronic	BM	4 significant improvement (100 %)	The study suggested the benefit of MSC therapy in treating sclerodermatous cGVHD
Weng et al. [67]	I	19	Chronic	BM	4 CR (21 %)	Pilot study of MSCs combined with immunosuppressive therapies for refractory cGVHD.
					10 PR (52 %)	Majority of the surviving patients were able to discontinue or taper immunosuppressants after MSC infusion
Wu et al. [62]	I	2	IV	UCB	2 CR (100 %)	First clinical trial using MSCs derived from UCB
						aGVHD patients that received UCB derived MSCs improved dramatically
Kuzmina et al. [74]	II	37	Prophylaxis	BM	1 out of 19 developed aGVHD (5.3 %)	Combination of MSCs with standard GVHD prophylaxis could significantly prevent development of aGVHD but not cGVHD

Abbreviations: *BM* bone marrow, *CR* complete response, *Gl* gastrointestinal, *HSCT* hematopoietic stem cell transplantation, *PR* partial response

clinical trials received bone marrow-derived MSCs. Thus, the majority of the complete responders also received bone marrow-derived MSCs. However, MSCs of other sources, such as adipose tissue [55] or umbilical cord blood (UCB) [62], have been used. Wu et al., who reported the first UCB-derived MSC-related GVHD trial, suggested that UCB-derived MSCs have suppressive potential superior to that of bone marrow-derived MSCs. Both patients treated with UCB-derived MSCs in this study showed complete responses. However, because of the lack of trials of UCB-derived MSCs, their superiority should be confirmed in further trials.

Overall, patients with skin-involved GVHD had a higher response rate to MSC treatment [57, 61, 65]. The skin is the organ most commonly involved during the development of aGVHD, which usually then spreads to the rest of the body [76]. However, some reports suggest that MSCs are more effective in GI or liver GVHD. The phase III double-blind, placebo-controlled trial by Osiris Therapeutics evaluated the efficacy of Prochymal® MSCs in combination with steroid therapy as the first line-treatment where the majority of patients were suffering from skin GVHD [77]. The combination of Prochymal® MSCs and steroid therapy was compared with steroid therapy alone. These patients responded significantly better to steroids alone which diminished the additional effects of Prochymal® MSCs in the combination group. In a different double-blind, placebo-controlled trial, Prochymal® MSCs was added as a second-line treatment in steroid-refractory liver and GI GVHD patients [77]. Significantly improved response rates were seen in both steroid-refractory liver GVHD (76 %) and GI GVHD (88 %) patients who received MSCs [77]. However, the difference in results may be attributed to the fact that the skin GVHD patients were newly diagnosed aGVHD patients whereas liver and GI GVHD patients had already failed to respond to corticosteroid treatment.

Moreover, most studies involved patients who are resistant to conventional steroids and failed at least their first-line treatment [55, 56, 60–62]. Overall, there is a lack of studies of de novo aGVHD, cGVHD, and GVHD prophylaxis; however, there are some studies that suggest that MSCs may be less effective in the cGVHD [57] and GVHD prophylaxis [61] settings. In studies that included both aGVHD and cGVHD patients, the response rate was higher in aGVHD than in cGVHD patients [57, 58]. More recently, the infusion of MSCs following HSCT could prevent the development of aGVHD compared with the control group but the development of cGVHD was unaffected [74]. While the mechanisms remain unclear, this may be due to their highly environment-dependent nature, similar to preclinical results. Thus, the results differ from case to case, and more specific patient recruitment and study designs may allow critical analysis of the effects of MSC treatment in GVHD.

Side effects of MSC therapy

No MSC infusion-related side effects, acute or late, have been reported in any of the clinical trials mentioned above. Also, no ectopic tissue formation has been reported. Furthermore, MSCs, regardless of their cellular source, have been proven to be safe in both adult and pediatric patients, and all of these patients tolerated multiple infusions of MSCs.

