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Umbilical cord mesenchymal stromal cell transplantations: A systemic analysis of clinical trials

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Abstract

The advances and success of umbilical cord–derived mesenchymal stromal cells (UC-MSCs) in experimental disease animal models have fueled the development of targeted therapies in humans. The therapeutic potential of allogeneic transplantation of UC-MSCs has been under examination since 2009. The purpose of this systematic analysis was to review the published results, limitations and obstacles for UC-MSC transplantation. An extensive search strategy was applied to the published literature, 93 peer-reviewed full-text articles and abstracts were found published by early August 2017 that investigated the safety, efficacy and feasibility of UC-MSCs in 2001 patients with 53 distinct pathologies including many systemic/local, acute/chronic conditions. Few data were extracted from the abstracts and/or Chinese-written articles (n = 7, 8%). Importantly, no long-term adverse effects, tumor formation or cell rejection were reported. All studies noted certain degrees of therapeutic benefit as evidenced by clinical symptoms and/or laboratory findings. Thirty-seven percent (n = 34) of studies were found published as a single case (n = 10; 11%) or 2–10 case reports (n = 24; 26%) with no control group. Due to the nature of many stem cell–based studies, the majority of patients also received conventional therapy regimens, which obscured the pure efficacy of the cells transplanted. Randomized, blind, phase 1/2 trials with control groups (placebo-controlled) showed more plausible results. Given that most UC-MSC trials are early phase, the internationally recognized cell isolation and preparation standards should be extended to future phase 2/3 trials to reach more convincing conclusions regarding the safety and efficacy of UC-MSC therapies.

Key Words: *clinical trial, mesenchymal stem/stromal cell, regenerative medicine, systemic review, umbilical cord, Wharton's jelly*

Introduction

The safety and therapeutic potential of human umbilical cord–derived mesenchymal stromal cells (UC-MSCs) have been increasingly studied in the context of regenerative medicine and immune modulation. Alongside their stem cell properties, *ex vivo*–expanded UC-MSCs possess immunomodulatory, anti-apoptotic, angiogenic and anti-fibrotic properties, which are achieved via paracrine and juxtacrine factors such as interferon (IFN)-γ [1,2] and are largely mediated by factors such as indoleamine 2,3-dioxygenase or nitric oxide synthase, inhibiting both T- and B-cell proliferation and function [3]. Furthermore, UC-MSCs suppress innate immunity by inhibiting dendritic cell formation and function, decreasing the expression of human leukocyte antigen (HLA)-DR, CD80 and CD86 co-stimulatory molecules on antigen-presenting cells and decreasing the proliferation of both resting and interleukin (IL)-2-activated natural killer cells, their cytotoxic capabilities and IFN-γ production [2,4]. Systemic or local infusions of large numbers of non-HLA-matched UC-MSCs seem relatively safe without significant graft-versus-host disease (GVHD) in the absence of pre-conditioning or immunosuppression. Moreover, UC-MSCs lack HLA class II antigens and T-cell co-stimulatory molecules [3,5] and have been shown to reduce the graft-versus-host rejection after allogeneic bone marrow (BM) transplantations [4].

In vivo experiments showed that UC-MSCs could repair ischemic tissue by promoting neovascularization and reendothelialization [6]. Although the exact mechanism of action is still under investigation, they secrete angiogenic factors and transdifferentiate into endothelial cells to promote tissue regeneration [7].

The immunosuppressive and anti-inflammatory properties of cultured/expanded UC-MSCs have led these cells to be tested for their therapeutic potential in preclinical animal models since mid-2000s, and their differentiation characteristics and responses to external environment have been extensively been documented in *in vitro* single and co-culture setups [8–11].

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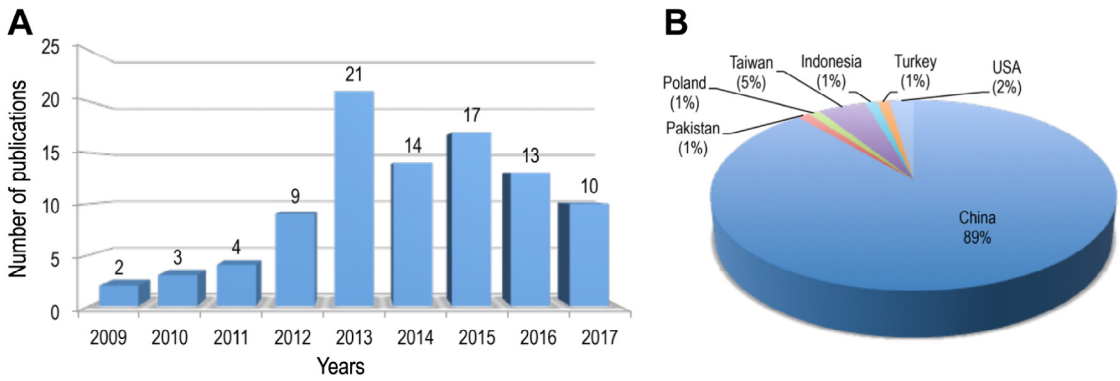

Figure 1. Published cases and trials through August 2017.

Preclinical animal studies in the literature reaching to hundreds of research articles were out of the scope of this review because many preclinical conditions do not absolutely reflect the clinical states and chronic diseases, whereas clinical trials and case reports stand as valuable tools to conclude the ultimate outcome of feasibility, safety and efficacy of UC-MSCs, delivery routes, concurrent procedures, age and sex differences. Due to the growing number of trials in various clinical disorders, it is becoming essential to cumulate and analyze the current status of those efforts. Therefore, we aimed to extensively search and systematically review UC-MSC-based clinical trials.

Here we report the analysis of all clinical trials listed on the National Library of Medicine Medline Database as of August 1, 2017, with an emphasis of their use in various pathological states and diseases, some of which were chronic clinical conditions for which patients had no other options for healing or survival. Obviously, many ongoing registered studies were not included in this review because they are still in progress. However, they can be viewed by a search in clinical trial databases such as the U.S. National Institute of Health database (www.clinicaltrials.gov) and the European Union Clinical Trials Registry (www.clinicaltrialsregister.eu).

The first report was published in 2009 as a single multiple sclerosis case by Liang *et al.* [12]. The number of published cases and trials reached 93 by August 2017, as summarized in Figure 1 and Table I. The peak number of trials appeared in 2013 when 21 trials were reported in the literature.

Methods

Literature searching strategy

We electronically searched the National Library of Medicine Medline Database using the following keyword sets (refer to Supplementary Data 1).

Classification of clinical states and table parameters

The 93 clinical studies listed in the present analysis were classified according to the clinical states they present. In the case of some relatively rare conditions such as multiple sclerosis, which is an autoimmune

Table I. Overview of 93 clinical studies following a multisession search in National Library of Medicine Medline Database by August 1, 2017.

Clinical conditions	Full articles	Letter to editor/ Single case reports	Abstracts[a]	Text in English	Text in other language	Total
Neurological diseases	18	5	—	23	—	23
Hematological diseases	18	1	—	12	7	19
Immunological diseases	14	1	—	13	2	15
Liver diseases	9	—	1	8	2	10
Cardiac diseases	5	1	1	7	—	7
Endocrine diseases	6	—	—	5	1	6
Musculoskeletal diseases	5	1	1	6	1	7
Pulmonary diseases	2	1	—	1	2	3
Skin diseases	2	—	—	2	—	2
Ophthalmological diseases	—	—	1	1	—	1
Total	79	10	4	78	15	93

[a]Presented exclusively as an abstract in a congress/symposium proceeding.

disorder of motor neurons in the central nervous system, we preferred to list these trials under "neurological diseases." Diseases that have an immunologic basis transpired to be the most extensively studied clinical conditions so far because MSCs in general, and UC-MSCs in particular, exhibit a series of immunomodulatory effects. The clinical states/diseases are given in the order of abundance of trials, meaning that the greatest number of trials in a given group of diseases (e.g., neurologic diseases) is given first in order. We classified and summarized the clinical trials and cases in Figure 1 and Tables II through XI using 12 parameters (see Supplementary Data 2).

Results

Neurologic diseases

Among all the clinical trials analyzing the effect of UC-MSCs on various diseases, neurological disorders seem to be the most prominent field with 23 manuscripts (Table II).

Chen *et al.* [13] analyzed the conceivable beneficial effects of UC-MSCs together with olfactory unsheathing cells, Schwann cells and neural progenitors in chronic stroke. Ten patients were enrolled in the study; various doses of UC-MSCs were administered to two patients along with the administration of other cells. One patient was diagnosed as having right-side cerebral infarction and received three intravenous (IV) cell injections (1×10^7). During a 12-month follow-up period, the authors observed decreased muscular hypertension and improved walking and left upper limb strength. Another patient was diagnosed as having left basal ganglia cerebral hemorrhage and received two IV cell injection (2.3×10^7). After 6 months, improvements in speech, movement of fingers on the right hand, gait and walking distance were noted. Jiang *et al.* [14] delivered 2.3×10^7 of UC-MSCs using a catheter to the lesion site through the middle cerebral artery in three patients with ischemic stroke and one with hemorrhagic acute stroke. The authors reported that two (67%) of the patients with ischemic stroke demonstrated improved muscle strength and modified-Rankin scale scores, a scale used to evaluate the degree of disability or dependence in daily activities. On the other hand, the patient with hemorrhagic stroke failed to improve in his daily activities. No adverse effects were reported in any of the patients during the 6-month follow-up period.

Three studies were found regarding UC-MSC application in multiple sclerosis (MS), an immunological disease that affects the central nervous system and frequently leads to severe physical and cognitive impairment. In a single case reported by Liang *et al.* [12], UC-MSCs were applied via intrathecal (1×10^7 cells) and IV injections (2×10^7 cells) to a 55-year-old woman with MS. The authors observed improvement in quality of life and disease-based disabilities. The Expanded Disability Status Scale (EDSS) score, which quantifies disability in MS, reduced 5 months following cell transplantation. In another MS case report by Hou *et al.* [15], UC-MSCs were IV applied four times at different doses (1.2×10^8–3.2×10^8) after five autologous BM-MSC transplantation to a 25-year-old man with MS. The authors reported that the patient was able to walk more that 500 meters unaided and he was completely free of clinical and radiologic disease activity; no new lesions were reported on the magnetic resonance imaging performed after 4 year of treatment. Considering safety, the researchers reported short-term adverse effects including dizziness, headache, rash, and fever due to UC-MSC application but not in the long-term surveillance. In Li *et al.*'s [16] phase 1/2 study, 23 patients with MS (13 in the cell-treated group, 10 controls) were enrolled to evaluate safety and efficacy. The authors administered 4×10^6 UC-MSCs/kg in three consecutive IV injections every 2 weeks to the cell-treated group, and the control group received saline infusions. They determined the EDSS scores as the endpoint of the study. After 12 months' follow-up, the authors found that both the EDSS scores and relapse occurrence were significantly lower than in the control patients, and they observed no significant adverse effects.

Spinal cord injury (SCI) is considered among the serious injuries and leads to motor and sensory dysfunctions accompanied by neuropathic pain. Liu *et al.* [17] treated 22 patients with SCI (16 incomplete, 6 complete) with two to four intrathecal injections of 1×10^6 UC-MSCs/kg. They noted that 13 (81%) patients with incomplete SCI had significant improvement in their clinical symptoms, such as scores of pain sensation, touch sensation, motor function and activities of daily living; no improvement was observed in patients with complete SCI during the 36 months of follow-up. The authors also reported that one patient experienced lumbago and one experienced headache, but for 1–3 days only. Cheng *et al.* [18] analyzed the efficacy of UC-MSC administration (two injections of 2×10^6 cells into the spinal cord parenchyma) in 10 patients with thoracolumbar spinal cord injury by comparing them with a rehabilitation group (n = 14) that received rehabilitation therapy only, and a blank control group (n = 10) in which patients received no specific treatment during a 6-month follow-up period. They noted that motion, muscle tension and Barthel index, a daily life ability measurement, significantly improved, whereas improvement in sensation was not significant compared with the pre-treatment values. On the other hand, the improvement in the scores of the rehabilitation group did not reach significant levels

Table II. Administration of UC-MSCs in neurologic diseases.

