Review Article

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Mesenchymal stem cells and connective tissue diseases: From bench to bedside

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ABSTRACT

The pathogenesis of connective tissue diseases (CTDs), represented by systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), systemic sclerosis (SSc), primary Sjögren's syndrome (pSS), and idiopathic inflammatory myopathies (IIM), includes various immune cells involved in both innate and adaptive immunity. The mesenchymal stem cells (MSCs) are unique due to their regulatory effect on immunity. This makes them a promising therapeutic approach for patients with immune-mediated disorders such as CTD. The safety and clinical efficacy of MSC treatment in CTD have been tested in a growing number of preclinical and clinical studies. Administration of MSCs has consistently shown benefits with both symptomatic and histologic improvement in CTD animal models. MSC therapies in severe and drug-resistant CTD patients have shown promise in a number of the pilot studies, cohort studies, and randomized controlled trials in SLE, RA, and SSc, but some problems still need to be resolved in the transition from the bench to the bedside. The relevant studies in pSS and IIM are still in their infancy, but have displayed encouraging outcomes. Considerable efficacy variations have been observed in terms of the route of delivery, time of MSC injection, origin of the MSCs and dosage. Furthermore, the optimization of conventional drugs combined with MSC therapies and the applications of novel cell engineering approaches requires additional research. In this review, we summarize the current evidence about the immunoregulatory mechanism of MSCs, as well as the preclinical and clinical studies of MSC-based therapy for the treatment of CTDs.

Key words: mesenchymal stem cells, connective tissue diseases, systemic lupus erythematosus, rheumatoid arthritis, treatment, translational medicine

INTRODUCTION

Mesenchymal stem cells (MSCs), also referred to as multipotent stromal cells or mesenchymal stromal cells, have profound immunomodulatory functions and have been shown to have promising therapeutic effects for autoimmune diseases. They are found to be capable of interacting with immune cells *via* direct cell contact or through the secretion of various cytokines *in vitro* and *in vivo*.[1] MSCs can be isolated from almost all adult tissues, in particular bone marrow, umbilical cord, adipose tissue, and placenta. Bone marrow-derived MSCs (BM-MSCs) are the most extensively used MSCs and are characterized by remarkable osteogenic and chondrogenic differentiation potential.[2] However, the effectiveness of BM-MSCs is dependent on the donor's condition, and the risk of infection during extraction cannot be ignored. Human umbilical cord-derived MSCs (UC-MSCs) can be obtained more easily with painless extraction procedures. In terms of proliferation and immunosuppressive potential, UC-MSCs have the most rapid growth rate and they secret multiple growth factors that can reduce inflammation and reverse tissue damage.[3] Adipose tissue-derived MSCs (AD-MSCs) have gained increasing

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attention since they can be extracted in large quantities from various sites of human body. Hence, the current studies have focused on exploring the cell surface markers and secretome of AD-MSCs from different body sites because this knowledge is critical to improve the clinical efficacy of AD-MSCs. Placenta-derived stem cells (PDSCs) have a longer culture period and higher proliferative capacity, which is related to their short population doubling time. The therapeutic efficacy of PDSCs varies depending on the anatomical site, and they have been reported to have a better effect for vascular disease.[4]

Autoimmune connective tissue diseases (CTDs) are a group of chronic multisystem disorders characterized by immune-mediated inflammation of connective tissues. Conventional treatments of CTD include corticosteroids, nonsteroidal anti-inflammatory drugs (NSAIDs), immunosuppressants, and biologic agents. This treatment approach has had a significant impact on improving the prognosis of CTD patients. However, disease control remains unsatisfactory in a subset of these patients, and conventional immunotherapy often results in serious adverse effects including infection, haemocytopenia, impairment of liver and kidney function, and metabolic disorders. Therefore, the development of novel treatments for CTD patients is an important unmet need. A growing understanding of the immune system has identified a group of cells that could be the potential therapeutic targets for CTDs, such as B cells, regulatory T (Treg) cells, natural killer (NK) cells, and MSCs.[5] Furthermore, accumulating evidence has suggested that the differentiation and function of stem cells are dysregulated in CTD patients, and thus MSC-based therapies have emerged as a potential therapeutic modality to restore immune tolerance in autoimmune diseases. MSCs have been approved for the treatment of some immune-mediated disorders, such as Crohn's disease and graft *versus* host disease (GvHD), by the European Medicines Agency (EMA) and the Japanese Ministry of Health, Labour, and Welfare (MHLW). Currently, hundreds of clinical trials focusing on the reparative capabilities of MSC therapy in CTD patients have either been completed or are in progress.[6] In this review, we summarize the studies on the immunoregulatory mechanism of MSCs, as well as the preclinical and clinical evidence for MSC-based therapy for CTD.

IMMUNOREGULATORY MECHANISM OF MSCS IN CTD

MSCs can interact with various immune cells and secrete soluble factors and extracellular vesicles (EVs), thus representing a powerful tool to modulate the immune system in CTD. The immunoregulatory activity of MSCs could be promoted by the participation of some types of immune cells, including T-lymphocytes, B-lymphocytes, macrophages, NK cells, and monocytes, which are discussed in detail below. In terms of soluble inflammatory factors, MSCs can secrete cytokines, growth factors, and chemokines, that are crucial to their autocrine or paracrine activities. The autocrine effect of MSCs is characterized by the secretion of these factors, which then act on themselves. The autocrine signalling activities of interleukin (IL)-6, IL-8, prostaglandin E2 (PGE2), and vascular endothelial growth factor (VEGF) was reported to enhance the stemness of MSCs.[7] The main beneficial effects of MSC-based therapy are attributed to these secreted factors or the packaging of these factors in EVs that act on nearby cells *via* paracrine signalling. Key factors have been identified, such as IL-1 receptor antagonists, VEGF, transforming growth factor-β (TGF-β), stromal cell-derived factor-1 (SDF-1),[8] tumour necrosis factor-α (TNF-α)–stimulated TNF-inducible gene 6 (TSG6),[9] PGE2,[10] and others. Through these paracrine pathways and intercellular contact, MSCs have been shown to significantly downregulate T helper (Th) 1 cytokines (TNF-α), IL-1, interferon-γ (IFN-γ), inducible nitric oxide synthase (iNOS), matrix metalloprotein-9 (MMP-9), TGF-β1, and granulocyte–macrophage colony-stimulating factor (GM-CSF), as well as upregulate Th2 cytokine (IL-10).[11,12] These findings provide a basis for promoting cell-based treatment through combination therapies and bioengineering.[13,14] Therefore, we summarize the immunoregulatory mechanisms of MSCs in CTD (Figure 1) and address the importance of understanding the properties of MSCs before their further application in clinical trials.