The biggest concern regarding the use of MSCs is attenuation of the graft-versus-leukemia (GVL) effect. The induction of regulatory cells and immunosuppression caused by MSCs is a major issue for patients with hematologic malignancies. Various preclinical models have shown that MSCs promote tumor growth by supporting the tumor microenvironment [78–80]. Co-transplantation of MSCs with a tumor cell line increased the proliferative capacity of tumor cells and enhanced metastasis [80]. In a clinical trial using MSCs to prevent GVHD in patients with hematologic malignancies, MSCs reduced the development of GVHD, but the relapse rate among patients was higher than that in the control group [73]. Six of ten patients in the MSC group experienced tumor relapse, compared with 3 of 15 in the non-MSC group. The significantly higher relapse rate in the MSC group may suggest that the infusion of MSCs weakens the GVL effect; however, the sample size of this study is too small to draw any final conclusions. Still, the results demonstrate that caution should be taken when administering MSCS in nonmalignant hematopoietic diseases. On the other hand, there is also a clinical trial that suggests that the infusion of MSCs can prevent GVHD without abrogating GVL effects. In this study, MSCs were transplanted in patients with hematologic malignancies before nonmyeloablative HSCT [71]. MSCs reduced the incidence of aGVHD as well as graft rejection while the relapse rate remained similar to the historic group that did not receive MSCs. These results contradict the previous data by suggesting that MSC treatment may not weaken the GVL effect. The impact of MSCs on the GVL effect still remains to be elucidated, as there is lack of data in both preclinical and clinical studies that clearly demonstrate the prevention of GVHD while sparing GVL effect by using MSCs.

The pro-tumorigenic effects demonstrated by MSCs are due to their immunosuppressive properties, their ability to enhance tumor stroma, and their potential to transform malignantly. Recently, concerns about the possibility of malignant transformation of MSCs have been raised [81]. Murine MSCs are more susceptible to malignant transformation during long-term culture [82], while ex vivo human MSC (hMSC) expansion seems safer [83]. Whether hMSCs are safe from malignant transformation remains controversial since other studies have reported malignant transformation even in hMSCs [84]; however, malignant transformation of MSCs in GVHD clinical trials has not yet been observed. Therefore, avoidance of unnecessary manipulation and prolonged culture of MSCs is recommended.

Limitations of MSC therapy

Considerable progress has been made in the development of MSC treatment for GVHD; however, MSCs have a number of limitations. The contradictory results in animal models show that the therapeutic efficacy of MSCs varies according to the setting [44, 68, 69]. Often, MSCs fail to control GVHD, even with use of a variety of timing and dose protocols. MSC treatment for GVHD in clinical trials similarly appears to have inherent constraints from preclinical experiments. Osiris Therapeutics, which showed encouraging results in phase II studies, reported contradictory reports in their phase III trial. This phase III trial was double blinded and placebo controlled and evaluated the safety and efficacy of third-party MSCs (Prochymal®) in patients with steroid-resistant aGVHD and de novo patients [77]. Surprisingly, there was no significant difference between the MSC treatment group and the placebo group in either the steroid-refractory or de novo GVHD trials. Only selected patients with severe liver GVHD and pediatric patients exhibited significantly improved response rates. In addition, murine MSCs do not always provide data that can be replicated with the use of human MSCs. The characteristics and functional differences of MSCs are minimal between species [85]; however, the discrepancy between results from mice and human emphasizes that MSCs are highly dependent on their environment.

These studies do not undermine the efficacy of MSCs but indicate the need for critical analysis of their therapeutic benefit. First, the need for MSCs to be licensed allows only a narrow window for their administration. While MSCs show therapeutic effects in established GVHD, the effects are less clear when they are co-infused as a preventive measure at the time of bone marrow transplant, especially in murine models [44, 45, 68, 69]. Similarly, the majority of clinical trials are of treatment of established GVHD. There have been three completed trials on GVHD prophylaxis to-date; these have suggested the safety and feasibility of coadministration of MSCs during HSCT [71–73]. All of these studies demonstrated that the coadministration of MSCs during HSCT decreased the incidence of GVHD and the incidence of death from GVHD. However, the number of participating subjects and the number of trials are low, which may explain the inconclusive effects of MSCs as a preventive measure. One possible explanation is that after myeloablative conditioning regimen, a temporal gap may exist until the endogenous donor-derived Tregs are induced, limiting MSCs' full suppressive potential.