Disease/ pathology	Authors, year (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period	Clinical/laboratory outcome
						C	T				
Chronic stroke	Chen et al., 2013 [13], China	Pilot	Safety and efficacy	Intrathecal (OEC, SC, NPC) Intravenous (hUC-MSC)	$1–5 \times 10^6$ (OEC, SC, NPC) $1–2.3 \times 10^7$ (hUC-MSC)	None	2	42–87	2/0	24 months	Decrease in muscular hypertension Improvement in speech, movement of right fingers, left upper limb strength, gait, walking distance
Acute stroke (>2 months)	Jiang et al., 2013 [14], China	Pilot	Feasibility and efficacy of cell delivery to MCA	MCA	2×10^7	None	4	40–59	4/0	6 months	No major accidents (stroke or death) Improved muscle strength, modified Rankin scale (50%)
Multiple sclerosis	Liang et al., 2009 [12], China	Case report	Efficacy	Intrathecal Intravenous	1×10^7 2×10^7	None	1	55	0/1	5 months	Improved quality of life, disease disability Reduced EDSS score
Multiple sclerosis	Hou et al., 2013 [15], China	Case report	Efficacy	Intravenous	$1.2–3.2 \times 10^8$ (hUC-MSC) 1.4×10^5-8.9×10^7 (BM-MSC)	None	1	25	1/0	48 months	No adverse effect Patient able to walk unaided for > 500 meters No new lesions were reported on the MRI
Multiple sclerosis	Li et al., 2014 [16], China	Phase 1/2	Safety and efficacy	Intravenous	4×10^6/kg 3 injections	10	13	35–47	3/7	12 months	Reduced EDSS score, relapse occurrence
Spinal cord injury (2–104 months)	Liu et al., 2013 [17], China	Phase 1/2 Single arm	Safety and efficacy	Intrathecal	1×10^6/kg 2–4 injections	None	22	18–51	17/5	3–36 months	Response to treatment 81.25%, 41% nonresponsive, 27% nonresponsive (incomplete injury) Improved motor or sensory functions, bowel, bladder control ability, Improved algesia, tactile sensation, motion and activity of daily living scale
Spinal cord injury (9–33 months)	Cheng et al., 2014 [18], China	Phase 2 Triple arms	Efficacy	Intraparenchymal (spinal cord	2×10^7 2 injections	10	10 (hUC-MSC) 14 (rehab)	19–57	ND	6 months	No/minimal (10%) adverse effect Improved movement, self-care ability, muscular tension (70%) Increased maximum urinary flow rate, maximum bladder capacity Decreased residue urine volume, maximum detrusor pressure
Spinal cord injury (24 months)	Hua et al., 2016 [19], China	Case report	Efficacy	Intrathecal	1×10^7 4 injections	None	1	25	1/0	36 months	Improved SSEP, PRI, NPP Decreased MPQ pain score

(*continued*)

Table II. Continued

Disease/ pathology	Authors, year (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number C	Pt number T	Pt age	Pt sex (M/F)	FU period	Clinical/laboratory outcome
Spinal cord injury (2–36 months)	Zhao et al. 2017 [20] China	Pilot	Efficacy	Cells were loaded onto NeuroRegen® scaffolds	4×10^7	None	8	18–65	7/1	12 months	No adverse events In majority of patients, sensation level and motor-evoked potential, motor-evoked potential responsive area expanded Increased finger activity, enhanced trunk stability, defecation sensation, autonomic neural function recovery
Hereditary spinocerebellar ataxia	Jin et al., 2013 [21], China	Phase 1/2 Single arm	Safety and efficacy	Intrathecal Intravenous (twice each)	4×10^7 4 injections	None	16	21–56	10/6	12 months	No adverse effect Improved BBS (44%) and ICARS scores (63%)
Spinocerebellar ataxia Multiple system cerebellar atrophy	Dongmei et al., 2011 [22], China	Phase 1/2 Single arm	Safety and efficacy	Intrathecal	1×10^6/kg 4 injections (Repeated in 3 patients)	None	24	24 (avg)	15/9	6–15 months	Improved posture and gait disorder (89%), coordination and mapping (78%), language use (33%), ocular motility (7%), self-care ability (79%)
Radial nerve injury	Xue et al., 2011 [23], China	Case report	Safety and efficacy	Intravenous	No data	None	1	No data	No data	12 months	No adverse effect Return of nerve reflex Increased muscle tone, strength, nerve conduction velocity
Radial nerve injury	Li et al., 2013 [24], China	Phase 1/2 Double arms	Safety and efficacy	Local implantation with amniotic membrane	1.75×10^7	20	12	37–60	20/12	3 months	No adverse effect Improved muscle strength, touch and pain sensation
Neuromyelitis optica	Lu et al., 2012 [25], China	Case report	Safety and efficacy	Intravenous intrathecal	$2–4 \times 10^7$ Several infusions	None	5	19–45	0/5	24 months	No adverse effect EDSS improvement in 4 patients and worsening in 1 Decreased relapse occurrences
Radiation myelitis	Liang et al., 2015 [26], China	Case report	Efficacy	Intrathecal Intravenous	5.2×10^7 1.1×10^7	None	1	37	1/0	18 months	No adverse effect No change in MRI scan Attenuated neurological symptoms

(*continued*)

Table II. Continued

Disease/ pathology	Authors, year (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period	Clinical/laboratory outcome
						C	T				
Cerebral hemorrhage	Chang et al., 2016 [27], China	Phase 1/2 Triple arms	Safety and efficacy	Hematoma cavity via tube	1.8×10^8 (BM-MNC) ND (hUC-MSC) 2 injections	8	7 (BM-MNC) 9 (hUC-MSC)	38–58	16/8	60 months	Reduction in NIHSS score (in both treatment groups)
Traumatic brain injury	Wang et al., 2013 [28], China	Phase 1/2	Safety and efficacy	Intrathecal	1×10^7 4 injections	20	20	5–57	32/8	6 months	Improvement in extremity motor, sensation, balance subscores Increased FIM scores
Cerebral palsy	Wang et al,. 2015 [29]. China	Case report	Safety and efficacy	Intrathecal	$1–1.5 \times 10^7$ 4 injections	None	16	3–12	6/10	6 months	Improved GMFM scores
Autism	Lv et al. 2013 [30],, China	Phase 1/2	Safety and efficacy	Intravenous Intrathecal	2×10^6/kg (CB-MNC) 1×10^6/kg (hUC-MSC + CB-MNC) 4 injections	14	14 (CB-MNC) 9 (HUC-MSC + CB-MNC)	3–12	36/1	6 months	No adverse effect Decreased CARS, ABC and CGIS scores
Hypoxic ischemic encephalopathy	Xie et al., 2016 [31], China	Double arms	Safety and efficacy	Intravenous	1×10^8	10	12	45–71	14/8	6 months	No adverse effect Decline of NIHSS score Increased Barthel index Cognitive impairment in MMSE (in treatment)
Vascular dementia	He et al., 2017 [32], China	Phase 1	Safety and efficacy	Intravenous	$1–2 \times 10^6$/kg 3 injections	None	10	63–79	5/5	6 months	No adverse effect Temporary increase in MMSE and Barthel Index scores at 3 months
Various pathologies	Miao et al., 2015 [33], China	Phase 1/2	Safety and efficacy	Intrathecal	ND 4–6 injections	None	35 (SCI), 20 (CP), 20 (TBI), 9 (PBIS) 8 (SCA), 8 (motor neuron disease)	2–68	53/47	12 months	Short-term side effects (22%) Improved functional indices (47%)
Various pathologies	Zhang et al., 2015 [34], China	Phase 1/2	Safety and efficacy	Intrathecal	No data 4–6 injections	None	35 (SCI), 20 (CP), 20 (TBI), 9 (PBIS) 8 (SCA), 8 (motor neuron disease)	2–68	53/47	12 months	Short-term side effects (22%) Improved functional indices (47%)

ABC, Aberrant Behavior Checklist; avg, average; BBS, Berg Balance Scale; CARS, Childhood Autism Rating Scale; CGI, Clinical Global Impression; C, control; F, female; FIM, Functional Independence Measures; FMFM, Fine Motor Function Measure; FU, follow-up; GMFM, Gross Motor Function Measure; m, male; MCA, middle cerebral artery; MPQ, McGill Pain Questionnaire; MRI, magnetic resonance imaging; NPC, neural progenitor cells; NPP, neuropathic pain; OEC, olfactory ensheathing cells; PBIS, post-brain infarction syndrome; PRI, Pain Rating Index; Pt, patient; SC, Schwann cells; SSEP, somatosensory evoked potential; T, treatment.

when compared with their initial scores. Considering urodynamic changes, the researchers recorded increased maximum urinary flow rate and maximum bladder capacity, and decreased residual urine volume and maximum detrusor pressure in the cell treatment group. They also noted that one patient in the cell treatment group presented with radiating neuralgia that spontaneously alleviated in 1 day, but no adverse effects were observed in the other patients. In a case report by Hua *et al.* [19], the authors intrathecally injected 1×10^7 UC-MSCs four times with 3-day intervals to a 25-year-old patient with a 2-year history of complete cervical SCI. They noted that recordings of somatosensory-evoked potentials from the posterior tibial nerve and median nerve, pain rating index, and clinical presentations of neuropathic pain significantly improved after cell therapy. More recently, Zhao *et al.* [20] tested the efficacy of organic scaffolds (NeuroRegen made from bovine aponeurosis) pre-loaded and soaked with UC-MSCs to reduce diffusion of the cells from the injury site and promote reconstruction of the spinal cord injury microenvironment. They loaded 4×10^7 cells in eight patients and followed them for a year. No adverse events were reported. In the majority of the patients, sensation level and motor-evoked potential (MEP)-responsive area expanded; finger activity increased, and enhanced trunk stability, defecation sensation and autonomic neural function recovery were seen. They also analyzed MEPs in patients and found marked expansion of the MEP-responsive area in 87.5% of patients, which suggests partial recovery of neurological function. Two patients reported defecation sensation, although without achieving sphincter control. Increased stability and trunk equilibrium in the sitting position were reported in four patients, but no improvement was observed in the American Spinal Injury Association classification of the patients.

Spinocerebellar ataxias (SCAs) are a group of autosomal dominant neurodegenerative disorders that may cause oculomotor dysfunction, dysarthria, retinopathy, peripheral neuropathy, cognitive impairment and other symptoms [35]. In an open-label clinical trial by Jin *et al.* [21], feasibility, efficacy and safety of UC-MSCs were investigated in 16 patients who were clinically and genetically diagnosed as having SCA over a 1-year follow-up period. They applied four consecutive cell treatments at 1-week intervals to each patient. Approximately 4×10^7 cells were infused IV in the first session, and the same number of cells were divided into two and then simultaneously infused both IV and intrathecally during subsequent treatments. The Berg Balance Scale (BBS) significantly increased and the International Cooperative Ataxia Rating Scale (ICARS) significantly decreased at the third and sixth months of therapy, which indicated a beneficial effect of cell application. At the end of the 1-year follow-up period, improved BBS and ICARS scores were observed in 44% and 63% of patients, respectively. They noted certain self-limiting short-term adverse effects including 39°C fever (n = 1), dizziness due to lumbar puncture (n = 2), lumbago (n = 3) and headache (n = 2); the authors declared no long-term adverse effect due to cell application. Dongmei *et al.* [22] analyzed the safety and efficacy of UC-MSCs on patients with SCA (n = 14) and multiple system atrophy—cerebellar type (n = 10). The researchers intrathecally injected 1×10^6/kg cells four times at 1-week intervals and noted that ICARS and Activities of Daily Living Scale scores significantly decreased after the first month of the treatment, in addition to improvement of symptoms including posture and gait disorder (89%), co-ordination and mapping (78%), language use (33%), ocular motility (7%) and self-care ability (79%). At the end of the 6–15 months' follow-up, 57% of patients with SCA and 20% of patients with multiple system atrophy—cerebellar type were found stable; the remainder had progressed. In a similar way to Jin *et al.*'s study, Dongmei *et al.* declared short-term adverse effects including dizziness (n = 4), back pain (n = 2) and headache (n = 1) but no long-term adverse effects.

Xue *et al.* [23] injected 5×10^6/kg UC-MSCs IV and 1×10^7 cells/kg 3 weeks later to a 50-year-old woman with both bone nonunion and nerve injury in mid-distal third of the right humerus, and evaluated the possible therapeutic effects for a 1-year follow-up period. They reported that nerve reflex returned, muscle tone and strength increased and motor functions such as writing and extending the wrist improved; they also noted that the fracture gap disappeared and nerve conduction velocity increased with shorter latency and higher amplitude after X-ray and electromyography analysis. The authors observed no adverse effects. In another study, Li *et al.* [24] recruited 32 patients with radial nerve injury and applied UC-MSC therapy by injecting cells to the proximal and distal ends of the injured nerve and simultaneously implanting an amniotic membrane carrying a total of 1.75×10^7 UC-MSCs to 12 patients. Twenty patients in the control group received neurolysis only, a conventional treatment approach. After 3 months' follow-up, they observed significantly improved muscle strength, touch and pain sensation and muscular electrophysiologic function with no adverse effects.

Lu *et al.* [25] analyzed the safety and efficacy of UC-MSCs on neuromyelitis optica, which is a rare, inflammatory and demyelinating disease that causes myelitis and optic neuritis. The authors recruited five patients and their treatment regimen was (i) IV injection of 4×10^7 cells on day 0 and then (ii) IV injections of 2×10^7 cells and intrathecal infusion of

2×10^7 cells on days 7, 14 and 21. After 2 years' follow-up, EDSS scores improved in four patients (80%) but deteriorated in one, and relapse occurrences significantly decreased in all 5 patients. Magnetic resonance imaging revealed that the volume and number of lesions significantly decreased six months after transplantation. The authors observed no significant adverse effects. Liang *et al.* [26] reported the effects of UC-MSCs (IV injection of 5.2×10^7 cells and intrathecal infusion of 1.1×10^7 cells) on a 37-year-old man with laryngeal carcinoma who had developed radiation-induced myelitis in his spinal cord. The researchers noted that the clinical symptoms of the patient gradually improved, and neither new lesions nor adverse effects were detected during 18 months of follow-up.