T-lymphocytes

Various types of MSCs have been proven to have the capacity to inhibit T cell responses and T-cell–mediated diseases.[15] Increased apoptosis of peripheral T cells has been reported in systemic lupus erythematosus (SLE) patients. MSCs could rescue T-cell by decreasing apoptosis, which is mediated by mitochondrial transfer.[16] However, the immunosuppressive effect of MSCs on T-cell proliferation could be reversed in the presence of TNF-α, and this is associated with an increase in the level of IL-6.[17] IL-3, a cytokine secreted by activated T-lymphocytes, was proven to enhance the migration of MSCs through the C–X–C motif chemokine receptor 4 (CXCR4)/SDF-1α axis.[18] Secretion of human leukocyte antigen-G5 (HLA-G5) by MSCs contributes to the direct inhibition of T-cell responses.[19] Accumulating evidence supports the crucial role of microRNAs in the therapeutic effects of MSCs. MSCs may upregulate microRNA (miR)-181a in T-lymphocytes to improve the efficacy of MSC-based therapies.[20] Th1 and Th17 cells that mediate responses to cartilage antigens and joint components are the important causes of joint inflammation in CTD. MSCs have been proven to ameliorate autoimmune

arthritis by increasing the number of different subsets of T cells in the draining lymph nodes, including Th17 and Th1 cells.[21,22] The inhibition of Th1/Th17 responses has also been shown in the treatment of experimental arthritis by MSCs.[23] Epigenetic modification of MSCs can regulate the Th17-related immune responses and enhance the immunomodulatory potential of MSCs.[24]

It is well established that Treg cells are critical for the maintenance of immunological self-tolerance and immune homeostasis *via* TGF-β, IL-10, and the newly described IL-12 family member, IL-35. Darlan *et al.*[25] suggested that MSCs could upregulate the functional Treg cells by releasing TGF-β1 to control SLE disease activity. In rheumatoid arthritis (RA), the role of MSCs in controlling the development of the disease also depends on the induction of particular functional Treg cells.[15,22] IL-10 was found to be critical in the generation of Treg cells. MSCs increased the level of IL-10 in lymph nodes and joints and then induced *de novo* generation of Treg cells, thus restoring the regulatory/inflammatory balance.[22] Moreover, miR-663 impaired MSC-mediated regulation of Treg cells by inhibiting TGF-β1 production.[26] Meanwhile, miR-663 overexpression impaired the therapeutic effect of MSCs *in vivo*. Breaking the Th17/Treg balance could be responsible for the development of SLE. It is clear that MSCs can reset the immune balance by upregulating Tregs and downregulating Th17 cells, Th1 cells, and follicular helper T (Tfh) cells.[10] MSCs secrete TGF-β and PGE2 to mediate this process. Tregs/Th17 cells also influence the gut microbiota in MSC-treated RA *via* the aryl hydrocarbon receptor, which is a cytoplasmic receptor that modulates the response to environmental stimuli.[27] Cell-to-cell contact may hamper the immunoregulatory function of MSCs in CTD, thus, the use of a microencapsulation technology could provide additional benefits in MSC-based therapies.[28] MSC-derived exosomes and microparticles also have the capacity to decrease the percentage of T-cell subsets and increase the number of Treg cells in inflammatory arthritis.[29] T cells are a key source of GM-CSF cytokines, which are pivotal during the induction phase of CTD.[30] MSCs modify the early adaptive T-cell responses by reducing the total number of pathogenic GM-CSF$^+$CD4$^+$ (cluster of differentiation 4 receptors) T cells in RA.[22]

B-lymphocytes

B cells are of great importance in the pathogenesis of CTD through autoantibody-dependent and autoantibody-independent mechanisms. MSCs can inhibit B-lymphocyte proliferation, differentiation, and antibody secretion *via* many cytokines and chemokines. Che *et al.*[31] showed that CC chemokine ligand 2 (CCL2), a chemokine that induces the migration of monocytes and macrophages to inflammatory loci, played an important role in MSC-mediated B-cell immunoregulation. Schena *et al.*[32] noted that MSCs affected both follicular and marginal zone B-cell activation after stimulation with B-cell receptor (BCR) and Toll-like receptor 9 (TLR-9) agonists, which was dependent on IFN-γ and cell-to-cell contact. In the absence of BCR triggering, MSCs induced both polyclonal expansion and differentiation of B cells into plasma cells after being stimulated with a TLR-9 agonist.[33] Tfh cells promote the development of CTD by assisting B cells in producing autoantibodies. Alunno *et al.*[34] suggested an inhibitory effect of MSCs on circulating Tfh cells through the secretion of indoleamine 2,3-dioxygenase (IDO).

Macrophages and dendritic cells

Macrophages are a key component of innate immunity. MSC–macrophage interaction interactions occur during anti-inflammatory processes. Németh *et al.*[35] showed that MSCs could reprogram the IL-10 secretion signalling pathway of macrophages by releasing PGE2, and macrophages produce more IL-10 when cultured with MSCs. In addition, macrophages are re-educated to attenuate inflammation and facilitate repair due to the effects of MSCs, which manipulate their metabolic programs.[36] The anti-inflammatory protein TSG-6 secreted by the MSCs suppresses nuclear factor-κB (NF-κB) signalling in resident macrophages through the CD44 receptor.[9]

Dendritic cells (DCs) are professional antigen-presenting cells characterized by a unique primary immune response initiation ability. Regulation of DCs differentiation is relevant to the immunoregulatory function of MSCs. MSCs inhibit the differentiation and function of monocyte-derived DCs *via* either cell-to-cell contact or soluble factors.[37] MSCs induce peripheral blood CD1c$^+$DCs through a recombinant FMS-like tyrosine kinase-3 ligand (FLT3 L)–FLT3 interaction, which is a key regulator of DCs haematopoiesis.[38] MSCs can also drive mature DCs to differentiate into regulatory DCs and rescue them from apoptosis.[39] MSCs suppress IL-12 production by DCs and inhibit the initial differentiation of monocytes to DCs *via* GM-CSF and IL-4. These results further support the immunomodulatory function of MSCs in the treatment of CTD.

