

MSC and Neurological Diseases

Subjects: **Neurosciences**

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Several studies have shown that mesenchymal stromal/stem cells (MSCs) exert their neuroprotective and neurorestorative efficacy via the secretion of neurotrophic factors. Based on these studies, many clinical trials using MSCs for the treatment of neurological disorders have been conducted, and results regarding their feasibility and efficacy have been reported.

mesenchymal stromal cell

umbilical cord

neurological disorders

cerebral palsy

neurotrophic factor

1. Introduction

Mesenchymal stromal/stem cells (MSCs) have been the focus of new cell therapy development due to their potential to treat neurological disorders ^[1]. MSCs were first discussed in 1991 when they were introduced by Caplan as mesenchymal cells in bone marrow ^[2]. Now, MSCs have been isolated from several sources, including bone marrow (BM), the umbilical cord (UC), umbilical cord blood (UCB), dental pulp (DP), and adipose tissue (AD) ^{[1][3][4][5][6][7][8]}.

The characteristics of MSCs are defined by a set of criteria that form the basis for their clinical use (**Figure 1**). The International Society for Cellular Therapy proposed the criteria for defining human MSCs ^{[9][10]}. Firstly, the MSCs must be plastic-adherent when maintained in standard culture conditions. Secondly, they must express CD105, CD73, and CD90, but not CD45, CD34, CD14 or CD11b, CD79 α or CD19, and HLA-DR surface molecules. Thirdly, MSCs must be able to differentiate into adipocytes, chondroblasts, and osteoblasts in vitro. Immunomodulatory effects are the most important and popular property of MSCs in their clinical use ^[11]. MSCs lack HLA-class II expression and do not express the co-stimulatory surface antigens CD80 or CD86, which activate T-cells ^[12]. As a result, these cells are able to escape from activated T-cells. MSC-mediated immunomodulation results from the MSC secretome, which includes components such as indoleamine 2,3-dioxygenase (IDO), PGE2, galectin-1, and HLA-G5 ^[13]. With these anti-inflammatory properties, MSCs could be useful therapeutic candidates for use in the treatment of neurological disorders accompanying inflammation.

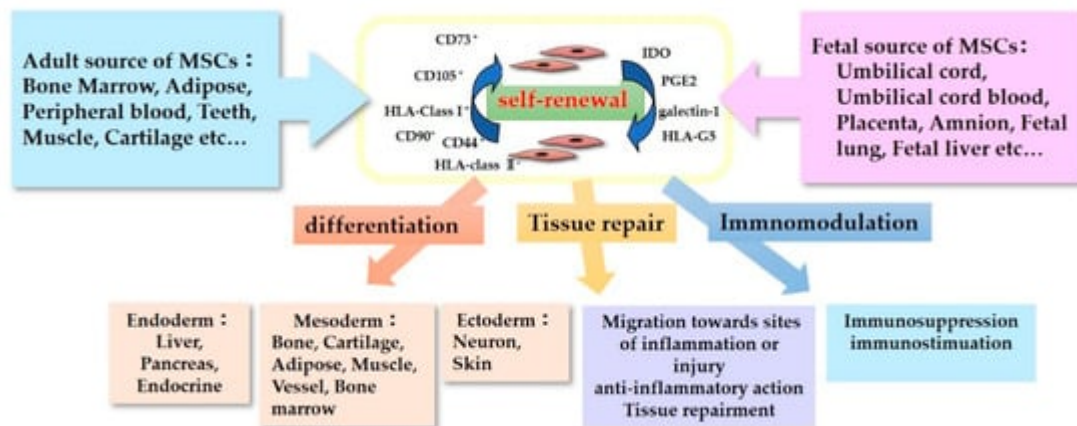


Figure 1. Characteristics of Mesenchymal stromal/stem cells (MSCs).