Chang *et al.* [27] compared the safety and efficacy of UC-MSCs to that of BM mononuclear cells (BM-MNCs) on patients with cerebral hemorrhage, which causes high morbidity and mortality. Twenty-four patients were enrolled, the controls (n = 8) received no cell application, seven patients received BM-MNCs, and nine received UC-MSCs; the cells were transferred via a tube to the hematoma cavity as 1.8×10^8 of BM-MNCs or UC-MSCs (the transferred cell amount was not indicated in the article). Beginning from the third month of treatment, a significant reduction in National Institutes of Health Stroke Scale (NIHSS) scores, which quantify stroke severity, obtained in UC-MSC group compared with both the control and BM-MNC groups was noted at the end of the 5 years' follow-up with no significant adverse effects. Wang *et al.* [28] tested the hypothesis that UC-MSC transplantation could safely and effectively improve neurologic function in patients with sequelae of traumatic brain injury (TBI) in 40 patients (control n = 20, cell therapy n = 20) during a 6- month follow-up period. They injected 1×10^7 UC-MSCs into the subarachnoid space from the lumbar region. The procedure was repeated four times at 5- to 7-day intervals. The authors found a significant improvement in the self-care, mobility, locomotion and communication subscores, and also in the motor, sensation and balance scores of both upper and lower extremities in the cell-administrated group. Regarding safety, they reported short-term adverse effects including decreased intracranial pressure, mild dizziness, headache, nausea and vomiting but no long-term adverse effects.

Cerebral palsy (CP) is caused by various injuries in the pre-, peri- or post-natal period and describes a group of non-progressive central disorders characterized by abnormal movement and posture. Wang *et al.* [29] transplanted a total of 4×10^6–6×10^6 UC-MSCs to the subarachnoid space of patients with CP (n = 16 with eight pairs of identical twins) via lumbar puncture with four separate courses over an interval of 5–7 days and then compared the first- and sixth-month scores of gross and fine motor functions with those from baseline. They noted that both gross and fine motor function scores improved at the first and sixth month, but only gross ones obtained from the sixth month's evaluations reached statistically significant levels.

Lv *et al.* [30] transplanted 1×10^6/kg UC-MSCs together with 2×10^6/kg cord blood (CB) MNCs, and 2×10^6/kg of CB-MNCs to patients with autism (n = 14 and n = 9, respectively) via IV and intrathecal routes. They reported improved Childhood Autism Rating Scale, Clinical Global Impression scale and Aberrant Behavior Checklist scores in both cell therapy groups compared with the control (n = 14), and there were no associated severe adverse effects. Here, we underline the issue that the authors did not purely test UC-MSC effects in this study.

Xie *et al.* [31] focused on hypoxic ischemic encephalopathy, which is a clinical phenomenon that generally occurs in the event of partial or general deficiency in oxygen supplementation of the brain. The authors intravenously infused 1×10^8 UC-MSCs to 12 patients with hypoxic ischemic encephalopathy and they found an improvement in scores including the NIHSS, Barthel index, cognitive and emotional assessment tests such as the Mini-Mental State Examination (MMSE) and Hamilton Anxiety Rating Scale, beginning from the second week of the study to the end of 180-days' follow-up when compared with the scores obtained from the control group (n = 10). They reported no adverse effects.

Recently, He *et al.* [32] published the results of a clinical trial in which they treated 10 older patients with vascular dementia with IV injections of 1–2×10^6/kg UC-MSCs, and then repeated this twice with 20-day intervals. They reported that the Barthel index and MMSE scores significantly improved at the third month of the study, but these scores were found comparable after 6 months of treatment when compared with baseline values, and also noted that only one patient exhibited soreness, numbness, swelling and pain in the infusion site at the time of the first intravenous infusion.

Lastly, two trials by Miao *et al.* [33] and Zhang *et al.* [34] reported 100% matching patient profiles, cell treatment protocols and results. A total of 100 patients (35 SCI, 20 CP, 20 TBI, 9 post-brain infarction syndrome, 8 SCA, 8 motor neuron disease) were enrolled in both studies. Short-terms adverse effects such as headache, low-grade fever, low back pain and lower limb pain were noted in 22% of patients 24 h post-transplantation, which were treated with symptomatic therapy within 48 h. The authors concluded that intrathecal administration of UC-MSCs is safe and

effective with no long-term adverse effects in neurological disorders.

Hematologic diseases

Previous studies demonstrated that co-transplantation of BM-MSCs and hematopoietic stem cells (HSCs) can enhance engraftment, prevent GVHD, accelerate lymphocyte recovery and reduce the risk of graft failure [36,37]. Given that the umbilical cord is a rich source of MSCs, which can be easily obtained and cultured, safety and efficacy of UC-MSCs are concomitantly examined in a series of hematologic diseases. By mid-2017, hematologic disorders were among the second most frequently used group of diseases in which UC-MSCs were tested to enhance hematopoiesis and engraftment after HSC transplantation (HSCT) and to alleviate acute GVHD (aGVHD; Table III).

Graft failure and GVHD have been major obstacles to HSCTs. UC-MSC application (alone or co-transplantation with HSCs) after haploidentical HSCT (haplo-HSCT) was the first clinical setting to be investigated in patients with acquired severe aplastic anemia refractory to immunosuppressive therapy and lacking HLA-matched, related or unrelated donors. Chao *et al.* [38] reported the first-in-human cases in severe aplastic anemia in two children in 2011. The authors co-transplanted UC-MSCs (~4×10^6/kg) and peripheral blood HSCs (PB-HSCs) from matched unrelated donors. No adverse events occurred during or after the procedures. Both patients achieved hematopoietic engraftment; the time needed to achieve neutrophil engraftment was 9 and 10 days, and platelet engraftment was 13 and 15 days, respectively. At 30 days after co-transplantation, blood cells achieved 100% donor chimerism, as assessed using short tandem repeat analysis. No aGVHD or chronic GVHD (cGVHD) were detected. Two years later, Wang *et al.* [39] used a similar therapeutic approach in that they co-transfused UC-MSCs and allogeneic HSCs in the treatment of 22 patients with severe aplastic anemia. All patients had rapid engraftment; the mean time for neutrophil and platelet recovery was 13.95 and 20.27 days, respectively. No acute toxicity associated with UC-MSC transfusion was reported. Acute GVHD developed in seven patients (grade I–II); however, none developed cGVHD. Twenty-one patients were alive at a median follow-up of 15 months and reached full donor chimerism at the time of reporting. Xu *et al.* [40] reported a single case of aplastic anemia in a girl aged 12 years who received UC-MSCs and haploidentical UC blood cells after haploidentical BM- and PB-HSCTs. On day 35 after UC-MSCs and UC blood HSCs, chimeras accounted for 94%. One year later, the same investigators reported an eight-patient series in which all patients achieved hematopoietic reconstitution [41]. The incidence of grade I–II aGVHD was25%, and that of grade III–IV was 12.5%. Li *et al.* [42] examined the transplantation efficiency of combined haploidentical HSCs and UC-MSCs in graft failure and GVHD in 17 patients with severe aplastic anemia. Sixteen patients achieved hematopoietic reconstitution. Grade III–IV aGVHD was seen in 23.5% of the cases, and moderate and severe cGVHD were seen in 14.2%. The 3-month and 6-month survival rates for all patients were 88.2% and 76.5%, respectively; the mean survival time was 56.5 months. Wang *et al.* [43] tested the same therapy regimen in 17 patients. The cumulative incidence of grade II–IV acute GVHD at day 100 was 30.53 ± 11.12%; grade III–IV aGVHD occurred in only one patient. The cumulative incidence of cGVHD was 21.25 ± 13.31%. Secondary graft failure with autologous hematopoiesis recovery occurred in one patient. Wu *et al.* [44] reported relative success in 21 patients with severe aplastic anemia.

In 2017, Wang *et al.* [45] reported a four-case study testing the efficacy of UC-MSCs on primary thrombocytopenia. They reported no severe adverse events, no bleeding in 50% patients and no need to use immunosuppressive drugs after 13–24 months of follow-up.

Wu *et al.* [46] were the first group to investigate the potential of UC-MSCs in enhancing hematopoiesis after cord blood (CB) transplantation. Twenty patients with high-risk leukemia were prospectively randomized to receive either co-transplantation of CB and *ex vivo*–expanded banked UC-MSCs or CB cells alone. The time to undergo neutrophil and platelet engraftment was significantly shorter in the eight patients who received co-transplantation than in those who received CB cells alone. Similarly, Wu *et al.* [47] tested the safety, efficacy and feasibility in HSCT engraftment and alleviation of aGVHD in five patients. Four of five patients survived after UC-MSC administration. Three patients did not develop aGVHD, and 2 patients (including the one who died) developed cGVHD.

Wang *et al.* [48] aimed to investigate the efficacy of haplo-HSCT combined with UC-MSCs using a modified conditioning regimen for the treatment of 30 patients with refractory and relapsed or high-risk malignant hematologic diseases (15 acute myeloid leukemia, 9 acute lymphoblastic leukemia, 3 proT lymphoblastic lymphoma/leukemia, 1 spleen boundary zone stage IVB lymphoma, 1 natural killer/T lymphoma and 1 stage IVB Burkitt lymphoma. The results showed that implantation was achieved in all 30 cases, among them 19 (63%) patients had aGVHD and 6 (20%) patients had grade III–IV aGVHD, 8 patients (32%) had cGVHD comprising 1 case of ex-

Table III. Administration of UC-MSCs in hematologic diseases.

Disease/ pathology	Authors, year (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period	Clinical/laboratory outcome
						C	T				
Aplastic anemia	Chao *et al.*, 2011 [38], Taiwan	Case report	Safety and efficacy in enhancing engraftment	No data	4.2–4.3 × 10^6/kg	None	2	11, 13	0/2	37, 39 months	No adverse event No detected aGVHD and cGVHD Blood cells achieved 100% donor chimerism
Aplastic anemia	Wang *et al.*, 2013 [39], China	Single arm	Safety and efficacy in enhancing engraftment	IV	0.2–2.5 × 10^6/kg	None	22	3–52	10/12	4–39 months	Survival: 95.4% 31.8% aGVHD (grade I–II) No detected cGVHD 50% CMV reactivation
Aplastic anemia	Xu *et al.*, 2013[a] [40], China	Case report	Safety and efficacy	No data	No data	None	1	12	0/1	ND	No adverse event
Aplastic anemia	Xu *et al.*, 2014[b] [41], China	Case report	Safety and efficacy in severe aplastic anemia	IV	1 × 10^7	None	8	8–25	3/5	3–28 months	Survival: 75% 25% aGVHD (grade I–II) 12.5% aGVHD (grade III–IV) 37.5% cGVHD
Aplastic anemia	Li *et al.*, 2014 [42], China	Single arm	Safety and efficacy in enhancing engraftment and alleviation of aGVHD	IV	2.8–10 × 10^6/kg	None	17	4–29	10/7	2.5–80 months	Survival: 70.6% 23.5% aGVHD (grade III–IV) 14.2% cGVHD
Aplastic anemia	Wang *et al.*, (2014) [43], China	Single arm	Safety and efficacy in severe aplastic anemia and aGVHD	IV	0.5–8 × 10^7	None	17	4–19	6/11	36–1321 days	Survival: 82.3% 76.4% aGVHD 29.4% cGVHD
Aplastic anemia	Wu *et al.*, 2014 [44], China	Single arm	Safety and efficacy in prophylaxis of aGVHD	ND	5 × 10^5/kg	None	21	4–31	11/10	2.5–78 months	No adverse events Survival: 80.9% No relapse or progression
Primary thrombo-cytopenia	Wang *et al.*, 2017 [45], China	Pilot	Efficacy	IV	5 × 10^7–1 × 10^8	None	4	26–54	1/3	13–24 months	No severe adverse event No bleeding in 50% patients No need to use immunosuppressive drug
Acute leukemia	Wu *et al.*, 2013 [46], Taiwan	Two arms	Safety and efficacy to enhance hematopoiesis	IV	2.4–10.1 × 10^6/kg	None	8 (hUC-MSC + CB) 12 (CB)	3.2–13.1	11/9	2–31 months	Death: 25% Remission: 75% (in hUC-MSC group) Death: 33% Remission: 67% (in CB group) Shorter time for neutrophil, platelet engraftment
Leukemia	Wu *et al.*, 2013 [47], Taiwan	Pilot	Safety, efficacy and feasibility in engraftment and alleviation of aGVHD	IV	3.1–8.2 × 10^6/kg	None	5	4.1–11.6	3/2	24–31 months	No adverse events Survival: 80% 40% aGVHD 20% cGVHD
Hematologic malignancies	Wang *et al.*, 2013[a] [48], China	Single arm	Efficacy	No data	No data	None	30	No data	No data	128–455 days	Survival: 73.3% 63% aGVHD 20% III–IV aGVHD 32% cGVHD 10% relapse

(*continued*)

Table III. Continued

Disease/ pathology	Authors, year (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period	Clinical/laboratory outcome
						C	T				
Myeloid leukemia	Wu *et al.*, 2014[a] [49], China	Single arm	Efficacy in refractory/ relapsed myeloid leukemia	No data	No data	None	36	No data	No data	2 years	Survival: 76.9% 8.3% relapse 13.8% aGVHD 37.5% cGVHD 5.5% extensive cGVHD 8.3% relapse
Acute leukemia in children	Zhu *et al.*, 2015 [50], China	Single arm	Safety and efficacy in enhancing engraftment and alleviation of aGVHD	IV	1–1.3 × 10^6/kg	None	25	4–17	18/7	3–25 months	Survival: 66% 32% aGVHD 8% late aGVHD 24% cGVHD
HSCT	Wu *et al.*, 2013 [51], China	Single arm	Safety, efficacy and feasibility in engraftment and alleviation of aGVHD	IV	5 × 10^5/kg	None	50	9–58	24/26	1–58 months	No adverse events Survival: 66% 42% aGVHD 37.7% cGVHD 10% relapse
Acute GVHD	Wu *et al.* 2011 52), Taiwan	Case report	Efficacy	IV	3.3–8.0 × 10^6/kg 4 injections	None	2	4, 6	2/0	15–18 months	No adverse effects Diminished clinical symptoms Discontinued immunosuppressive drugs
Acute GVHD	Chen *et al.*, 2012[b] [52], China	Single arm	Safety and efficacy	IV	0.6–7.2 × 10^6/kg 1–3 injections	None	19	No data	No data	No data	No side and adverse effects Survival: 58% 58% complete response 21% partial response 21% no response
Acute GVHD	Qiao *et al.* 2013[a] [53], China	Pilot?	Safety and efficacy	No data	0.5 × 10^6/kg	None	5	No data	No data	No data	No adverse events Remission: 100% Improved GI symptoms, subsided rash, normalized liver function
Acute GVHD	Zheng *et al.* 2015[b] [54], China	Case report	Efficacy	IV	8.68 × 10^6/kg 1–7 injections	None	10	2.1–11.5	No data	2–21 months	Survival: 80%; death: 20% 30% partial response 70% no response No GVHD recurrence
GVHD	Gao *et al.*, 2016 [55], China	Phase 2 Two arms	Safety and efficacy in prevention of cGVHD	No data	3 × 10^7 4 injections	62	62	18–40	59/65	24–70 months	No adverse events Survival: 66% (in treatment), 61% (in control) GVHD: 27.4% (in treatment), 48.4% (in control) Increased Th1/Th2 ratio, Treg cells, B memory cells; decreased NK cells