PRECLINICAL STUDIES OF MSC THERAPIES IN CTD

Systemic lupus erythematosus

Studies have shown that BM-MSCs from patients with SLE are impaired in proliferation, cytokine production, and immune modulation, which might contribute to the pathogenesis of lupus.[40] BM-MSCs from active SLE patients were reported to have defective IDO production, which resulted in less responsiveness to IFN-γ and CD8$^+$

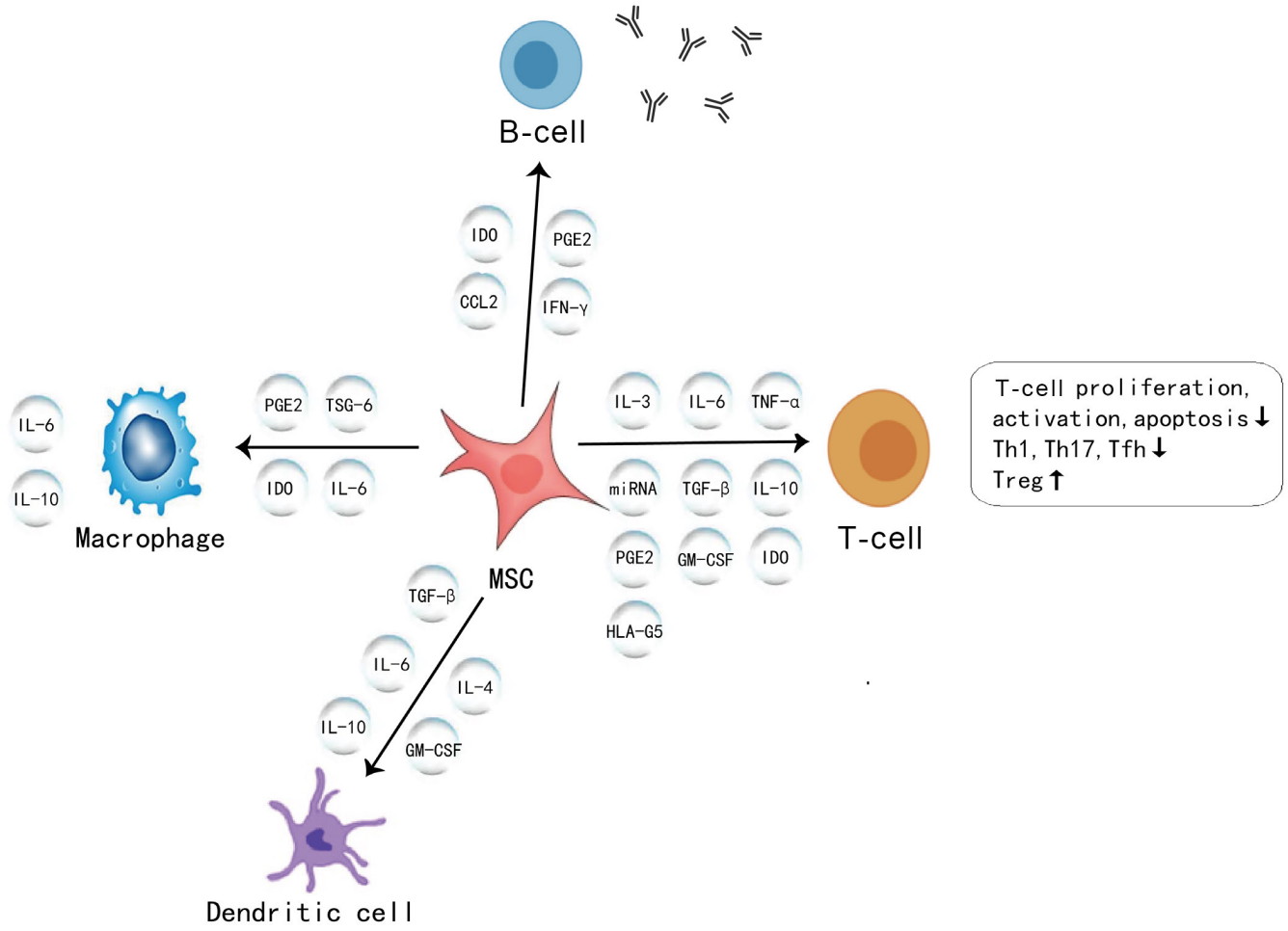

Figure 1: A diagrammatic representation of immunomodulatory properties of MSCs in connective tissue diseases. MSC: mesenchymal stromal cell; IL-16: interleukin-16; IFN-γ: interferon-γ; TNF: tumour necrosis factor; IDO: indoleamine 2,3-dioxygenase; PGE2: prostaglandin E2; CCL2: CC chemokine ligand 2; HLA-G5: human leukocyte antigen-G5; TSG-6: TNF-α–stimulated gene 6 protein; miRNA: microRNA; TGF-β: transforming growth factor β; GM-CSF: granulocyte–macrophage colony-stimulating growth factor; Th1: helper T-cell 1; Th 17: helper T-cell 17; Tfh: T follicular helper cells; Treg cells: regulatory T cells.

T-cell proliferation.[41] Abnormal expression of cytokines such as IL-10 and TGF-β was also found in lupus BM-MSCs.[42] Moreover, lupus BM-MSCs exhibited increased apoptosis, which was reflected by higher intracellular reactive oxygen species and increased levels of senescence-related genes in MSCs from SLE patients.[43] Thus, SLE was speculated by some experts to be a stem cell disease.

Current therapies for SLE are mainly aimed at mitigating disease activity, and the drugs have considerable side effects. Thus, MSCs have attracted much attention as a novel therapeutic cell type for lupus. The efficacy of MSC therapies in SLE animal models is summarized in Table 1. A total of 28 preclinical studies evaluated MSC treatment in animal models of lupus nephritis (LN).[44] These studies showed that MSC therapies resulted in a reduction of anti-double-stranded DNA (anti-dsDNA) antibody, antinuclear antibody (ANA), serum creatinine, blood urea nitrogen, and proteinuria levels. Other studies using murine SLE models demonstrated that allogeneic MSC transplantation could also decrease the levels of cytokines, autoantibody, and complement 3 (C3) deposition in glomeruli and prolong the lifespan.[45-47] Transplantation of human MSCs has also been found to ameliorate severe bone reduction through IL-17 suppression in an MRL/lpr SLE model.[48] The wide variation in the origin of MSCs, including UC-MSCs, BM-MSCs, AD-MSCs, and gingiva-derived MSCs, is one of the variables commonly encountered in preclinical studies. UC-MSCs were reported to be more potent immunosuppressors and less immunogenic than BM-MSCs.[49] However, other *in vitro* and *in vivo* studies showed that there was very little difference in the effect of different MSCs.[50] In addition, some new subsets of BM-MSCs, including those lacking the ability to adhere to plastic culture dishes, were identified and they showed increased immunomodulatory capacity in treating SLE mice compared to regular BM-MSCs. The efficacy of MSCs based on their source of origin remains controversial. The interaction between MSCs and other

drugs has also been investigated. Rapamycin, an inhibitor of the mammalian target of rapamycin (mTOR) signalling pathway, was proven to reverse the senescent phenotype and improve the immunoregulatory capacity in MRL/lpr mice.[51] Moreover, metformin-treated AD-MSCs had stronger anti-inflammatory effects mediated through signal transducer and activator of transcription 1 (STAT1).[52] Mutually reinforcing the interaction between IL-37 and MSCs enhanced immunosuppression *in vivo* in terms of improved survival and reduced signs of SLE.[53] These studies may help to improve the therapeutic potential of MSCs in the future.