The tissue repair properties of MSCs are also important to their neurorestorative effect. The neurorestorative and neuroprotective effects of MSCs regarding tissue repair can be divided into two main mechanisms: (1) neurogenic differentiation and eternal cell replacement and (2) the secretion of neurotrophic factors [14]. Regarding the former, we have observed in our experiments that MSCs do not engraft and differentiate into neural cells, and they disappear within two weeks of administration in non-immunocompromised mouse models [15]. In contrast, we found that UC-MSCs that secrete neurotrophic factors such as brain-derived neurotrophic factor (BDNF) and hepatocyte growth factor (HGF) but not nerve growth factor (NGF) attenuate brain injury [15][16]. This MSC paracrine effect is expected to contribute toward their use in therapeutics for neurological injuries. Many studies using neurological disorder models have reported improvements in the studied conditions after the administration of MSCs, and clinical studies using MSCs to treat neurological disorders have been already conducted.

2. Clinical Application of MSCs for Neurological Disorders

Based on the mechanisms suggested by the basic experiments mentioned above, several clinical trials using MSCs for neurological disorders have been conducted, and the recent clinical reports are summarized in this review.

Most of these clinical studies were performed with adult participants, while trials focusing on cerebral palsy were performed with children. Regarding the origin of MSCs; BM, UC, UCB, and AD sources have all been used. In addition, DPSCs are used for clinical trials for neurological disorders [17][18]. As for the administration of MSCs, most clinical studies adopt IV and/or IT. These clinical trials have mainly reported on the feasibility and efficacy of MSC therapies for neurological disorders, with some reporting adverse events, such as fever, vomiting, and headaches, while severe adverse events have not been observed.

2.1. Ischemic Stroke

The recent clinical reports using MSCs for the treatment of ischemic stroke are summarized in **Table 1**. Some studies have reported on the safety and feasibility of BM-MSCs in patients with ischemic stroke injury [19][20][21][22].

In these clinical trials, patients received intravenous injections of BM-MSCs, and an improvement in neurological functioning was observed, while no treatment-related adverse events were seen. Qiao et al. highlighted the safety and feasibility of the co-transplantation of neural stem/progenitor cells (NSPCs) and UC-MSCs in patients who had suffered from an ischemic stroke [23]. In the study, no tumorigenesis was found during a two-year follow-up, and the neurological functions, disability levels, and daily living abilities of the patients had improved. Jiang et al. reported on the safety and efficacy of UC-MSCs delivered via a catheter to a near-lesion site for treating an infarction in the middle cerebral artery territory [24]. UC-MSCs were infused via catheterization in the M1 segment of the middle cerebral artery. Cell delivery was performed successfully in all the patients, and no major accidents were observed. After this cellular therapy, two of the three ischemic stroke patients demonstrated improved muscle strength. These reports suggest that the transplantation of MSCs in subjects with ischemic stroke is safe and may promote neurological improvement. On the other hand, Nagpal et al. conducted a clinical trial using DPSC for stroke called TOOTH (The Open study of dental pulp stem cell Therapy in Humans) and are investigating the use of autologous stem cell therapy for stroke survivors with chronic disability [18].

Table 1. Summary of recent clinical trials using MSCs for ischemic stroke.

Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events
			Trial	Control						
Chung et al. [19]	Ischemic stroke (Phase 3)	BM	39	15	68 (28–83)	IV	$1 \times 10^6/\text{kg}$	1	Lower extremity motor functional recovery after 3 months	No
Bhasin et al. [20]	Ischemic stroke	BM	6	6	42.8 (20–60)	IV	$5\text{--}6 \times 10^7$ cells	1	Improvement in the activities of daily living (ADL) after 156 and 208 weeks	No
Qiao et al. [23]	Ischemic stroke (Phase 1/2)	UC	6	0	56.17 (3–85)	IVIV + IC	IV:MSC $0.5 \times 10^6/\text{kg}$ IC:MSC 5×10^6 cells NSPC 6×10^6 cells at one-	4 or 1 + 3	Improvement in the neurological functions and ADL after 3, 12, 24 months	Fever, dizziness

Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events
			Trial	Control						
Jiang et al. [24]	Ischemic and hemorrhagic stroke	UC	4	0	40–59	IA (intra-arterial) via catheterization	2 × 10 ⁷ cells	1	Motor functional recovery and improvement in the ADL after 3 and 6 months	No
Bhasin et al. [21]	Ischemic stroke	BM	20	20	45.1	IV	5–6 × 10 ⁷ cells	1	Improvement in the ADL after 8 and 24 weeks	No
Honmou et al. [22]	Ischemic stroke (Phase 1)	BM	12	0	59.2 (41–73)	IV	0.6–1.8 × 10 ⁸ cells	1	Incremental daily rate of change in the disability scales during 12 months	Fever, nausea, itching

in neurological function [26]. Transplanting collagen scaffolds with human UC-MSCs has also been reported to have therapeutic potential as a treatment for SCI. Collagen scaffolds with human UC-MSCs were transplanted into the injury site directly, and the recovery of sensory and motor functions was observed in both patients [27]. Oh et al. reported on the injection of autologous BM-MSCs into the intramedullary area and subdural space and concluded that this single MSCs application was safe, but it had a very weak therapeutic effect compared with multiple MSC injections [28]. Therefore, further clinical trials to enhance the effect of MSCs are necessary in the future. IV, intravenous injection; IT, intrathecal injection; IC, intracranial; BM, bone marrow; UC, umbilical cord.

Table 2. Summary of recent clinical trials using MSCs for SCI.

Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events
			Trial	Control						
Xiao et al. [27]	Spinal cord injury (Phase 1)	UCB	2	0	28, 30	Transplantation into the lesion with collagen scaffolds	4 × 10 ⁷ cells	1	Motor functional recovery after 3, 6, 12 months Sensory functional recovery after 2, 4, 12 months	No
Vaquero et al. [25]	Spinal cord injury (Phase 2)	BM	11	0	44.91 (28–62)	IT	100 × 10 ⁶ cells at 3 months interval	3	Motor, sensory and bladder–bowel functional	No

Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events
			Trial	Control					recovery after 4, 7, 10 months	
Vaquero et al. [29]	Post-traumatic syringomyelia (Phase 2)	BM	6	0	39 (30–50)	Direct injection into the lesion	300×10^6 cells	1	Achieving reduction of syrinx and valuable clinical improvements after 6 months	No
Vaquero et al. [30]	Spinal cord injury (Phase 2)	BM	10	0	42.2 (34–59)	IT	30×10^6 cells at 3-months interval	4	Motor, sensory and bladder–bowel functional recovery after 3, 6, 9, 12 months	Headache, puncture pain
Satti et al. [31]	Spinal cord injury (Phase 1)	BM	9	0	31.6 (24–38)	IT	1.2×10^6 /kg at 4 weeks interval	2 or 3	Only safety assessment	No
Oh et al. [28]	Spinal cord injury (Phase 3)	BM	16	0	40.9 (18–65)	Direct injection into the lesion + IT	1.6×10^7 cells 3.2×10^7 cells	1	Very weak therapeutic efficacy after 6 months	Sensory deterioration, muscle rigidity, tingling sense
Hur et al. [26]	Spinal cord injury (Phase 1)	AD	14	0	41.9 (20–66)	IT	3×10^7 at 1-month interval	3	Motor and sensory functional recovery after 8 months	Nausea, vomit, headache
Mendonça et al. [32]	Spinal cord injury (Phase 1)	BM	14	0	35.7 (23–61)	Direct injection into the lesion	5×10^6 cells/cm ³ per lesion volume	1	Motor, sensory, and bladder–bowel functional recovery after 6 months	Low-intensity pain at the incision site, cerebrospinal fluid leak