CMV, cytomegalovirus; C, control; F, female; FU, follow-up; GI, gastrointestinal; M, male; NK, natural killer; SAA, severe aplastic anemia; Treg, regulatory T cell; Th, T helper cells; T, treatment.
[a]Data extracted from the abstract.
[b]Article translated from Chinese.

tensive cGVHD and 7 cases of limited cGVHD. The authors concluded that the efficacy of haplo-HSCT combined with UC-MSCs for the treatment of patients with refractory and relapsed or high-risk malignant hematologic diseases was favorable. Wu *et al.* [49] reported the results of a similar clinical arrangement for 36 patients with refractory/relapsed myeloid leukemia. Their results showed that grade III–IV aGVHD occurred in 5 of 36 (13.8%) patients. Chronic GVHD occurred in 12 of 32 (37.5%) patients and extensive cGVHD occurred in two patients. The 2-year overall survival rate of the patients was 76.9%. Zhu *et al.* [50] published the results of the same procedure in 25 children with high-risk acute leukemia reporting that myeloid engraftment was rapid, and the median time to neutrophil and platelet recovery was 15.12 days and 20.08 days, respectively. Eight patients developed grade I skin aGVHD, which responded well to standard steroid therapy. Of note, cytomegalovirus viremia was observed in most patients (23 of 25 cases). Sixteen (33%) patients died, mainly of leukemia relapse and pulmonary complication. Fourteen patients were alive and remained with full donor chimerism at the time of reporting.

Wu *et al.* [51] tested the efficacy of UC-MSCs to support hematopoiesis and enhance the engraftment of HSCs in 50 patients with refractory/relapsed acute leukemia undergoing haplo-HSCT using myeloablative conditioning. They observed that all patients given UC-MSCs showed sustained hematopoietic engraftment without any adverse infusion-related reaction. Grade II–IV aGVHD was observed in 12 of 50 (24.0%) patients. Chronic GVHD was observed in 17 of 45 (37.7%) patients and was extensive in 3 patients. The authors concluded that UC-MSC transplantation was effective in improving donor engraftment and reducing severe GVHD, which could provide a feasible option for the therapy of high-risk hematologic malignancies.

The therapeutic efficiency of UC-MSCs was tested in steroid-resistant aGVHD after allo/haplo HSCTs. Wu *et al.* [56] documented the first two case reports in 2011 in which they found UC-MSCs had superior proliferative potential and more suppressive effects on PB-MNC proliferation compared with BM-MSCs. Acute GVHD improved after each IV cell infusion of four into the two patients. No adverse effects were noted. In the following year, Chen *et al.* [52] reported the results of 19 patients with grade II–IV aGVHD who received one, two or three IV injections of UC-MSCs. They reported no side or adverse effects, 58% survival rate, 58% complete response, 21% partial response and 21% no response. Qiao *et al.* [53] reported the results of five children with grade III–IV aGVHD. Rash subsided after UC-MSC infusions, liver functions returned to normal values and their gastrointestinal symptoms improved. No infusion-related adverse reactions occurred. All children were in remission at the time of reporting. More recently, Zheng *et al.* [54] reported the results of a 10-patient study after a 2- to 21-month follow-up period. They reported an 80% survival rate, 30% partial response and 70% no response. They also reported no GVHD recurrence. Gao *et al.* [55] reported the safety and efficacy of UC-MSCs in the prevention of cGVHD in 62 patients in a phase 2, multicenter, randomized, double-blind controlled study. They performed repeated infusions of UC-MSCs once a month for a total of four rounds for each patient. Overall, they administered a total of 230 infusions of UC-MSCs to 62 patients. All infusions were well tolerated, with no acute infusional toxicity and no adverse events associated with MSC infusions. Forty-one patients in the UC-MSC group and 38 patients in the control group were alive at the time of reporting at the median follow-up of 51 months. The 2-year cumulative incidence of cGVHD in the UC-MSCs group was significantly lower (27.4%) than in the control group (49.0%).

Immunologic diseases

One of the main reasons for using UC-MSCs in immunologic diseases is to take advantage of their unique immunomodulatory potentials. UC-MSCs are capable of immune suppression and immune avoidance similar to MSCs obtained from other sources. They express MHC class I (HLA-ABC) at low levels but not class II (HLA-DR) and co-stimulatory antigens such as CD80 and CD86, which are implicated in activation of both T- and B-cell responses [2]. Additionally, UC-MSCs produce large amounts of tolerogenic IL-10 and higher levels of tumor growth factor (TGF)-β than BM-MSCs and express HLA-G, which is not expressed in BM-MSCs.

Systemic lupus erythematosus (SLE), which is characterized by the presence of autoreactive T and B lymphocytes with polyclonal activation of B cells and the consequent production of autoantibodies by plasma cells and release of cytokines [57], was the first disease with which UC-MSCs were examined in several clinical settings (Table IV). The first report was a single case by Liang *et al.* in 2010 [58]. Double injections of 2 million cells per kilogram of a 19-year-old female patient with alveolar hemorrhage resulted an improvement in respiratory failure, oxygen saturation levels and resolution of lung infiltrates during a 5-month follow-up period. Just after that case, Sun *et al.* [59] published a 16-case trial in which patients aged 17–56 years with severe and refractory SLE were monitored for up to 28 months. They reported decreased SLE Disease Activity Index (SLEDAI) scores, improved renal function, controlled hypotension and

Table IV. Administration of UC-MSCs in immunologic diseases.

Disease/ pathology	Authors, year (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period (months)	Clinical/laboratory outcome
						C	T				
SLE	Liang *et al.*, 2010 [58], China	Single case report	Safety and efficacy in diffuse alveolar hemorrhage associated with SLE	IV	2×10^6/kg 2 injections	None	1	19	0/1	5	No adverse effect Improvement in respiratory failure, O_2 saturation level Removal of mechanical respiratory support at 5 days; resolution of lung infiltrates
SLE	Sun *et al.*, 2010 [59], China	Single arm	Safety and efficacy in severe and refractory SLE	IV	1×10^6/kg	None	16	17–56	2/14	3–28	No serious adverse effect
SLE	Shi *et al.*, 2012 [60], China	Case report	Safety and efficacy in diffuse alveolar hemorrhage in SLE	IV	1×10^6/kg	None	4	19–46	0/4	9–21	Cessation of hemoptysis and Hb drop Improved pulmonary function
SLE	Wang *et al.*, 2013 [61], China	Single arm	Safety and efficacy in severe and refractory SLE	IV	1×10^6/kg 1–4 injections	None	46 (hUC MSC) 23 (BM-MSC)	12–56	7/80	48	Results specific to hUC-MSCs not given Complete remission rate: 50%, Relapse rate: 23%
SLE	Wang *et al.*, 2014 [62], China	Phase 1/2 Single arm	Safety and efficacy in active and refractory SLE	IV	1×10^6/kg 2 injections	None	40	17–54	2/38	12	Deaths: 7.5% (in treatment) Decreased SLEDAI scores, BILAG scores, serum creatinine, BUN, anti-dsDNA antibody Improved ALB level, C3 level
SLE	Yang *et al.*, 2014[a] [63], China	Phase 1/2 Two arms	Safety and efficacy in refractory SLE	IV	3×10^7	20	17	No data	No data	12	No adverse effect Decrease in SLEDAI score, recurrence rate Improved in ALB and C3 level
SLE	Wang *et al.*, 2015 [64], China	Case report	Investigate mechanism of hUC-MSCs in regulation of peripheral regulatory Treg cells and Th17 cells	IV	1×10^6/kg 1–3 injections	None	30	13–38	2/5	2	hUC-MSCs dose-dependently up-regulated peripheral Treg proportion; down-regulation of Th17 cells was not dose-dependent
SLE nephritis	Gu *et al.*, 2014 [65], China	Single arm	Efficacy in refractory nephritis	IV	1×10^6/kg	None	58 (hUC MSC) 23 (BM-MSC)	12–55	7/74	12	Results specific to hUC-MSCs not given Decreased BILAG score, proteinuria, serum creatinine, BUN Increased GFR and SLEDAI score
SLE nephritis	Deng *et al.*, 2017 [66], China	Double arms Placebo-controlled, randomized	Efficacy in refractory nephritis	IV	1×10^8 2 injections	6	12	29	1/17	12	Similar proportion of patients on hUC-MSC and placebo achieved complete remission and SLEDAI score hUC-MSC has no additional effect over and above standard immunosuppression.

(*continued*)

Table IV. Continued

Disease/ pathology	Authors, year (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period (months)	Clinical/laboratory outcome
						C	T				
Hemorrhagic cystitis	Jia *et al.*, 2012[b] [67], China	Case report	Efficacy in hemorrhagic cystitis after HSCT	IV	0.6–6.9 × 10^6/kg 1–3 injections	None	8	6–12	No data	2–75	No recurrence of cystitis
Hemorrhagic cystitis	Wang *et al.* 2015 [68], China	Case report	Efficacy in hemorrhagic cystitis after HSCT	IV	10.8–1.6 × 10^6/kg 1–3 injections	None	7	11–38	5/2	No data	No acute or late complications Hematuria disappeared, no remission Death: 43% related to GVHD, infection
Ulcerative colitis	Hu *et al.*, 2016 [69], China	Phase 1/2 Double arms Placebo-controlled	Safety and efficacy	IV & SMA	0.5 × 10^6/kg 2 injections	36	34	18–52	43/27	24	No adverse effect Improved inflammatory mucosa (decreased median histology score), IBDQ scores (in treatment) Decreased CRP and ESR (in both groups), Mayo score (in treatment)
HIV-1 infection	Zhang *et al.* 2013 [70], China	Phase 1/2 Placebo-controlled	Safety and efficacy	IV	0.5 × 10^6/kg 3 injections	6	13	19–55	10/3	12	Increased CD4 T-cell count Decreased plasma CRP and LPS levels Reduced cytokine, TNF-α, G-CSF, PDGF-BB, VEGF, INR levels
Rheumatoid arthritis	Liang *et al.*, 2012 [71], China	Case report	Safety and efficacy	IV	1 × 10^6/kg	None	4	38–53	0/4	7–29 months	No adverse event No remission based on DAS-28 score Reduction in ESR, pain VAS score
RA	Wang *et al.* 2013 [72], China	Phase Phase 2/3 Two arms	Safety and efficacy	IV	4 × 10^7 2 injections (24 and 136 weeks)	36	136 (76; 3 mo; 45; 6 mo; 15; >8 mo)	Avg 45.8	9/127 (Tx only)	3, 6 >8 months	No adverse event Decreased serum protein, globulin, CRP, RF, DAS28, HAQ score, ACR response Increased serum ALB, hemoglobin, Treg cell Improvements in diet, sleep, physical strength

ACR, American College of Rheumatology; ALB, albumin; BILAG, British Isles Lupus Assessment Group; BUN, blood urea nitrogen; C3, complement 3; CRP, C, control; C-reactive protein; DAS28, 28-joint disease activity score; ESR, erythrocyte sedimentation rate; F, female; FU, follow-up; G-CSF: granulocyte-colony stimulating factor; HAQ, Health Assessment Questionnaire; HbA1c, Hemoglobin A1c; IBDQ score, Inflammatory Bowel Disease Questionnaire; ILT2, immunoglobulin-like transcript 2; LO-HC, late-onset hemorrhagic cystitis; LPS, lipopolysaccharides; M, male; mo, months; PBSC, peripheral blood stem cells; PDGF-BB, platelet-derived growth factor-BB; PPG, postprandial plasma glucose; Pt, patient; RA, Rheumatoid arthritis; RF, rheumatoid factor; SMA, superior mesenteric artery; TNF-α, tumor necrosis factor-α; Treg, T regulatory cell; T, treatment; VAS, visual analog scale; VEGF, vascular endothelial growth factor.

[a]Data extracted from abstract.