An important advantage of MSC therapies using MSCs is that they exert therapeutic effects in various ways. B cells play an important role in the pathogenesis of SLE through autoantibody-dependent mechanisms. Ma *et al.*[54] reported that MSCs could inhibit B cell activation and immunoglobulin production *via* suppression of the B cell activating factor (BAFF). Lee *et al.*[55] recently reported that MSCs inhibited mouse T cells in the early stage after injection, whereas priming of MSCs with IFN-γ improved their ability to inhibit B cells in SLE.

Meanwhile, epigenetic modification, such as DNA methylation, is also crucial in the mechanisms underlying MSC treatment. MSCs could rescue the global hypomethylation pattern of the recipient BM-MSCs and improve osteopenia in mice.[56] Furthermore, epigenetic modulation appears to constitute a promising experimental target in MSC research. Kim *et al.*[57,58] reported that a combination of hypomethylating agents and histone deacetylase inhibitors could increase the gene expression of IL-10 and IDO in MSCs, which enhanced the Th17-related immune responses of MSC-based therapy in RA. Accumulating evidence has shown that priming of MSCs with epigenetic modifiers may enhance cell proliferation, cell survival, and cell differentiation potential, but more studies are needed in CTD. MSC transplantation in animal models helps us to better understand the function of MSCs *in vivo*, which might be useful to generate more responsive MSCs in different SLE host microenvironments.

Rheumatoid arthritis

Reports have shown that the function of MSCs is altered in RA patients. Anti-citrullinated protein antibodies (ACPAs) have been identified as an important biomarkers for the aetiology of RA. It has been proven that ACPAs can reduce the efficacy of BM-MSCs by increasing IL-6, IL-8, and CCL2 expression and decreasing the production of IDO.[59] Another defect of BM-MSCs from RA patients is the loss of A20, also called TNF-α–induced protein 3, which leads to increased IL-6 secretion and further affects the pathogenesis of RA.[60] It is important to explore the functional features of MSCs in RA patients, as they may be a potential targets for the cell-based therapies.

There are more than 100 articles that have reported the use of MSCs in experimental models of RA. Among these, the most widely used animal model was collagen-induced arthritis (CIA) mice. The most commonly used routes of delivery were intravenous (IV), intraperitoneal, intra-articular, intramuscular, and subcutaneous delivery. The effective dosage of MSCs reported was in the range of 2×10^6–3×10^6 cells per injection, as noted in a meta-analysis preclinical studies.[61] In some studies, a single MSC injection could prevent the occurrence of bone damage and lead to disease remission, without the need for multiple administrations.[15,62] In most of the studies, the efficacy of MSC treatment was evaluated by joint swelling, histologic assessment, serum antibody, and joint imaging (Table 1). Most of the studies concluded that MSC therapies were effective in reducing inflammation, joint swelling, and cartilage destruction in RA without adverse effects. However, some studies have demonstrated that allogeneic and syngeneic transplantation do not influence the disease course of RA.[63,64] These conflicting results suggest that further studies investigating the effect of different sources, quantities, and administration regimens of MSCs are warranted. MSCs can interact with many immune cells *via* both direct contact and secreted anti-inflammatory factors. In preclinical studies of RA, the therapeutic effect of MSCs was mediated by downregulating Th1 and Th17 cells and upregulating Treg cells.[21,23] Furthermore, an increase in anti-inflammatory factors such as TGF-β and IL-10,[65] together with a reduction in TNF-α, IL-6, and monocyte chemoattractant protein-1 have been reported.[65]

Recently, some researchers have developed novel approaches to improve the efficacy and long-lasting beneficial effects of MSCs in arthritis. Cosenza *et al.*[29] suggested that MSC-derived exosomes, one of the main types of EVs containing a large variety of proteins, messenger RNAs, and miRNAs, were efficient in suppressing inflammation in inflammatory arthritis. In addition, a three-dimensional (3D) priming strategy to improve the efficacy of the resulting UC-MSC secretomes induced a faster remission of local and systemic RA manifestations, compared to secretomes produced under conventional two-dimensional (2D) monolayer conditions.[66] The therapeutic potential of exosomes has attracted increasing attention because they reduce the risks of triggering immune reactions against MSCs. TNF-α plays a critical role in the pathogenesis of RA. Liu *et al.*[14] genetically modified MSCs to deliver human soluble TNF receptor II (hsTNFR). They reported that the sTNFR-transduced rat MSCs have the same effect of inhibiting joint inflammation as etanercept, which is a recombinant fusion protein of hsTNFR used to treat RA. Moreover,

combined MSC and IL-4 therapy showed decreased rheumatoid factor (RF) and C-reactive protein (CRP) levels, compared to MSCs alone.[13] All of these favorable results achieved in preclinical studies demonstrated that modified MSCs might have improved safety and efficacy in the clinic.

Other CTDs

MSC therapies have been used in several animal models of systemic sclerosis (SSc) including bleomycin-induced models and hypochlorite (HOCI)-injected models (Table 1). In the bleomycin-induced SSc model, a single infusion of 2×10^5 AD-MSCs attenuated the skin and lung fibrosis by inhibiting the infiltration of T cells and macrophages into the dermis.[67] The effect of UC-MSCs on skin fibrosis and collagen formation was confirmed in this model. At present, BM-MSC-derived EVs have also been proven to be effective in treating skin dysfunction and fibrosis of skin.[68] The injection time point after disease induction is an important factor affecting the impact of MSCs during the fibrogenesis process. Maria *et al*.[69] identified a three-phase process leading to skin fibrosis in the HOCI-induced model, and MSC-based therapies exerted different benefits in all these three phases through immunosuppressive, trophic, or regenerative properties. This team also indicated that iNOS is required for the antifibrotic function of MSCs in HOCI-SSc mice, which highlighted the importance of the antioxidant activity of MSCs in future applications. Taken together, MSCs have immunosuppressive, antifibrotic, and antioxidative properties, all providing a promising approach for the treatment of SSc.

Preclinical studies in primary Sjögren's syndrome (pSS) have revealed the expected capacity of MSCs in controlling the inflammation and preserving salivary function. A single intraperitoneal injection of BM-MSCs into a NOD mouse model was able to increase the tear production, although the number of lymphocytic foci in the lacrimal glands did not decrease.[70] In another study, BM-MSCs alleviated the disease progression in an experimental Sjögren's syndrome model induced by salivary gland (SG) protein by upregulating the immunosuppressive effect of myeloid-derived suppressor cells.[71] Further experiments are needed to explore in detail the underlying mechanisms of improved lacrimal gland function after MSC transplantation.