Second, there is some evidence that MSCs are limited in their ability to regulate Th17 responses. Initially, it was thought that GVHD was a primarily Th1-mediated immune response; however, there is increasing evidence that GVHD involves both Th1 and Th17 responses [86]. To determine the role of Th17 responses in GVHD, Yu et al. disrupted the transcription factors, T-bet and RORγt which are critical for Th1 and Th17 differentiation, respectively of the donor T cells [87]. While the disruption of Th1 or Th17 separately could attenuate GVHD to some degree, the disruption of both Th1 and Th17 cells could strongly ameliorate symptoms of GVHD indicating that there is a complex interaction between Th1 and Th17 responses. Most studies of MSCs for the treatment of GVHD have focused on Th1 responses, especially IFN-γ [42, 46]. In the presence of Th1-dominant responses with the elevated levels of IFN-γ, the immunosuppressive activity of MSCs is enhanced. However, the effects of the Th17 response on MSCs is less clear. Many studies suggest that the systemic infusion of MSCs alone does not suppress the development of Th17-mediated autoimmune diseases, such as autoimmune arthritis and joint inflammation [78, 88, 89]. In our study, we observed that MSCs are ineffective for treatment of a Th17-mediated collagen-induced arthritis (CIA) [90]. These observations suggest that the presence of Th17 response do not enhance the immunomodulatory properties of MSCs. Furthermore, MSCs are known producers of TGF-β and IL-6, which are key factors that reciprocally regulate the differentiation of naïve T cells into Tregs or Th17 cells [88, 91, 92]. In the absence of stimulatory cytokines, MSCs produce only TGF-β; however, in the presence of pro-inflammatory cytokines, such as IFN-γ or TNF-α, MSCs produce significant levels of IL-6. While TGF-β promotes the differentiation of naïve T cells into anti-inflammatory Tregs, the combination of TGF-β and IL-6 polarizes T cells into pro-inflammatory Th17 cells. Several studies, including our own, have shown that MSCs can promote the expansion of Th17 cells, both in vitro and in vivo, in the appropriate environment [93]. With regard to GVHD, the presence of both pro-inflammatory Th1 and Th17 cytokines may induce secretion of IL-6 by MSCs and thus promote Th17 cell expansion and aggravate symptoms of GVHD. While MSCs do have the potential to regulate Th17 cells, they may not be able to fully suppress Th17 cells in certain microenvironments containing pro-inflammatory cytokines such as the CIA or GVHD settings. In addition, as previously mentioned, few clinical trials have used MSCs to treat cGVHD [57, 58, 67]. Recently, it was demonstrated in a clinical study that co-infusion of MSCs as a GVHD prophylaxis method could prevent the onset of aGVHD but could not affect the development of cGVHD [74]. Taken together, these data suggest that the immunomodulatory capacity of MSCs may be less effective against Th17 response-mediated diseases. Therefore, a regulatory strategy for elevated Th17 responses may be required to effectively treat aGVHD, as well as cGVHD.

Future considerations

Gene-transduced MSCs

In the past few years, there has been increasing evidence that MSCs can be utilized as vehicles for gene therapy. The

inherent homing abilities of MSCs to inflammatory sites of injury [48, 94, 95] represent an opportunity to deliver various therapeutic proteins. In vivo imaging of MSCs in murine aGVHD model revealed that MSCs co-localize to clinical sites of aGVHD where donor BM cells exist [49]. Thus, genetically engineered MSCs can provide the means for sustained expression of therapeutic genes to targeted sites.

For example, the transduction of IL-10 has shown attenuation of the severity of aGVHD. The recipient mice treated with IL-10-transduced MSCs showed decreased mortality which was associated with decreased levels of pro-inflammatory cytokines, such as IFN-γ [96]. The study suggested that the genetically engineered MSCs were especially advantageous because they could be administered during the early stage of GVHD without the need for a licensing period. In contrast, the systemic administration of recombinant IL-10 alone failed to significantly decrease GVHD mortality. This suggests that IL-10 delivered by MSCs can specifically target the sites of GVHD and thus, induce a more potent immumodulatory response. Furthermore, other studies have demonstrated genetically engineered MSCs with anti-inflammatory cytokines in different models and could later be applied in GVHD models. In our study, we transduced human TGF-β in CIA models which potently suppressed the development of autoimmune arthritis and joint inflammation [90]. MSCs have also been engineered to overexpress the anti-inflammatory cytokine IL-4 and were infused in mice with experimental autoimmune encephalomyelitis. The early administration of IL-4-transduced MSCs attenuated the clinical disease and promoted an anti-inflammatory cytokine response [97]. However, one concern with the use of anti-inflammatory cytokine-transduced MSCs is the potential to prevent the GVL effect as a result of severe immunosuppression. Further experiments are needed to determine whether genetically engineered MSCs can preserve GVL effects. Overall, current preclinical studies suggest that the use of MSCs engineered with cytokines is likely to be a more powerful method in overcoming GVHD mortality and will need to be investigated further to determine its safety in the clinical setting.