[b]Articles translated from Chinese.

increased IFNγ and Treg cell numbers, which overall suggested that UC-MSCs stabilized and somewhat reversed the SLE. The second case report (n = 4) on diffuse alveolar hemorrhage due to SLE was published in 2012 by Shi *et al.* [60], which concluded that UC-MSC transplantation resulted in amelioration of oxygen saturation as well as hematologic and serologic changes. In 2013, Wang *et al.* [61] published their 4-year experience in 87 patients with SLE who received IV injections of UC-MSCs compared with allogeneic BM-MSCs. Although results specific to UC-MSCs were not given, the complete remission rate was reported as 50%, whereas the relapse rate was 23%. Wang *et al.* [62], and Yang *et al.* [63] published similar results in patients with refractory SLE. In 2015, Wang *et al.* [64] investigated the mechanism of UC-MSCs in the regulation of peripheral regulatory Treg and T helper 17 (Th17) cells in 30 patients with SLE. They found that UC-MSCs up-regulated Treg cells through a cell–cell contact mechanism, whereas down-regulation of Th17 cells was not dose-dependent and also did not depend on cell–cell contact, rather through the regulation of TGF-β and prostaglandin E2 (PGE2). Gu *et al.* [65] examined the efficacy of BM-MSCs and UC-MSCs in 23 and 58 patients with SLE, respectively, who had refractory nephritis. Although the results were not specifically given for the cell types administered, overall cell transplantation decreased British Isles Lupus Assessment (BILAG) scores, proteinuria, serum creatinine and blood urea nitrogen (BUN) levels and increased glomerular filtration rate (GFR) and SLEDAI scores. In contrast, a recent placebo-controlled, double-blind randomized study by Deng *et al.* [66] reported no difference between the proportion of patients treated with UC-MSCs versus placebo regarding the rate of complete remission. Improvements in serum albumin, complement, renal function, SLEDAI scores and British Isles Lupus Assessment Group scores were also found similar in both groups. Therefore, the authors concluded that UC-MSCs had no apparent additional effect over and above standard immunosuppression.

The efficacy of UC-MSC infusion was also examined in patients with hemorrhagic cystitis occurring after HSCT. So far, two articles, one in Chinese, were published by Jia *et al.* [67] and Wang *et al.* [68]. A total of 15 patients whose ages ranged from 6 to 38 years were enrolled in those two single-arm studies. Both groups reported no remission. Wang *et al.* reported the cessation of hematuria; however, there was a 43% death rate due to GVHD and infection.

Recently, Hu *et al.* [69] examined UC-MSCs in ulcerative colitis in a double-arm (34 in treatment/36 in control), placebo-controlled trial. In the cell-treated group, diffuse and deep ulcer formations and severe inflammatory mucosa improved markedly. The Mayo score and histology score in this group decreased, and inflammatory bowel disease questionnaire (IBDQ) scores significantly improved compared with baseline and the control group's levels.

Zhang *et al.* [70] evaluated the safety and immunologic responses of UC-MSCs in 13 immune non-responding patients with HIV-1 for up to 12 months. Seven patients were administered triple cell transfusions at 1-month intervals, whereas 6 control patients were treated with saline. They noted an increase in circulating $CD4^+$ T-cell counts, a decrease in plasma CRP and LPS levels, reduced cytokines, tumor necrosis factor-α, granulocyte-colony stimulating factor, platelet-derived growth factor-BB, vascular endothelial growth factor and international normalized ratio (INR) levels.

UC-MSCs were also investigated in active and refractory rheumatoid arthritis (RA) in a four-case report by Liang *et al.* [71] and then by Wang *et al.* [72] in a phase 2 study in which 136 patients received IV cell infusions at different time intervals and were followed up for different periods. In the UC-MSC group, evidence of clinical benefits was reported, and the improvements of clinical manifestations were found likely related to the decreased expression levels of various inflammatory cytokines and chemokines (i.e., tumor necrosis factor-α and IL-6), the increased percentage of regulatory T cells in peripheral blood and the up-regulated IL-4 producing Th2 cells, which suggested that the anti-inflammation along with improved immune-modulation and induced immune-tolerance were likely to be the major mechanisms.

Liver diseases

A total of 10 studies were found related with clinical trials of UC-MSCs on liver diseases such as cirrhosis (n = 8), primary biliary cirrhosis (n = 1) and ischemic biliary cirrhosis (n = 1) (Table V).

The Chinese-language article by Lin *et al.* [73] presented the efficacy of IV 0.5×10^6–1.0×10^6/kg of UC-MSCs applied to 38 patients with decompensated liver cirrhosis by comparing the outcomes of 16 control patients. They noted that quality of life of most patients treated with the UC-MSCs improved; however, no difference was found between the two groups when blood glucose, total cholesterol, urea nitrogen, α-fetoprotein (AFP) levels, leucocyte count and prothrombin activity (PA) were taken into consideration. In contrast, Zhang *et al.* [74] noted (i) a significant reduction in ascites volume; (ii) improvement in liver function based on alterations of blood albumin levels and total serum bilirubin (TBIL), international normalized ratio and Model for End-Stage Liver Disease (MELD) scores; and (iii) decrease of the liver fibrosis markers such as serum laminin, hyaluronic acid, pro-collagen type III N-terminal peptide and type IV collagen levels in patients with decompensated liver cirrhosis (n = 30) who

Table V. Administration of UC-MSCs in liver diseases.

Disease/ pathology	Authors, year (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period (months)	Clinical/laboratory outcome
						C	T				
Cirrhosis	Lin *et al.*, 2012[a] [73], China	Phase 1/2 Two arms	Safety and efficacy	IV	0.5–1.0 × 10^6/kg	16	38	25–74	ND	12	Increased quality of life in varying degrees No change in GLU, TC, BUN, AFP, WBC and PA
Cirrhosis	Zhang *et al.*, 2012 [74], China	Phase 1/2 Two arms	Safety and efficacy	IV	0.5 × 10^6/kg/infusion 3 injections	15	30	25–64	40/5	12	No adverse effect Reduced ascites volume (in treatment) Improved liver function Increased ALB, decreased TBIL, INR, MELD Na score (in treatment)
Cirrhosis	Xue *et al.*, 2015 [75], China	Phase 2 Single arm	Safety and efficacy	Hepatic artery	30 × 10^6	None	50 (18 alcoholic liver, 37 hepatitis B, 2 hepatitis C)	32–78	36/14	6	Increased ALB, PALB, TBIL, ALT, AST Decreased APTT, MELD score
Cirrhosis	Liang *et al.*, 2017 [76], China	Phase 1	Safety and efficacy	IV	1 × 10^6/kg	None	23	35–70	1/22	8–70	Four patients died during follow-up Decreased TBIL, PT Increased serum ALB
Cirrhosis (HBV infected)	Shi *et al.*, 2012 [77], China	Phase 1/2 Two arms	Safety and efficacy	IV	0.5 × 10^6/kg 3 injections	19	24	24–59	35/8	12–18	No adverse effect Deaths: 72-week follow-up 20.8% (in treatment) 47.4% (in control) Decreased MELD score, ALT, TBIL, increased platelet count, ALB, TC, total protein
Cirrhosis (HBV infected)	Li *et al.* 2016 [78]. China	Phase 1/2 Two arms	Safety and efficacy	Hepatic artery	1 × 10^8	34	11	40–62	34/11	24	Survival at 24 months Deaths: 45% (in treatment) 76.5% (in control) Improved ALB, PT, INR HCC: 10% (in treatment) 3% (in control)
Cirrhosis (HBV infected)	Yu *et al.* 2016[a] [79]. China	Phase 2 Two arms	Efficacy	IV	0.5–1.0 × 10^6/kg 3 injections	120	60	18–70	156/24	24	Increased CHE, globulin and ALP Decreased Child-Pugh scores (in treatment) No change in ALT, TBIL, ALB, TC or PA
Cirrhosis (HBV infected)	Shi *et al.*, 2017[b] [80], China	Phase 3 Double arm	Efficacy	IV	0.5–1.0 × 10^6/kg 3 injections	120	110	ND	ND	80	No complication or side effect Increased survival rate
Primary biliary cirrhosis	Wang *et al.*, 2013 [81], China	Phase 1 Single arm	Safety and efficacy	IV	0.5 × 10^6/kg 3 injections	None	7	33–58	1/6	12	No adverse effect Decrease in serum ALP, GGT levels Alleviation of fatigue
Ischemic-type biliary cirrhosis	Zhang *et al.*, 2017 [82], China	Phase 1/2 Two arms	Safety and efficacy	IV	1 × 10^6/kg 6 injections	70	12	31–57	13/69	24 months	Short-term fever, allergic reaction, hypotension (in treatment) No long-term adverse effect Deaths: 8% (in treatment) 14% (in control) RT: 16% (in treatment) 31% (in control) No change in TBIL, GGT, ALP (in treatment)

ALB, serum albumin; APTT, activated partial thromboplastin time; BUN, blood urea nitrogen; CHE, cholinesterase; C, control; F, female; FU, follow-up; GLU, serum glucose; HB, hemoglobin; HCC, hepatocellular carcinoma; PALB, serum pre-albumin; Pt, patient; PT, prothrombin time; RT, repeat transplantation; TBIL, total serum bilirubin; TC, total cholesterol; T, treatment; WBC, white blood cell.

[a]Manuscripts translated from Chinese.

[b]Data extracted from the abstract.

were treated with 0.5×10^6/kg of UC-MSCs (triple injections with 1-month intervals) compared with saline-injected patients (n = 15) as a control group after a 12-month follow-up period. Xue *et al.* [75] tested the efficacy of 30×10^6 UC-MSCs delivered via the hepatic artery to 50 patients with decompensated cirrhosis caused by miscellaneous etiologies such as alcoholic liver disease, chronic hepatitis B and chronic hepatitis C. They found improvements in disease symptoms including abdominal distension, oliguria, edema and inappetence compared with baseline. They also noted that serum albumin and pre-albumin levels, and MELD scores increased significantly, but the decrease in coagulation markers and increase in AFP levels were not significant during the 6 months of follow-up. The differences in the liver and thrombin functions were found significant in all groups with the exception of the hepatitis B virus group. Liang *et al.* [76] reported the results of a phase 1 trial on 23 patients with cirrhosis. The authors reported the death of four patients during follow-up (8–70 months). The remaining patients displayed decreased TBIL, prothrombin time (PT) and increased serum albumin levels.

The efficacy of UC-MSC treatment in liver cirrhosis due to HBV infection was reported in three full articles and one symposium abstract. In 2012, Shi *et al.* [77] reported that triple IV injections of 0.5×10^6/kg of UC-MSCs with 4-week intervals to 24 patients caused a reduction in MELD scores, serum alanine aminotransferase (ALT) and TBIL and an increase in platelet counts, PA, serum albumin, hemoglobin and protein levels, indicating that UC-MSC treatment improved liver function and alleviated liver damage compared with control patients (n = 10) over a 12-month follow-up period. Survival rates were also found higher in the treatment group after 18 months of follow-up. Similarly, Li *et al.* [78] transfused 1×10^8 UC-MSCs to 11 patients via the hepatic artery. They documents improved levels of albumin, ALT, aspartate aminotransferase (AST), TBIL, direct bilirubin, PT, INR and MELD scores, many of which became manifest from the fourth week of follow-up until the 24th week. They also noted that the cell-treated group had higher cumulative survival rates, but comparable levels of creatinine, white blood cells, hemoglobin, and platelet counts compared with the outcomes of 34 control patients. Yu *et al.* [79] tested the efficacy of a similar cell dose and delivery route in 60 patients compared with 120 control patients and reported a significant increase in cholinesterase, globulin and alkaline phosphatase (ALP) and decreased Child-Pugh score, which assesses the prognosis of chronic liver disease. They noted no significant difference in the levels of ALT, TBIL, albumin, total cholesterol or PA between the groups during their 24-month follow-up period. Recently, the survival rate of 110 patients with HBV-infected liver cirrhosis was reported to increase after cell infusion compared with 120 control patients [80].

Wang *et al.* [81] analyzed the efficacy of UC-MSCs (0.5×10^6/kg, three IV injections with 1-month intervals) on seven patients with primary biliary cirrhosis, a progressive autoimmune liver disease, during 48 months of follow-up by comparing baseline values. They reported a significant decrease in serum ALP and gamma-glutamyltransferase (GGT) levels along with improvements in symptoms such as fatigue and pruritus. They found no significant changes in serum ALT, AST, TBIL, albumin, PA, INR or immunoglobulin M levels. Recently, Zhang *et al.* [82] published the results of 12 patients with ischemic biliary cirrhosis who had undergone liver transplantation and 70 control patients; all patients were monitored during a 2-year follow-up period. They injected 1×10^6/kg UC-MSCs IV six times with 1- to 4-week intervals and noted that cell treatment significantly reduced the requirement of interventional therapies, including endoscopic retrograde cholangiopancreatography or percutaneous cholangio-drainage and biliary stenting. Cell transplantation also improved 1-year graft survival rates, whereas TBIL, GGT and ALP levels were comparable.

Seven of the aforementioned studies also evaluated the safety of UC-MSC application. None noted any long-term cell-based adverse effects. Nonetheless, a self-limiting short-term (<6 hours) fever (<38°C) was noted by Shi *et al.* (2/24 patients) [77], Zhang *et al.* (4 /45) [74], Wang *et al.* (1/7) [81] and Zhang *et al.* (1/12) [82] as a short-term adverse effect of the application. Interestingly, perhaps coincidentally, cells were administered IV at least three times in the fever-reporting studies, whereas the two studies in which cells were given through the hepatic artery did not report fever. Therefore, we propose that this should be considered as a safety issue for future studies.