CLINICAL EVIDENCE OF MSC THERAPIES IN CTD

Systemic lupus erythematosus

Some SLE patients do not respond to conventional immunosuppressive and immunomodulatory therapies and are in urgent need of newer therapeutic approaches. Over the last few decades, increasing evidence has suggested that MSCs are a potential therapeutic tool for refractory SLE. The first case series study using allogenic MSCs in SLE patients was published in 2009.[88] Four LN patients enrolled in this study were drug resistant, and all achieved stable remission after MSC therapy for 12–18 months. Subsequently, several initial pilot studies that involving patients with severe LN or multiorgan involvement reported that systemic administration of BM-MSCs or UC-MSCs decreased disease activity and improved renal function (Table 2). Meanwhile, few serious adverse effects attributed to the MSCs were observed. In these studies, the popular treatment regimens were transfusions for one to three times, each dosed at 1×10^6 cells/kg body weight. The transplanted stem cells were derived from either the bone marrow of healthy donors or umbilical cords from healthy mothers after normal deliveries. A multicentre clinical study including 40 active SLE patients showed that MSCs resulted in a significant decline of the SLE disease activity index (SLEDAI) and British Isles Lupus Assessment Group (BILAG) scores and ameliorated the hematological and cutaneous manifestations.[89] In their investigation of the long-term efficacy and safety, Wang *et al.* reported the long-term follow-up results of MSC-treated patients in their series of cohort studies.[90–92] The 5-year disease remission rate was 34%, and the 5-year overall rate of relapse was 24%.[90] To date, there have been no reports of MSC-associated tumour formation or changes in serum tumour biomarkers after infusion in SLE patients. A double-blind placebo-controlled trial was conducted in 18 newly diagnosed severe LN patients from a single centre. However, this study showed that UC-MSCs did not achieve a better therapeutic effect than standard immunosuppressive therapies.[93] This controversial result indicated that there still remain some challenges in designing appropriate study protocols for randomized controlled trial (RCT) to determine the efficacy of MSCs for SLE.

Although MSCs have powerful anti-inflammatory properties in SLE, a challenge for improving their therapeutic efficacy is that their mechanism of action is still unclear. In LN patients, MSC transplantation inhibited the common complement terminal pathways, which may contribute to controlling excessive complement activation in glomerular diseases.[94] In addition, MSCs can engulf accumulated apoptotic cells and subsequently exhibit enhanced immunosuppression *via* PGE2 activation. In MSC-treated SLE patients, the plasma PGE2 levels increased significantly, which revealed another mechanism active in MSC-based therapy in SLE.[95] By analysing the baseline cytokine levels and the treatment effect of MSCs, serum IFN-γ was proven to be a potential predictor of a clinical response to MSC therapy.[96] The pathogenesis of SLE is very complicated, and a certain subgroup of SLE patients would benefit from MSC treatment. Further

Table 1: Preclinical studies investigating the efficacy of MSCs in CTD animal models

Author (year)	Disease	Species, model	Groups	MSC origin	MSC dose	Infusion	Efficacy	Follow-up (weeks)
Akiyama *et al.* (2012)[72]	SLE	Mouse, MRL/lpr	PBS group (n = 5) MSC group (n = 24)	BM	1 × 10^5 cells/10 g body weight	Intravenous	Proteinuria↓, mesangial proliferation↓, anti-dsDNA↓, ANA↓, serum albumin↑	2
Chang *et al.* (2011)[45]	SLE	Mouse, NZB/W F1	Control group (n = 8) MSC group (n = 15)	UC	1 × 10^6 cells	Intravenous	Proteinuria↓, creatinine↓, anti-dsDNA↓, mesangial proliferation and sclerosis↓, survival rates↑	8
Cheng *et al.* (2021)[73]	SLE	Mouse, MRL/lpr	Control group (n = 5) PBS group (n = 5) MSC group (n = 5)	UC	5 × 10^5 cells	Intravenous	Proteinuria↓, kidney lesion↓	4
Choi *et al.* (2016)[74]	SLE	Mouse, MRL/lpr	Control group (n = 20) C3H/HeJ normal group (n = 15) CTX group (n = 20) MSC group (n = 20)	AD	1 × 10^6 cells/2 weeks (18 times)	Intravenous	anti-dsDNA↓, survival rates↑	35
Choi *et al.* (2012)[75]	SLE	Mouse, NZB/W F1	Control group (n = 41) MSC group (n = 56) CTX group (n = 14)	AD	5 × 10^5 cells (28 times) or 2 × 10^6 cells (11 times)	Intravenous	Proteinuria↓, BUN↓, anti-dsDNA↓, survival rates↑	54
Dang *et al.* (2020)[76]	SLE	Mouse, NZM2328	PDF control group MSC group	GMSCs	2 × 10^6 cells	Intravenous	Proteinuria↓, anti-dsDNA↓, survival rates↑	23
Gu *et al.* (2016)[51]	SLE	Mouse, MRL/lpr	Control group (n = 12) RAPA group (n = 12) MSC group (n = 24)	BM	1 × 10^6 cells	Intravenous	24 h proteinuria↓, anti-dsDNA↓, survival rates↑, glomerular sclerosis↓, interstitial fibrosis↓	12
Jang *et al.* (2020)[52]	SLE	Mouse, MRL/lpr	Control group (n = 6) MSC group (n = 10)	AD	1 × 10^6 cells (8 times)	Intravenous	Proteinuria↓, anti-dsDNA↓, glomerulonephritis↓	7
Ma *et al.* (2015)[48]	SLE	Mouse, MRL/lpr	PBS group MSC group	BM	1 × 10^5 cells/10 g body weight	Intravenous	Secondary bone loss↓, osteoblast and osteoclast dysregulation↓	4
Xu *et al.* (2020)[53]	SLE	Mouse, MRL/lpr	PBS group MSC group	BM	1 × 10^6 cells (4 times)	Intravenous	Proteinuria↓, renal pathologic score↓, survival rates↑, total antibody↓, anti-dsDNA↓, ANA↓	7
Ahmed *et al.* (2021)[12]	RA	Rat, CFA subcutaneous	Normal group CFA group CFA + MSC group CFA + IMC group CFA + IMC + MSC group	BM	1 × 10^6 cells (4 times)	Intravenous	Right hind leg paw diameter and circumference↓, serum anti-CCP↓	3
Papadopoulou *et al.* (2012)[77]	RA	Rat, rAIA and SSEA	PBS group Bortezomib group MSC group Bortezomib + MSC group	BM	rAIA: 20 × 10^6 cells (2 times) SSEA: 12 × 10^6 cells (2 times)	Intraperitoneal	Histologic improvement	NA
Park *et al.* (2011)[78]	RA	Mouse, CIA	PBS group MSC group	BM	1 × 10^6 cells	Intraperitoneal	Bone erosion↓, cartilage destruction↓	NA
Rui *et al.* (2016)[79]	RA	Mouse, CIA	PBS group BM-MSC group OE-MSC group	OE or BM	1 × 10^6 cells (2 times)	Intravenous	Arthritis onset↓, disease severity↓, anti-CII↓	3

(Continued...)