Other adherent cell therapies: MAPCs

The use of adult stem cell-based cell therapy, including MSCs, is highly attractive in the clinical setting because of their proliferative and multi-lineage differentiation potential. In addition to MSCs, multipotent adult progenitor cells (MAPCs) are a type of adult stem cells derived from the bone marrow similar to MSCs and these cells are also currently being investigated in various clinical settings. In 2002, MAPCs were first described in the rat and mouse BM as cells with the potential to proliferate without senescence and to differentiate into cells of the three germ layers [98]. Recently, a comparative analysis between MAPCs and MSCs has been performed [99, 100] suggesting that the two cell types are similar but distinct cell populations. In comparison to MSCs, MAPCs are significantly smaller in size and can expand significantly longer in vitro for over 70 passages [98]. Furthermore, in addition to the absence of MHC class II and costimulatory molecules, MAPCs express low levels of MHC class I which implies their potential as off-the-shelf products in the clinical settings [101]. Similar to MSCs, MAPCs exert strong immunomodulatory effects on T cell proliferation through cell–cell contact and the production of soluble factors [101].

Based on their immunomodulatory properties and low immunogenicity, a clinical grade, large-scale expanded product has been developed by Multistem [102]. The safety and efficacy of MAPCs has been confirmed in various preclinical models[103, 104] and is now currently being evaluated in a number of phase I/II clinical trials in patients with stroke, acute myocardial infarction, inflammatory bowel disease, and also for the prevention of GVHD [102, 105]. The systemic administrations of MAPCs have specifically been reported to inhibit aGVHD in both mouse and rat models [106, 107]. These encouraging results had led to an open-label phase I clinical dose escalation study to assess the safety of MAPCs as a prophylaxic treatment for patients undergoing myeloablative allogeneic HSCT for hematologic malignancies. The administration of MAPCs was well-tolerated without any infusional toxicity or adverse events. Moreover, there was substantial reduction in the incidence of aGVHD relative to the historical data at the highest dose (1×10^7/kg). These results suggest that in contrast to MSC therapy, MAPCs may provide more benefit in preventing the incidence of GVHD. Both MSCs and MAPCs present promising results for the development of adherent stem cell-based therapies for GVHD. Whether MSCs and MAPCs represent truly different cell types in vivo remains to be elucidated. Nonetheless, adherent adult-stem cell-based therapies are promising and will continue to be investigated for clinical use.

Conclusions

The immunosuppressive effects of MSCs in vitro have provided sufficient evidence for their application to animal models. With an appropriate dosage, timing, and setting, MSCs have the potential to ameliorate the clinical symptoms of GVHD. Their translation from “bench to bed” has been successful in that MSC administration has been proven to be safe, without any infusion-related toxicity. However, the data are incomplete and inconsistencies exist in preclinical and clinical trials. Most studies of MSC treatment have been on steroid-refractory aGVHD, but the efficacy of MSCs as a preventive measure during HSCT and in cGVHD patients is less clear. To improve the therapeutic efficiency of MSCs,

elucidation of specific markers of MSC phenotypes, standardized protocols for expansion, and dosage and timing and route of administration are crucial. Also, recent observations suggest MSCs to be a less effective treatment when applied alone and may require an additional factor to enhance their immunomodulatory properties. It is likely that safely engineered MSCs that overexpress immunosuppressive cytokines represent a better targeted, more effective cell therapy for aGVHD. The combination of MSCs with pharmaceutical drugs may enhance and prolong the immunosuppressive effects of MSCs in vivo. Finally, further multicenter clinical trials that use standardized protocols will increase our understanding of MSCs and facilitate the development of an improved MSC therapy for GVHD. MSCs came to light as a promising treatment for GVHD and many clinical trials of the potential of MSCs as a therapeutic agent are in progress.

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