Cardiac disease

Ischemic coronary artery diseases such as acute myocardial infarction (AMI), frequently followed by a varying degree of heart failure (HF), are still the primary cause of deaths worldwide. Cellular therapy approaches to necrotic myocardium include the administration of various stem/progenitor cells, some of which are obtained from healthy donors. Among those, human umbilical cord stroma is a relatively new tissue that gives rise to the isolation of clinical grade MSCs used in allogeneic transplantations to restore cardiac function, mostly in phase 1/2 trials since the early 2010s. To date, seven trials have been reported as full articles [83–88] and one study design [89] and one

abstract of preliminary results [90] in ischemic cardiomyopathies (Table VI). Safety was targeted as the primary endpoint in almost all of these studies. In general, transplanted cells ranging from 3×10^6 to 30×10^6 cells per patient were found safe with no major adverse effects during and/or after delivery of cells into coronary arteries via percutaneous coronary intervention (PCI) (Table VI). All deliveries were tested only once in a single session of intervention. With the exception of one report by Zhao *et al.*, the other authors reported no adverse effects that were different between the treatment and control groups. Zhao *et al.* [88] reported a series of adverse effects in patients with decompensated congestive HF after intracoronary injections of UC-MSCs. Among the 30 patients in the treatment group, one experienced chest discomfort and showed ST-T changes. Nonetheless, spontaneous remission was achieved 15 min after the physiologic chest pain, chest tightness, dyspnea, or other symptoms.

As the secondary endpoint, the efficacy and feasibility of infused UC-MSCs were tested in various delivery routes such as intracoronary [85,86,88], intramyocardial (HUC-HEART Trial) [90], transcoronary [87] and IV [84]. Li *et al.* [86] infused three dosages of cells (3×10^6–5×10^6) intracoronary to 15 older patients (aged 81–92 years) with chronic total coronary occlusion and found a 15% increase in left ventricular ejection fraction (LVEF) after 24 months, a 21% decrease in infarct area, and a decline of New York Heart Association (NYHA) class III to I. The LVEF values, however, obtained using echocardiography and single-photon emission computed tomography (SPECT) revealed no significant difference between the cell doses given. Gao *et al.* [85] conducted a randomized, double-blind, placebo-controlled (1:1) study in patients with MI (n = 116) with ST elevation. After 18 months of follow-up, they reported a 7.8% LVEF increase in the treatment group compared with 2.8% in the placebo-controlled group. Significant improvements were also noted in left ventricle end-diastolic volume (LVEDV) and left ventricle end-systolic volume (LVESV) at 18 months. Musialek *et al.* [87] applied 30×10^6 UC-MSCs to coronary arteries using a technique called "trans–infarct-related artery (IRA)" to 10 patients with AMI and monitored them for 12 months for the safety of the procedure. They reported no adverse effects; no data were given regarding the efficacy of the infused cells. Zhao *et al.* [88] and Fang *et al.* [84] evaluated the therapeutic efficiency of intracoronary (n = 30) and IV (n = 3) administered cells in patients with congestive HF, respectively. Zhao *et al.* found that after 6 months of follow-up, LVEF increased 19% in treated patients versus 11% in controls. They also reported an increase in 6-minute walking distance and a decrease in serum B-type natriuretic peptide levels. Fang *et al.* reported 12-month results of three patients, some of whom demonstrated a 16% decrease in LVEF, even though all three patients' NYHA classes improved significantly.

Conclusively, UC-MSC transplantations were found safe and efficient in restoring cardiac function, as detected using routine or sophisticated imaging techniques such as positron emission tomography and single-photon emission tomography in a relatively short post-transplantation period. However, there are certain discrepancies regarding the route of cell delivery, patient inclusion criteria, age range, state of disease and duration of follow-up, all of which give rise to two main concerns in the efficacy of the therapeutic intervention: (i) inconsistency of results and (ii) difficulty of cohort analysis due to the aforementioned variables. Therefore, for the clarity of efficacy, we suggest that more precise inclusion and exclusion criteria should be taken into account for future studies.

Endocrine diseases

We found a total of six clinical studies related to endocrine disorders after the literature database search (Table VII). In brief, three studies evaluated the efficacy of UC-MSCs on type 2 diabetes mellitus (T2DM) [91–93] and one focused on diabetic foot in T2DM [94]. The remaining two studies analyzed the safety and efficacy of UC-MSC administration on type 1 diabetes mellitus (T1DM), which is an autoimmune disease. Among these, five studies took into consideration the safety of cell administration, and none reported any long-term adverse effects.

Although little information could be extracted from the English abstract by Kong *et al.*'s [91] cell (quantity not specified) injections to 18 patients, it resulted in a decrease in both fasting and post-prandial blood glucose levels after 6 months. In Liu *et al.*'s phase 1/2 study [92], cells (1×10^6/kg) were given to 23 patients with T2DM via the peripheral vein, and 5 days later into the pancreatic artery, and changes in levels of glycated hemoglobin (HbA1c) and C-peptide were determined as primary endpoints. Additionally, insulin dosage, fasting, and post-prandial blood glucose levels, inflammatory markers, and T-lymphocyte counts were considered as secondary endpoints after 12-month follow-up. They noted a progressive and significant decrease in HbA1c levels following the first month of treatment as evidenced by reaching the lowest levels ($6.89 \pm 0.90\%$) after 3 months. After the first 3 months, HbA1c levels were stable to the end of the follow-up period. The authors also indicated that blood glucose and C-peptide levels showed a similar decreasing pattern. One of the five patients, who had been treated with oral anti-diabetic drugs, became completely drug-free, and the oral drug use of the remaining four

Table VI. Administration of UC-MSCs in cardiac disease.

Disease/ pathology	Authors, year (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period (months)	Concurrent procedure	Clinical/laboratory outcome
						C	T					
Chronic coronary occlusion	Li *et al.*, 2015 [86], China	Phase 1/2 Single arm No randomization Single Blind	Safety and feasibility of dose escalating infusion	IC	3×10^6 4×10^6 5×10^6	None	15	81–92	9/6	24	PCI	No major adverse effect Increase in LVEF 8.2% (12 months); 15% (24 months) Decrease in infarct area 29% (12 months); 21% (24 months) Decline of NYHA class III to II (12 months); III to I (24 months)
Chronic ischemic cardiomyopathy	Can *et al.*, 2017[a] [90], Turkey	Phase 1/2 Three arms Randomized Double blind	Safety and efficacy	IMC	20×10^6	4	18 hUC-MSC; 4 BM-MNC	30–80	28/0	6	CABG	No major adverse effect Increased LVEF in hUC-MSC and BM-MNC groups
Acute ST elevation MI	Gao *et al.*, 2015 [85], China	Phase 1/2 Two arms Randomized, Double blind, Placebo-controlled	Safety and efficacy of	IC	6×10^6	58	58	32–65	58/58	18	PCI	No major adverse effect 7.8% LVEF increase (in treatment) 2.8% LVEF increase (in control group) Improvements in LVEDV at 18 months
Acute ST elevation MI	Bilal *et al.*, 2015 [83], Pakistan	Phase 1/2 Two arms Randomized Placebo-controlled Double blind	Safety and efficacy	IC	6×10^6	No data	116	No data	No data	18	PCI	No major adverse effect Increased myocardial viability and perfusion Increased LVEF
AMI	Musialek *et al.*, 2015 [87], Poland	Phase 1, Single arm No randomization	Safety and feasibility of a novel myocardial regeneration strategy	TC	30×10^6	None	10	18–80	5/5	12	PCI	No major adverse effect
Severe systolic heart failure	Zhao *et al.*, 2015 [88], China	Phase 1/2, Two arms No randomization	Efficacy in systolic heart failure	IC	ND	29	30	18–80	43/16	6	PCI	Increase in LVEF: 11 (control); 19% (treatment), Mortality low in treatment Chest discomfort, ST-T changes Increase in 6-minute walking distance Decrease in NT-proBNP levels
Congestive heart failure	Fang *et al.* 2016 [84], China	Pilot No randomization	Restore of cardiac muscle function	IV	$5–10 \times 10^6$	None	3	37, 53, 65	2/1	12	None	Decrease in LVEF: 16% (one patient) Increase in LVEF: 36% and 15% (2 patients) Decline of NYHA Class III to II and III to I

CABG, coronary artery bypass grafting; C, control; F, female; FU, follow-up; IC, intracoronary; IMC, intramyocardial; M, male; NT-proBNP, B-type natriuretic peptide; PCI, percutaneous coronary intervention; Pt, patient; TC, transcoronary; T, treatment.

[a]Data extracted from the abstract.

Table VII. Administration of UC-MSCs in endocrine diseases.

Disease/ pathology	Authors, year (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period (months)	Clinical/laboratory outcome
						C	T				
T2DM	Kong *et al.*, 2014 [91], China	Phase 1	Safety and efficacy	IV	No data	No data	18	No data	No data	6	No adverse effect Decreased FPG and PBG levels
T2DM	Liu *et al.*, 2014 [92], China	Phase 1/2	Safety and efficacy	IV, IPA	1×10^6/kg	None	23	42–62	16/7	12	No adverse effect Decreased plasma glucose, HbA1c, markers of systemic inflammation and T-lymphocyte counts Improvement in C-peptide levels and beta-cell function
T2DM	Chen *et al.*, 2016[a] [93], China	Phase 1	Efficacy	IV, IPA	1×10^6/kg	6	6	No data	No data	6	Decreased in FPG, PBG, HbA1c and HOMA-IR Increased in early-phase and total C-peptide secretion function
Diabetic foot	Qin *et al.*, 2016 [94], China	Phase 1/2	Safety and efficacy	Local implantation	$4.8–8.6 \times 10^7$	25	28	48–86	32/21	3	No adverse effect Improvements in skin temperature, ABPI, TOT, claudication distance, new vessel formation, ulcer healing.
T1DM	Hu *et al.*, 2013 [95], China	Phase 2 Double arms Randomized Double blind Placebo-controlled	Safety and efficacy	IV	$1.5–3.2 \times 10^7$ 2 injections	14	15	9–26	17/12	21	No adverse effect Decreased PPG, HbA1c, insulin requirement Increased fasting C-peptide, CPGR; no ketoacidosis appeared
T1DM	Cai *et al.*, 2016 [96], China	Phase 1/2 Double arms Randomized	Safety and efficacy	IPA	1.1×10^6/kg (hUC-MSC) 107×10^6/kg (BM-MNC)	21	21 (hUC-MSC+ BM-MNC)	18–40	20/22	12	Improved fasting C-peptide, insulin Decreased HbA1c, fasting glycaemia, daily insulin requirements No conversion from GADA negativity to GADA positivity

ABPI, ankle-brachial pressure index; C, control; CPGR, mean C-peptide/glucose ratio; F, female; FPG, fasting plasma glucose; FU, follow-up; HbA1c, Hemoglobin A1c; HOMA-IR, homeostasis model assessment of insulin resistance; IPA, intrapancreatic artery; m, male; PBG, postprandial blood glucose; Pt, patient; TOT, transcutaneous oxygen tension; T, treatment.

[a]Articles translated from Chinese.

patients reduced more than 50%. The authors also noted that insulin requirements of 17 patients who used insulin significantly decreased after the first month of treatment. Moreover, they found a significant drop in the number of $CD3^+$ and $CD4^+$ T lymphocytes, and also IL-6 and IL-1β levels after 6 months of the study. Therefore, they concluded a significant beneficial effect of UC-MSC application based on the aforementioned outcomes. Considering the safety issue, they reported a self-limiting short-term fever in three patients.

In the abstract of Chen *et al.*'s study [93], cells were administered to the pancreatic artery and then the peripheral vein in six patients who were compared with six saline-infused patients after a 6-month follow-up period. They reported a decrease in levels of fasting and post-prandial glucose, HbA1c and homeostasis model assessment of insulin resistance and an increase in early-phase and total C peptide secretion function, which indicated a beneficial effect of UC-MSC administration in their treatment group. Qin *et al.* [94] evaluated the safety and efficacy of local implantation of 4.8×10^7–8.6×10^7 UC-MSCs to 28 patients (34 limbs) receiving conventional T2DM therapy accompanied by lower extremity artery stenosis/occlusion by comparing them with 25 patients (38 limbs) receiving conventional therapy over a 3-month follow-up period. They found improvements in skin temperature, ankle-brachial pressure index, transcutaneous oxygen tension, claudication distance, new vessel formation and ulcer healing compared with control and/or baseline levels.

In Hu *et al.*'s [95] placebo-controlled, randomized, double-blind study, IV-injected saline as the control group (n = 14) was compared with a 1.5×10^7–3.2×10^7 cell-injected treatment group (n = 15) in patients with new-onset T1DM. They repeated cell injections 1 month later, and thereafter analyzed the safety and efficacy of UC-MSC administration during 21 months of follow-up. They noted an insignificant reduction in the levels and fluctuations of fasting blood glucose but a significant decrease in post-prandial blood glucose and HbA1c levels in the cell-treated group following the 9 months of follow-up compared with baseline values or the control group. Moreover, they indicated a significant improvement of insulin requirements, fasting C-peptide levels and C-peptide/glucose ratio after 6 months of follow-up. Considering the transition of glutamic acid decarboxylase antibody (GADA)-positive patients to a negative stage, they noted that 6 of 11 of patients in the cell treatment group and 3 of 10 patients in the control group who became negative meant that the difference was not significant.

The safety and efficiency of UC-MSCs were not investigated alone but in association with BM-MNCs infusions in patients with T1DM by Cai *et al.* [96]. The authors infused 1×10^6/kg UC-MSCs along with BM-MNCs to the pancreatic artery in patients (n = 21) and compared the outcomes to those in the standard clinical treatment group (n = 21) during 1-year follow-up. They found a significant decrease in HbA1c levels, exogenous insulin requirement and fasting blood glucose levels after 3 months. In contrast, Hu *et al.* [95] found no significant difference in fasting blood glucose levels. Improvements of the area under the curve results obtained from C-peptide and insulin during oral glucose tolerance tests were found significant in cell treatment groups compared with baseline and/or controls. They also reported no significant transition of GADA-positive patients to a GADA-negative stage in parallel to the Hu *et al.* study.