Author (year)	Disease	Species, model	Groups	MSC origin	MSC dose	Infusion	Efficacy	Follow-up (weeks)
Shin *et al.* (2016)[80]	RA	Mouse, CIA	Negative control (n = 5) Positive control (n = 10) Etanercept group (n = 7) Fibroblast-injected group (n = 7) MSC group (n = 10)	UC	1 × 10^6 cells (1 or 5 times)	Intraperitoneal	Clinical severity of CIA↓, histologic damages↓	3
Wei *et al.* (2021)[81]	RA	Rat, CIA	PBS group MSC group	BM	2 × 10^6 cells	Intraarticular	Ankle swelling↓, joint destruction↓, articular index score↓, ankle circumference↓	7
Wu *et al.* (2020)[82]	RA	Mouse, CIA	PBS group (n = 5) MSC group (n = 5)	GMSCs	2 × 10^6 cells	Intravenous	Anti-dsDNA↓, anti-CII↓, cartilage damage↓, histologic damages↓	7
Yu *et al.* (2019)[83]	RA	Mouse, CIA	PBS group MSC group (n = 5 in each group)	UC	1 or 3 or 5 × 10^6 cells (3 times)	Intravenous	Clinical arthritis score↓, cartilage damage↓	3
Jiang *et al.* (2017)[84]	SSc	Mouse, bleomycin subcutaneous	PBS group (n = 6) MSC group (n = 12)	BM	1 × 10^6 cells	Subcutaneous	Skin fibrosis and apoptosis↓	2
Jin *et al.* (2021)[68]	SSc	Mouse, bleomycin subcutaneous	PBS group (n = 6) MSC group (n = 12)	BM	1 × 10^6 cells	Subcutaneous	Skin fibrosis↓, collagen content↓	2
Maria *et al.* (2016)[85]	SSc	Mouse, HOCl intradermal	Control group (n = 4) MSC group (n = 4)	AD	2.5 × 10^5 cells	Intravenous	Skin and lung fibrosis↓, collagen content↓	3
Maria *et al.* (2018)[69]	SSc	Mouse, HOCl intradermal	HOCl Control (n = 7–10) PBS group (n = 7–10) MSC group (n = 7–10)	BM	2.5 × 10^5 cells	Intravenous	Skin inflammation↓, Skin thickness↓, collagen content↓	3
Yang *et al.* (2020)[86]	SSc	Mouse, bleomycin subcutaneous	Control group (n = 10) SSc group (n = 10) MSC group (n = 10)	UC	1 × 10^6 cells (2 times)	Intravenous	Skin fibrosis↓, collagen synthesis↓, local inflammation↓	2
Okamura *et al.* (2020)[67]	SSc	Mouse, bleomycin intradermal	PBS group (n = 5) MSC group (n = 5)	AD	2 × 10^5 cells	Intravenous	Skin and lung fibrosis↓, immune cell infiltration into the skin↓	4
Aluri *et al.* (2012)[70]	pSS	Mouse, NOD	PBS group (n = 10) MSC group (n = 10)	BM	1 × 10^6 cells	Intraperitoneal	Tear production↑	4
Xu *et al.* (2012)[87]	pSS	Mouse, NOD	Control group (n = 6) MSC group (n = 12)	BM	1 × 10^5 cells	Intravenous	Saliva flow rate↑, inflammatory area in SG↓	8 or 18
Tian *et al.* (2020)[71]	pSS	Mouse, SG protein subcutaneous	Control group (n = 6) MSC group (n = 6)	BM	5 × 10^5 cells (2 times)	Intravenous	Saliva flow rates↑, serum autoantibodies↓, ANA↓	2

ANA: antinuclear antibody; CTD: connective tissue disease; MSC: mesenchymal stem cells; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SSc: systemic sclerosis; pSS: primary Sjögren's syndrome; PDF: primary dermal fibroblast; RAPA: rapamycin; HOCl: hypochlorite; SG: salivary gland; CFA: complete Freund's adjuvant; IMC: indomethacin; rAIA: adjuvant-induced arthritis; SSEA: severe arthritis spontaneously; CIA: collagen-induced arthritis; PBS: phosphate-buffered saline; CTX: cyclophosphamide; BM: bone marrow-derived MSCs; UC: human umbilical cord-derived MSCs; AD: human adipose tissue-derived MSCs; OE: olfactory ecto-MSCs; GMSCs: gingiva-derived MSCs; BUN: blood urea nitrogen; NA: not available. The arrow pointing up indicates an increase in a numerical value, and the arrow pointing down indicates a decrease.

clinical and molecular studies are needed to explore the underlying mechanisms.

Rheumatoid arthritis

RA is an autoimmune disease that results in progressive joint damage and multiorgan comorbidities. The conventional therapies for RA are corticosteroids, nonbiologic disease-modifying antirheumatic drugs (DMARDs), and biologic agents. Recently, dozens of clinical trials on MSCs for RA have been conducted (Table 2) based on the evidence that they can regulate the immune response, stimulate injury repair, and reduce the inflammatory response, as shown in preclinical studies.[97]

The first pilot study of MSCs in RA was reported in 2011.[98] Three patients were infused IV with autologous

in one, two, or four doses.[98] This study proved that multiple infusions of up to 8×10^8 of AD-MSCs were safe and potentially effective. In another pilot study of a single IV infusion of autologous BM-MSCs in nine RA patients, significant decreases in the 28-joint disease activity score using erythrocyte sedimentation rate (ESR) (DAS28-ESR) and the visual analog scale (VAS) score were observed at 1 and 12 months after MSC transplantation. Serum anti-CCP showed no significant difference after the intervention. To assess the long-term safety and efficacy of MSC-based therapies in RA, Wang *et al.* conducted a 3-year prospective Phase I/II study in 64 RA patients.[99] They found improvements in ESR, CRP, RF, and DAS28 after 1 year and 3 years of UC-MSC treatment. Recently, several randomized placebo-controlled trials of autologous or allogeneic MSCs for RA were conducted. In a single-centre RCT with 172 patients, the MSC-treated group (n = 136) received DMARDs plus 4×10^7 UC-MSCs, while the control group received DMARDs plus medium.[100] The therapeutic effects of the MSCs were maintained for 3–6 months according to the American College of Rheumatology (ACR) criteria and DAS28 without serious adverse events. In a multicentre Phase Ib/IIa trial, 53 patients were treated with three IV infusions of AD-MSCs: 1×10^6/kg, 2×10^6/kg, 4×10^6/kg or placebo. There was one dose-limiting toxicity event, and a lacunar infarction occurred. Signs of clinical efficacy were observed in the ACR20 responses in all 4 groups.[101] In 2018, Shadmanfar *et al.*[102] conducted an RCT of intra-articular knee implantation of BM-MSCs in RA.[102] The MSC group had a superior effect according to the VAS, the Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the standing time. In summary, although the safety and efficacy of MSC therapies were reported in RA, there was a great heterogeneity in terms of the sources of MSCs, cell dosing, and routes of delivery. Further studies are needed to determine the optimal regimen and identify the subgroup of RA patients who are most likely to respond to MSC treatment.

Numerous immune responses and mechanisms of action have been explored in MSC-treated RA patients. Substantial changes in the serum levels of cytokines and T-cell subtypes, such as TGF-β, TNF-α, IL-10, IL-17, IFN-γ, Th17, and Treg cells, were detected after transplantation of MSCs into patients with refractory RA.[103-105] Recent studies also showed that the functions of MSCs could be affected by the inflammatory milieu, and some novel strategies have been employed to improve the ability of MSCs to modulate anti-inflammatory actions and promote tissue repair.[106,107] He *et al.*[107] demonstrated that the combination of IFN-γ and MSCs was safe and could synergistically improve the clinical efficacy. However, the safety profile of recombinant therapies still needs to be considered.

Other CTDs

There is evidence of efficacy of MSC therapies in other CTDs. The proangiogenic and antifibrotic properties of MSCs provide a strong rationale for their use in SSc. In 2011, a German team reported five cases of severe progressive SSc treated with BM-MSCs.[108] No immediate toxicity or severe infection was noted. The BM-MSCs exerted a marked effect on the healing of the skin ulcers. The stromal vascular fraction (SVF) consisting of AD-MSCs, as well as growth factors and cytokines, has been reported as a potential therapeutic option in SSc. A single-centre pilot study investigated the clinical efficacy of autologous SVF injection into each finger of 20 SSc patients with hand disability.[109] The amelioration of skin fibrosis was prominent, and 31.6% of active ulcers were healed at the 24-week follow-up. Additionally, the combined treatment effects of MSCs with other therapies have also been reported. Zhang *et al.*[110] investigated a combination of plasmapheresis and single MSC transplantation in 14 SSc patients. The modified Rodnan skin scores (MRSS) were significantly improved, and anti-topoisomerase I antibodies (anti-Scl70), serum TGF-β, and VEGF levels were also significantly decreased at 12 months of follow-up. In this trial, all three patients with interstitial lung disease had better pulmonary functions and improved computed tomography (CT) images. A relevant RCT has not yet been conducted for SSc.

One Chinese study investigated the responses to BM-MSC treatment in 24 pSS patients to treatment with BM-MSCs.[87] All patients had an improvement in the unstimulated salivary flow rate and oral dryness and a decrease in anti-SSA/anti-SSB without serious adverse events. Interestingly, this study also showed that the infused allogeneic MSCs migrated towards the inflammatory regions in an SDF-1–dependent manner, which indicated the key role of the SDF-1/CXCR4 signalling pathway in the immunoregulatory functions of MSCs. For idiopathic inflammatory myopathies (IIMs), a single-arm trial involving 10 drug-resistant polymyositis/dermatomyositis patients was conducted by Wang *et al.*[111] in 2011. Improvements were seen in serum creatine kinase (CK) and CK-MB in eight patients, and amelioration of muscle strength was seen in all patients. Two patients died due to disease recurrence and infection. The numbers of enrolled pSS and IIM patients in the published papers are low, so more evidence is required to draw a conclusion.

PERSPECTIVES ON THE USE OF MSCS AS A TREATMENT FOR CTD

In this review, we summarized the current status of the immunological mechanisms, preclinical studies, and clinical trials of MSC therapies for CTDs. MSC-based therapies modulate inflammation by affecting different immune cells

Table 2: Clinical studies of MSCs in connective tissue diseases

Author (year)	Disease	Study design	Patients (*n*)	MSC type	MSC dose	Infusion	AE	Efficacy	Follow-up (months)
Barbado *et al*. (2018) [112]	SLE	Case series	3	BM	9×10^7 cells	Intravenous	None	24 h proteinuria↓, SLEDAI↓, drug dosage↓	9
Wang *et al*. (2017)[92]	SLE	Observational	9	UC	1×10^6 cells/kg (2 times)	Intravenous	Mild dizzy and warm sensation (n = 1)	Normal liver function, no newly onset abnormality on electrocardiogram and chest radiography, no rise in serum tumour markers	72
Wang *et al*. (2013)[91]	SLE	Observational	87	UC, BM	1×10^6 cells/kg	Intravenous	Nontreatment-related events (n = 5)	Overall rate of survival (94%), complete clinical remission (28%, 31%, 42%, and 50% at 1, 2, 3, and 4 years, respectively)	27
Wen *et al*. (2019)[113]	SLE	Observational	69	UC, BM	1×10^6 cells/kg (1–2 times)	Intravenous	NA	Low disease activity (58%), clinical remission (23%)	12
Wang *et al*. (2018)[90]	SLE	Observational	81	UC, BM	1×10^6 cells/kg (1–3 times)	Intravenous	Death (n = 15), diarrhoea (n = 2), herpesvirus infection (n = 3), tuberculosis infection (n = 2), *Klebsiella pneumoniae* pneumonia (n = 2), cryptococcal meningitis (n = 1)	Five-year overall survival rate (84%), complete remission (27%), partial clinical remission (7%)	60
Wang *et al*. (2014)[89]	SLE	Single arm	40	UC	1×10^6 cells/kg	Intravenous	Herpesvirus infection (n = 4), death (n = 3)	SLEDAI↓, BILAG↓, 24 h proteinuria↑, anti-dsDNA↓, ANA↓	12
Sun *et al*. (2010)[114]	SLE	Single arm	16	UC	1×10^6 cells/kg	Intravenous	Severe nausea (n = 1)	SLEDAI↓, ANA↓, anti-dsDNA↓, serum albumin↑, C3↑, renal function↑	8.25
Liang *et al*. (2018)[115]	SLE, pSS, SSc	Observational	404	UC, BM	1×10^6 cells/kg	Intravenous	Malignancies (n = 5), death (n = 45), transplantation-related mortality (n = 1), infection (n = 119), serious infection (n = 52)	The 5- and 8-year survival rates were 90.4% and 88.9%, respectively	43.4 ± 25.9
Liang *et al*. (2010)[116]	SLE	Single arm	15	BM	1×10^6 cells/kg	Intravenous	None	SLEDAI↓, 24 h proteinuria↓, anti-dsDNA↓, GFR↓	12
Li *et al*. (2013)[117]	SLE	Single arm	35	UC, BM	1×10^6 cells/kg (2–3 times)	Intravenous	Uncontrolled disease recurrence after infection (n = 2)	Blood cell count↑↓, disease activity↓	21
Deng *et al*. (2017)[93]	SLE	RCT	18	UC	2×10^8 cells	Intravenous	Leukopenia, pneumonia, and subcutaneous abscess (n = 1), severe pneumonia (n = 1)	Remission occurred in 75% *versus* 83% (placebo)	12
Wang *et al*. (2013)[100]	RA	RCT	172	UC	4×10^4 cells (2 times)	Intravenous	Chills or fever (≤38.5°C) (n = 6)	DAS28↓, HAQ↓	8

(Continued...)