All the studies described in this section demonstrated that UC-MSC application in T1DM and T2DM was a safe and an efficient therapy option, even though the former is an autoimmune disease and the latter a metabolic disease. On the other hand, it seems that large-scale placebo-controlled, longer follow-up clinical studies in DM and other endocrine diseases, some of which are caused by immune system impairment, are still required.

Musculoskeletal diseases

We found seven studies that considered the effects of UC-MSCs on muscle or bone diseases (Table VIII). Interestingly, none focused on cartilage or related disorders.

In two studies, the therapeutic effects of UC-MSCs were evaluated in Duchenne and Becker muscular dystrophies (MD, respectively), which are X-linked genetic degenerative muscular disorders caused by a deficiency in dystrophin protein production, thus affecting the skeletal and cardiac muscles and leading to early death in the second or third decade. In the meeting abstract by Patel and Riordan [97], seven IV and intramuscular UC-MSC injections improved the life quality of a 28-year-old male patient with Duchenne MD with no significant adverse effects after 6 months of follow-up. Li *et al.* [98] analyzed the effects of UC-MSCs on patients with Becker MD (n = 3) who were members of the same family. They injected (IV) 3×10^7 cells to a 6-year-old boy who had a family history and disease symptoms but had not yet reached the age of Becker MD onset and 5×10^7 cells to two adult male patients who had typical clinical manifestations, including the degeneration of muscle fibers, progressive atrophy of proximal limb muscles and pseudo-hypertrophy of gastrocnemius muscles. The authors examined the patients at 1, 3, 4 and 12 weeks after cell transplantation and found increased muscle strength, appetite and food intake,

Table VIII. Administration of UC-MSCs in musculoskeletal diseases.

Disease/ pathology	Authors, year, (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period (months)	Clinical/laboratory outcome
						C	T				
Duchenne MD	Patel and Riordan 2015[a] [97], United States	Case report	Safety	IV and IM	No data 7 injections	None	1	28	1/0	6	No adverse effect
Becker MD	Li *et al.*, 2015 [98], China	Case report	Efficacy	IV	$3–5 \times 10^7$	None	3	6–50	3/0	3	Increased muscle strength, appetite, food intake Improved walking gait (1 patient) Decreased CK, LDH levels No obvious muscle regeneration
Bone nonunion	Qu *et al.*, 2009[a] [99], China	Phase 1/2 Two arms	Safety and efficacy	Local implantation with PRP and bone powder	$1–10 \times 10^6$	36 (auto-logous bone graft)	36 (hUC-MSC)	32–38	28/8	18	No adverse effect The time of bone union faster
Bone nonunion	Qu *et al.*, 2015 [100], China	Case report Two arms	Safety and efficacy	Local implantation with plasma	1×10^8	None	6 (hUC-MSC) 3 (BM-MNC)	19–54	6/3	36	No complications Better in promoting bone healing Reduced treatment-related dissatisfaction
Infected bone nonunion	Dilogo *et al.*, 2017 [101], Indonesia	Case report	Efficacy	Local implantation with BMP-2 and hydroxyapatite	5×10^7	None	1	54	0/1	12	No postoperative complications and adverse events Able to perform full weight-bearing walk with no pain, LEFS 65%, with no change in leg length discrepancy
Osteonecrosis of femoral head	Cai *et al.*, 2014 [102], China	Single arm	Efficacy	Femoral artery	BM-MNC (60×10^6/kg) hUC-MSC (1×10^6/kg)	None	30 (49 hips)	19–63	24/6	12	Relieved pain, improved joint function, extended walking distance
Osteonecrosis of femoral head	Chen *et al.*, 2016 [103], China	Retrospective	Efficacy	Femoral artery	$0.5–1.0 \times 10^7$	None	9	28–51	4/5	24	No adverse effect Increase in ODI, Harris score Decrease in necrotic volume of femoral heads

BMP-2, bone morphogenetic protein-2; C, control; F, female; FU, follow-up; IM, intramuscular; LEFS, Lower Extremity Function Scale; m, male; ODI, oxygen delivery index; PRP, platelet rich plasma; Pt, patient; T, treatment.

[a]Data extracted from the abstract.

but no obvious signs of muscle regeneration in all patients. Considering the 6-year-old boy, they noted that although the walking gait was gradually improving, blood creatine kinase (CK) and lactate dehydrogenase (LDH) levels, which are poor prognostic factors, gradually increased after the first week of the treatment, along with eosinophilic material deposition in his muscles. Walking gait did not change in the adults; however, blood CK and LDH levels remained stable during follow-up. The authors found no obvious muscle regeneration in the biopsies of any of the patients and reported no adverse reactions caused by the treatment.

Qu *et al.* [99] injected 1–10 $\times$ 10^6 of UC-MSCs together with platelet-rich plasma (PRP) and demineralized bone powder directly to the fracture areas of 36 patients with bone nonunion. After comparing them with 36 patients with bone nonunion who were receiving traditional treatment (controls), they found a significantly increased bone union time in the cell-treated group and no adverse effects such as deep infection, rejection and general fever reaction and/or loosening and breakage of internal fixation after 18 months of follow-up. A few years later, the same group published a comparative study [100] in which they applied UC-MSCs (1×10^8 cells) to the fractures of six patients with bone nonunion, while treating the fractures of three patients with autologous BM-MNCs. After 36 months of follow-up, they found comparable clinical healing times with no complications and reduced treatment-related dissatisfaction of patients. Recently, Dilogo *et al.* [101] reported a case of a 54-year-old female patient who had several surgeries and ended up with an infected nonunion right femoral shaft. The patient was treated with a combination of UC-MSCs, bone morphogenetic protein-2, hydroxyapatite and mechanical stabilization using Masquelet technique. The combined therapy and Masquelet technique was found successful in creating new bone with no apparent side effects.

Three studies evaluated the efficacy of UC-MSCs injections on osteonecrosis of femoral heads or shaft. Cai *et al.* [102] enrolled 30 patients with avascular necrosis of the femoral head and infused a mixture of autologous BM-MNCs (60×10^6/kg) and UC-MSCs (1×10^6/kg) to 49 hips via the femoral artery, and determined the study endpoints as follows: (i) Harris scores for the evaluation of pain relief, joint function and walking distance and ii) alterations in images obtained using computed tomography and radiography to analyze bone destruction during 12 months of follow-up. They found a significant increase in Harris scores beginning from the third month of the study and a reduction of bone destruction in 89.7% hips, which remained stable for 12 months. They reported no adverse effects. Chen *et al.* [103] infused 5×10^6–1×10^7/mL of UC-MSCs via the femoral artery to nine patients (nine hips) with early-stage osteonecrosis of the femoral head and monitored them for 24 months. They noted a significant decrease in the necrotic volume of the femoral heads, and an increase in Harris scores and oxygen delivery index. They also detected that the preoperative levels of red cell count, hemoglobin, hematocrit, mean cell volume, mean cell hemoglobin concentration and red cell distribution width significantly reduced 3 days after the operation and concluded that "this was advantageous to the red blood cells through newborn capillaries to carry oxygen."

Pulmonary diseases

We found three trials that analyzed the effects of UC-MSCs on pulmonary diseases (Table IX). Two articles were written in Chinese; therefore, we extracted data from the English abstracts and from the translated manuscripts.

Han *et al.* [104] investigated the effects of UC-MSCs on pulmonary infections in patients with haplo-HSCT (n = 41); 42 with haplo-HSCT who received no UC-MSC injections served as the control group. They reported no obvious statistical difference between the two groups and concluded that UC-MSC infusions did not increase the infection rate in patients with haplo-HSCT. Liu *et al.* [105] evaluated the safety and efficacy of 1×10^6/kg UC-MSCs on lung injury caused by acute paraquat poisoning (n = 5) by comparing a conventional treatment group as controls (n = 8). They used the Sequential Organ Failure Assessment for the evaluation of organ function and lung injury scores and found that both scores significantly decreased in the cell treatment group. They also noted that all patients survived with no discomfort and showed normal liver, kidney, and lung functions; only one patient survived in the control group. Additionally, they reported no adverse reactions such as chill and fever caused by cell application.

Recently, Zhang *et al.* [106] reported a 56-year-old male pulmonary fibrosis patient. After 12 months of IV injection of 5×10^7–1×10^8 cells, a reduction of long-term oxygen therapy requirement was noted; improvements in terms of physical performance, quality of life, and respiratory parameters were observed.

Skin diseases

To date, the safety and/or efficacy of UC-MSCs have been tested in only two clinical trials in generalized skin diseases (Table X). In a case report by Li *et al* [107]. UC-MSCs were transplanted (neither cell delivery route nor quantity were indicated in the manuscript) to three female patients with drug-induced Stevens-Johnson syndrome, which is an acute inflammatory disease of the skin and mucosal

Table IX. Administration of UC-MSCs in pulmonary diseases.

Disease/pathology	Authors, year, (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period	Clinical/laboratory outcome
						C	T				
Pulmonary infection	Han et al., 2014[a] [104], China	Two arms	Efficacy	No data	$6–8 \times 10^6$/kg	42	41	2–44	58/25	No data	No increased infection (bacterial, CMV) rate (in hUC-MSC-infused group)
Paraquat-induced lung injury	Liu et al., 2012[b] [105], China	Two arms	Efficacy	No data	1×10^6/kg	8	5	13–38	4/9	3–18 days	No adverse effect Decreased SOFA, LIS scores (in treatment) No death; normal liver, kidney and lung functions (in treatment); death: 12.5% (in control)
Pulmonary fibrosis	Zhang et al., 2017 [106], China	Case report	Efficacy	IV	5×10^7-1×10^8	0	1	56	1/0	12 months	Improvements in physical performance, quality of life, and respiratory parameters Reduction in long-term oxygen therapy

BPD, bronchopulmonary dysplasia; CMV, cytomegalovirus; C, control; F, female; FU, follow-up; LIS, Lung Injury Score; m, male; MMP, matrix metalloproteinases; SOFA, Sequential Organ Failure Assessment; TGF, transforming growth factor; TNF, tumor necrosis factor; Pt, patient; T, treatment.
[a]Data extracted from the abstract.
[b]Articles translated from Chinese.

Table X. Administration of UC-MSCs in skin diseases.

Disease/pathology	Authors, year, (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period	Clinical/laboratory outcome
						C	T				
Drug-induced Steven-Johnson syndrome	Li *et al.*, 2013 [107], China	Case report	Safety and efficacy	No data	No data	None	3	42–62	0/3	12 days	No adverse effect Mucosa ulcer gradually healed, skin became dry
Psoriasis vulgaris	Chen *et al.*, 2016 [108], China	Case report	Efficacy	No data	1.0×10^6/kg	None	2	26, 35	1/1	48–60 months	No adverse effect Decrease in lesions, skin returned to normal

C, control; F, female; FU, follow-up; m, male; Pt, patient; T, treatment.

membranes. The authors noted that the patient's mucosal ulcers gradually healed and their skin became dry at day 12 after cell transplantation.

Chen *et al*. [108] published a two-patient case report presenting the outcomes of UC-MSC treatment in psoriasis, an incurable immune-mediated skin disease. They administered one dose (1×10^6/kg) of cells to support the engraftment of autologous HSCT in patients who had had psoriasis for 12 years and were later diagnosed as having diffuse large B-cell lymphoma. The authors noted that skin lesions, as well as engraftments recovered gradually, and then lymphoma underwent complete remission, psoriasis lesions were significantly relieved after 6 months and the skin returned to normal after 12 months, their condition remained stable, and no recurrence of lymphoma or psoriasis after 5 years was noted. The other patient, who was diagnosed as having psoriasis vulgaris, initially received three infusions of UC-MSCs (1×10^6/kg each time) over 3 successive weeks. After the first three injections, the authors applied two more cell injections after 3 months because her whole body surface gradually turned smooth. They reported that the psoriasis had been in relapse for 4 years.

Ophthalmologic diseases

Only one meeting abstract was found regarding the use of UC-MSC treatment on retinitis pigmentosa, a hereditary, progressive retinal degeneration of retinal photoreceptor cells, which is characterized by severe vision loss (Table XI). In first-in-human study, Francis *et al*. [109] transplanted 47 500 to 470 000 cells transvitreally to the subretinal space after retinotomy in seven patients with advanced retinitis pigmentosa with decreased visual capacity and no better than hand-motion vision. They reported that none of the patients had any signs of immune rejection or postoperative visual loss. Two patients developed retinal detachment related to non-closure of the retinotomy site, and one patient improved in the full-field stimulus threshold test, which determines the luminance threshold for detection of a single stimulus flash [110] after more than 1 year of follow-up.

Discussion

It is tempting to speculate that UC-MSC treatment would control disease activity in a series of conditions including autoimmune disorders through immunosuppressive and anti-inflammatory functions and by contributing to tissue repair, thereby preventing tissue damage, once established, from continuing to trigger inflammation. The mechanisms through which UC-MSCs can influence disease processes are diverse and include immunosuppressive and anti-inflammatory effects, trophic/paracrine effects

Table XI. Administration of UC-MSCs in ophthalmologic diseases.