Author (year)	Disease	Study design	Patients (*n*)	MSC type	MSC dose	Infusion	AE	Efficacy	Follow-up (months)
Yang *et al.* (2018)[118]	RA	RCT	105	UC	1×10^6 cells/kg	Intravenous	Chills or fever (≤39°C) (*n* = 3)	DAS28↓, drug dosage↓	12
Wang *et al.* (2019)[99]	RA	Single arm	64	UC	4×10^7 cells	Intravenous	None	ESR↓, CRP↓, RF↓, anti-CCP↓, health index↓, DAS28↓	36
Shadmanfar *et al.* (2018)[102]	RA	RCT	30	BM	$42 \pm 4 \times 10^6$ Cells	Intraarticular	Minor AEs: postimplantation pain and/or articular swelling	WOMAC score↑, VAS score↓, standing time↑	12
Park *et al.* (2018)[105]	RA	Single arm	9	UC	2.5×10^7, 5×10^7, or 1×10^8 cells	Intravenous	None	DAS28↓	1
He *et al.* (2020)[107]	RA	RCT	63	UC	1×10^6 cells/kg	Intramuscular	None	ACR20 response rates were 53.3% in patients with MSCT monotherapy and 93.3% in patients with MSCT combined with IFN-γ treatment	12
Ghoryani *et al.* (2020)[103]	RA	Single arm	13	BM	1×10^6 cells/kg	Intravenous	None	DAS28-ESR↓	12
Ghoryani *et al.* (2019)[104]	RA	RCT	9	BM	1×10^6 cells/kg	Intravenous	None	DAS28-ESR↓, VAS score↓, no significant difference was found in serum CRP and anti-CCP	12
Alvaro-Gracia *et al.* (2017)[101]	RA	RCT	53	AD	1, 2, and 4×10^6 cells/kg (3 times)	Intravenous	Severe AEs (*n* = 8): lacunar infarction, diarrhoea, tendon rupture, rheumatoid nodule and arthritis, sciatica, asthenia	ACR20 responses were 20%–45% *versus* 29% (placebo) at month 1 and 15%–25% *versus* 0% at month 3	6
Del Papa *et al.* (2015)[119]	SSc	Single arm	15	AD	0.5–1 mL	NA	None	Blood flow without improvement, pain↓, improvement in ulcers without the appearance of new ones, number of capillaries↑	6
Takagi *et al.* (2014)[120]	SSc	Single arm	11	BM	$0.4–5.1 \times 10^{10}$ cells	Intramuscular	Amputation (*n* = 1, osteomyelitis prior to treatment)	Complete resolution of ulcer size (*n* = 9), recurrence (*n* = 1), VAS score↓, $TcPO_2$↑	1–24
Kamata *et al.* (2007)[121]	SSc	Case series	4	BM	3.5×10^8 cells	Intramuscular	NA	VAS score↓, arterial flow↓ (*n* = 1)	12
Keyszer *et al.* (2011)[108]	SSc	Case series	5	BM	1×10^6 cells/kg	Intravenous	Mild respiratory tract infections (*n* = 4)	Temporary MRSS↓, improved acral necrosis, oxygen saturation over the involved tissue↑	6
Park *et al.* (2020)[109]	SSc	Single arm	20	AD	3.61×10^6 cells/finger	Subcutaneous in hand	None	Skin fibrosis↓, hand oedema↓, 31.6% of active ulcers were healed at 24 weeks after injections	6
Zhang *et al.* (2017)[110]	SSc	Single arm	14	UC	1×10^6 cells/kg	Intravenous	Minor respiratory tract infection (*n* = 5), diarrhoea (*n* = 1)	MRSS↓, anti-Scl70↓, improvement of lung function and CT images in three ILD patients	12

(Continued...)

Author (year)	Disease	Study design	Patients (*n*)	MSC type	MSC dose	Infusion	AE	Efficacy	Follow-up (months)
Xu *et al.* (2012)[87]	pSS	Single arm	24	UC	1 × 10^6 cells/kg	Intravenous	None	SSDAI score↓, anti-SSA/Ro production↓, salivary flow rate↑, improved refractory haemolytic anaemia	12
Wang *et al.* (2011)[111]	IIM	Single arm	10	BM or UC	1 × 10^6 cells/kg	Intravenous	Disease recurrence (*n* = 2)	Improvements in CK, CK-MB, and muscle strength	6

MSC: mesenchymal stem cell; SLE: systemic lupus erythematosus; RA: rheumatoid arthritis; SSc: systemic sclerosis; pSS: primary Sjögren's syndrome; IIM: idiopathic inflammatory myopathies; RCT: randomized controlled trial; DM: dermatomyositis; PM: polymyositis; BM: bone marrow-derived MSCs; UC: human umbilical cord-derived MSCs; AD: human adipose tissue-derived MSCs; AEs: adverse events; SLEDAI: the SLE disease activity index; BILAG: British Isles Lupus Assessment Group; GFR: glomerular filtration rate; DAS28-ESR: disease activity score 28-ESR; HAQ: Health assessment questionnaire; WOMAC: Western Ontario and McMaster Universities Arthritis Index; VAS: visual analog scale; ACR: American College of Rheumatology; $TcPO_2$: transcutaneous (partial) pressure of oxygen; MRSS: modified Rodnan skin score; CT: computed tomography; ILD: interstitial lung disease; CK: serum creatine kinase; NA: not available. The arrow pointing up indicates an increase in a numerical value, and the arrow pointing down indicates a decrease.

and maintaining a balance of highly complex biochemical and cellular interactions. Preclinical results showed a reduction in disease activity and the degree of organ involvement in various CTD models. These experimental models also help us to better understand the pathogenesis of stem cell dysfunction in CTDs and improve the efficacy and increase the duration of the effects of MSCs *via* cell engineering approaches or combination therapies. To date, the safety and efficacy of MSC-based therapies for CTD have been investigated in pilot studies, long-term follow-up studies, and small randomized controlled clinical trials in CTDs, especially for SLE and RA. These clinical trials showed a low rate of adverse events, and most of them demonstrated positive clinical outcomes. Clinical studies of MSC therapies in other CTDs, such as SSc, pSS, and IIM, are still in their early stages and are worthy of further study in well-designed controlled trials for future evaluation. Cell therapy with MSCs is a very attractive new approach to address unresolved treatment difficulties for patients with CTD. Current reports indicate that MSCs have favourable prospects for the treatment of CTD, but the evidence is insufficient to come to a definite conclusion. RCTs with large sample sizes and studies on specific organ involvement need to be conducted. A better understanding of the mechanisms of action underlying MSC therapies would contribute to the development of an optimized regimen and allow for exploring serum biomarkers of CTD patients to predict treatment outcomes.

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Author Contributions

Li M, Zeng X, and Tian X conceived and designed this study. Shi Y and Jiang N searched for and extracted data from the included articles and drafted the manuscript. Tian X critically revised the manuscript. All authors have read and approved the final manuscript.

Conflict of Interest

The authors have no conflicts of interest to disclose.

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