Disease/ pathology	Authors, year, (reference), study location	Study design	Rationale	Delivery route	Cell quantity	Pt number		Pt age	Pt sex (M/F)	FU period	Clinical/laboratory outcome
						C	T				
Retinitis pigmentosa	Francis *et al*., 2010[a] [109], United States	Phase 1	Safety and efficacy of subretinal cell injection	Subretinal	47×10^3–47×10^4	None	7	41–70	3/4	>12 months	No immune rejection or postoperative visual loss Retinal detachment in 2 patients Improvement in FFST

C, control; F, female; FFST, full-field stimulus thresholds; FU, follow-up; m, male; Pt, patient; T, treatment.
[a]Data extracted from the abstract.

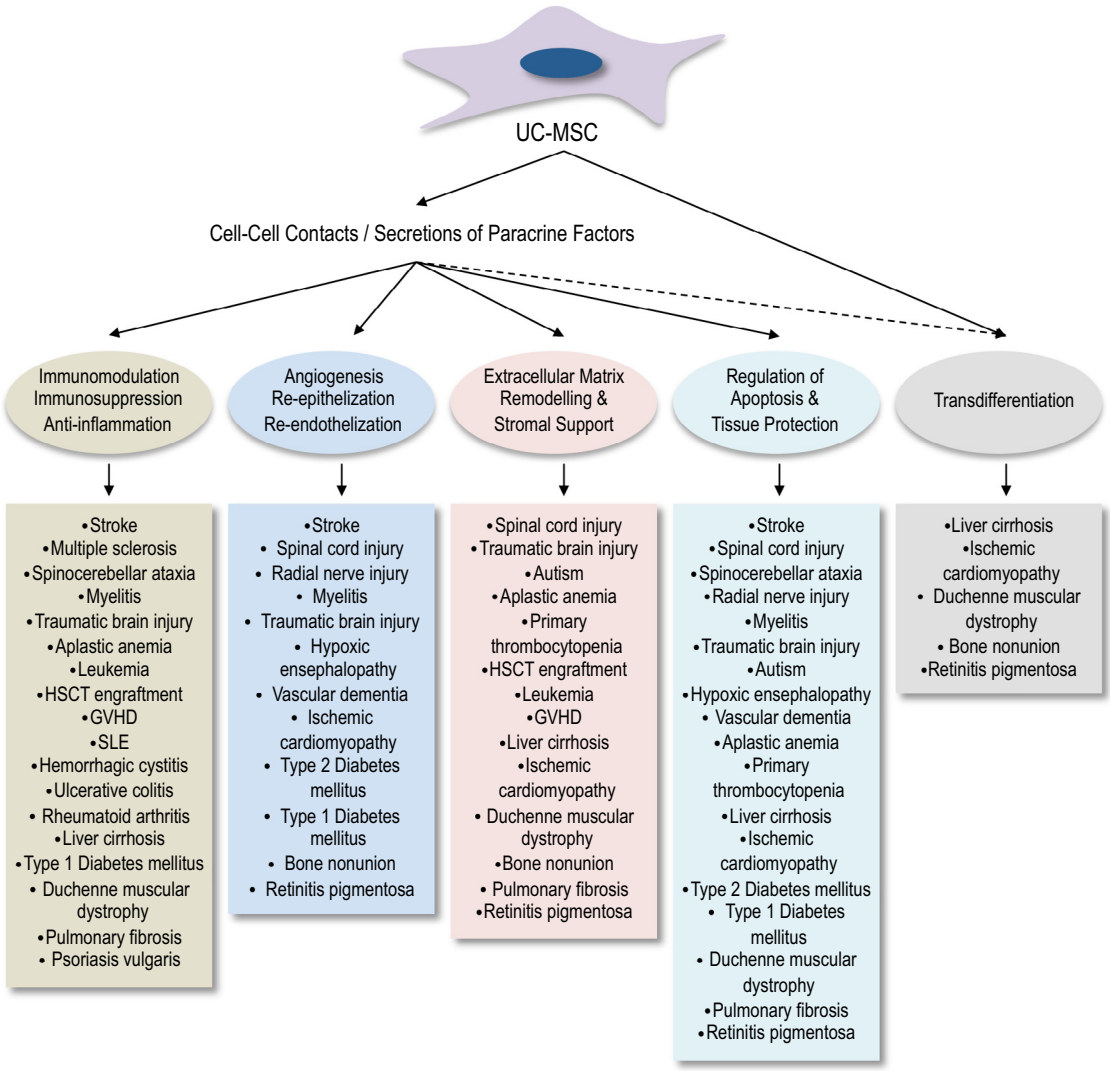

Figure 2. Proposed mechanisms of action of UC-MSCs in therapeutic approaches.

and a direct contribution to tissue repair via transdifferentiation. The elucidation of the mechanisms of action of UC-MSCs in these diverse therapeutic approaches is out of the scope of this systemic analysis; however, a list of proposed mechanisms of action is given in Figure 2 with regard to the aforementioned diseases and disorders. It is apparently essential to optimize cell dose and delivery frequency as well as route(s) of delivery when the clinical goal of restoration of tissue homeostasis is likely to be crucial to halt disease progression.

Here, we would like to emphasize a few points that we noted as problematic. The first is the naming and thus the origin of cells used. One should be cautious regarding the naming and origin of the cells used in a trial because MSCs originate from diverse sources used in heterotopic and allogeneic transplantations. UC-originated stromal cells, currently known as "multipotent stromal cells," have a series of stem cell–like properties [9]. Therefore, they are a distinctive cell type and should be considered different from MSCs isolated from placenta, amnion and cord blood. We had difficulties in refining some trials where cord blood– or placenta-derived MSCs or MNCs were used, but no clear explanation was noted in the article. For the uniformity of naming umbilical cord mesenchymal stromal/stem cells throughout the present review, we preferred to use the most common abbreviation "UC-MSCs" for cells encoded by several acronyms including UC-MSCs, WJMSCs (Wharton's jelly) and UMSCs elsewhere.

The route of application followed by the biodistribution of MSCs is one of the most controversial topics in the MSC field. Starting from the 2000s, MSCs have been increasingly administered intravenously. The first MSC transplants from isolated

bone marrow aspirates provided that MSCs are able to synthesize some intercellular proteins such as collagen, replacing deficient patient cell function and ameliorating disease symptoms [111]. In systemic diseases such as SLE, MS and type 1 and type 2 diabetes, IV injection has been the first choice, usually with multiple repetitions. In contrast, in local pathologic states such as bone nonunions and spinal cord injuries, *in situ* administration of cells are preferable. As far the ethical and technical issues are concerned, none of the studies cited in this article could trace the administered cells in a living human body. In fact, cell-tracing efforts were mainly conducted in rodents. These studies exhibited that UC-MSCs distribute to a variety of tissues after IV injection. They are detectable at very low frequencies in tissues after transplantation, and signals from the IV-injected MSCs were found early after administration at the highest frequencies in the lungs, followed by the liver and spleen [112]. Similar cell accumulation was also reported in humans [113].

On the other hand, intra-arterial delivery may be advantageous in some cases to deliver MSCs to the site of injury [114], minimize the deposition of cells in the lungs, and increase uptake in other organs, especially the liver. Thus, the intra-arterial route may improve the biodistribution and bioavailability of transplanted MSCs in tissue repair. In the 93 articles cited here, the IV route was chosen at a significantly higher percentage (n = 45, 48%), particularly in immunologic and hematologic diseases, followed by the intra-arterial route (n = 11, 12%). In nine trials (10%), the intra-arterial, intrathecal or intramuscular route was accompanied by the IV route. In a relatively high number of studies (n = 11, 12%), the cell delivery route was not stated. In nine trials (10%), cells were administered into local injury sites such as the spinal cord parenchyma, myocardium or subretina.

The dose of cell administration (i.e., amount of cells per transplantation, the number of cell deliveries and the intervals between multiple deliveries) stand as an important and controversial issue. Injection repeats were clearly depicted in 78 out of 93 articles. Single injections were applied in 50 trials (54%); double injections in 8 trials (9%), triple injections in 12 trials (13%), and multiple (≥4 times) injections were applied in 13 trials (14%). The highest cell delivery repeats were reported as seven by Zheng *et al.* [54] in patients with aGVHD patients and by Patel and Riordan [97] in patients with DMD. Although UC-MSCs lack HLA class II antigens and T-cell co-stimulatory molecules, and therefore do not require immunosuppression, repeated local or systemic use may generate reactive antibodies [115], and thus hinder the therapeutic outcome. The amount of cells administered varied between 0.2×10^6/kg and 8.68×10^6/kg. Some exceptions were also noticed as 47×10^3 cells were injected into the subretinal compartment in retinitis pigmentosa by Francis *et al.* [109] and a total of 3.2×10^8 cells were injected to patients with MS by Hou *et al.* [15]. Although cell number was often aligned to the patients' weights in many cases (1×10^6 cells was chosen as the most common cell dose), there were also many trials where cell number was arbitrarily chosen with no proven scientific and/or clinical base. In some clinical trials, the amount of cells given reached as high as hundreds of millions, implying that "the more cells given, the greater the therapeutic benefit will be." The amount of cells administered was not indicated in nine studies (10%). Further clinical trials are needed to clarify the dose and duration for a given disease or clinical condition.

Trials using UC-MSCs dominated in adult patients. However, a significant number of pediatric participants were also enrolled in certain clinical conditions. Cells were administered to pediatric patients in traumatic brain injury, cerebral palsy (age range 3–12 years), autism (age range 3–12 years), aplastic anemia, acute leukemia, HSCT, aGVHD (age range 2.2–11.5 years), SLE, hemorrhagic cystitis, T1DM, Becker MD, pulmonary infection and lung injury. UC-MSCs have not been administered to pediatric patients in any liver, cardiac, ophthalmologic or skin disease. Tremendous efforts are still given in isolation, expansion, storage and immunophenotyping of stem/stromal cells before they are administered to patients. Current good manufacturing practice (GMP) is the golden standard for (i) the prevention of use of contaminated cells (e.g., AIDS or hepatitis), (ii) the prevention of inadequate handling or processing that may damage or contaminate cells and (iii) the clinical safety of all cells that may be processed, used for functions other than normal functions, combined with components other than tissues or used for metabolic purposes. Thus, clinical-grade stem cells are required to be produced under internationally recognized current GMP conditions. However, on the cell isolation and preparation methods described in these 93 trials, there is still a significant gap between the required quality conditions and the *de facto* status. Only 26 (28%) trials described current GMP conditions when preparing their clinical-grade UC-MSCs. Cell viability assessment as an important issue in GMP protocols, has only reported 18 (19%) trials. Immunophenotypic characterization of UC-MSCs by flow cytometry, on the other hand, has been applied in the majority of trials (n = 66, 71%). In 29 (31%) trials, functional analysis (*in vitro* differentiation assay into three lineages) was also reported for validation of cell isolation and expansion protocols. In a few studies (n = 3, 3%), cells were also characterized by cytokine production assay using an enzyme-linked immunosorbent assay before transplantation. It is

obvious that most, if not all, assays should be broadened to all trials to raise the plausibility and legitimacy of the results given.

Commercialization of UC-MSCs and related products might offer manufacturing and usage standards in clinical trials. However, there are only a few commercialized primary UC-MSC lines that are available on the market in many countries. Interestingly, we did not note any use of these commercially available UC-MSCs lines. This may give credence to the fact that human advanced therapy medicinal products are not easily registered and/or do not meet the demand for clinical purposes. Local cell banks (profit or nonprofit), on the other hand, provide "off-the-shelf" UC-MSCs, as we noted in a number of clinical trials, especially from China. Because the quality of cells is extremely sensitive to transportation and storage conditions, local procurement of cells seems mandatory in diverse geographic regions. Additionally, international transport of human GMP-grade UC-MSCs may face custom clearance formalities, which would inhibit their immediate use in clinics. UC-MSCs are generally cultured in Dulbecco's Modified Eagle's medium (DMEM), DMEM-Ham's F-12 or α-MEM culture media, all of which are widely available on the market. These media, which are generally used for research purposes, are frequently supplemented with fetal calf serum or human AB serum. There are also a number of culture media available that are "specifically" designed for human MSCs. However, they strictly require serum-free supplements to avoid the use of animal products during harvesting. Interestingly, these relatively expensive formulations were used in only two studies [17,20].

The last but not least significant issue is the overall safety of UC-MSC transplantation. In the stem cell field, there are many examples of bias given toward the publication of positive results in the literature [116]. Positive findings are more likely to be published, and published much more quickly, than negative and null findings. In this systemic analysis, the majority (n = 67, 72%) of the 93 trials reported the safety of the intervention without serious acute and/or chronic adverse events. Headache, fever, dizziness, and local pain were occasionally reported in the remaining 29% of reports; many of those symptoms were also reported to disappear a few days post-transplantation. One important issue that remains to be carefully evaluated is whether these short-term signs were specific to cell injections or had no direct relation to cell transplantation. The intensity of clinical adverse effects could be easily ignored when a "likely to predict efficacy" is concerned.

The relative ease through which UC-MSCs can be harvested and expanded to large numbers *in vitro*, coupled with their potent trophic, anti-inflammatory and immunomodulatory activity and lack of infusion-related toxicity in patients, has made UC-MSCs an attractive tool for cellular therapy; this is reflected by the rapid increase in the number of ongoing UC-MSC–based clinical trials. Apparently, more trials are to published in the near future because many are already registered in clinical trial databases. Although research focused on basic UC-MSC biology continues to be important for advancing cellular therapies in humans, placebo-controlled, multicenter dose-escalation studies will improve the power of clinical research.

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Appendix: Supplementary material

Supplementary data to this article can be found online at doi:10.1016/j.jcyt.2017.08.004.