2.3. Cerebral Palsy

Recently, MSCs have been emerging for use in potential new therapeutic treatments for children with cerebral palsy. The recent clinical reports using MSCs for the treatment of cerebral palsy are summarized in **Table 3**. Huang et al. reported on a randomized, placebo-controlled trial of UCB-MSC infusion in children with cerebral palsy [36]. The infusion group was comprised of 27 patients, each of whom received four infusions of UCB-MSCs and basic rehabilitation treatment, whereas another 27 patients were assigned to the control group and received 0.9% normal saline and basic rehabilitation treatment. The changes in the gross motor and comprehensive functional scale in

Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events	
			Trial	Control							
Cheng et al. [33]	Spinal cord injury (Phase 2)	UC	10	34	35.3 (19–57)	Direct injection into the lesion	2 × 10 ⁷ cells at 10 days interval	[37] 2	Motor, sensory, and bladder functional recovery after 6 months Superior efficacy than that of rehabilitation therapy	Radiating neuralgia	1-months had any that BM-function associated new cell
Spinal cord									Motor, sensory, and	Fever	
Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events	
Gu et al. [38]	Cerebral palsy (Phase 1/2)	UC	19	20	4.29	IV	4.5–5.5 × 10 ⁷ cells at 7-day intervals	4	Gross motor and comprehensive functional recovery and improvement in the ADL after 3, 6, 12 months	No	
Ahn et al. [39]	Intraventricular hemorrhage (Phase 1)	UCB	9	0	11.6 (7–15) (days)	Intraventricular	5 × 10 ⁶ /kg or 1 × 10 ⁷ /kg	1	Only safety assessment	No	
Huang et al. [36]	Cerebral palsy (Phase 1/2)	UCB	27	27	7.4 (3–12)	IV	5 × 10 ⁷ cells at 7-day intervals	4	Gross motor and comprehensive functional recovery after 3, 6, 12, 24 months	No	
Liu et al. [37]	Cerebral palsy (Phase 1/2)	BM	MSC 33 MNC34	35	7–132 (months)	IT	1 × 10 ⁶ /kg at 3–4-day intervals	4	Motor functional recovery after 12 months	No	
Wang et al. [40]	Cerebral palsy (Phase 4)	UC	16 (8 twins)	0	6.29 (3–12)	IT	1–2 × 10 ⁶ cells at 3–5-day intervals	4	Motor functional recovery after 1 and 6 months	No	

2.4. Amyotrophic Lateral Sclerosis (ALS)

ALS is a fatal neurodegenerative disease characterized by the degeneration of motor neurons in the brain and spinal cord, resulting in progressive muscle weakness and respiratory failure. The recent clinical reports using

Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events	Efficacy of secreted phase 2 SFRS-R) while in a points.
			Trial	Control							
Wang X et al. [41]	Cerebral palsy	BM [42]	46	0	6–180 (months)	IT Intra- Parenchymal	2 × 10 ⁷ cells 4 × 10 ⁷ cells at 5-day intervals	2 + 1 or 4	Gross motor functional recovery after 1, 6, 18 months	No	

Furthermore, CSF neurotrophic factors increased, and associated inflammatory biomarker levels decreased in the treated participants post-NTF-secreting MSC transplantation. Another report showed that intrathecal and intramuscular administration of BM-MSC secreting neurotrophic factors in patients with ALS is safe and may provide clinical benefits [43]. Syková et al. demonstrated that the intrathecal application of BM-MSCs in ALS patients is a safe procedure and that this treatment could slow down the progression of the disease; a reduction in ALSFRS decline at three months after application was observed which, in some cases, persisted for six months [44]. Oh et al. reported that two repeated intrathecal injections of autologous BM-MSCs was a safe and feasible treatment for ALS patients throughout the duration of a 12-month follow-up period [45]. These results support the possibility that the use of MSCs in ALS patients could slow down the progression of the disease.

Table 4. Summary of recent clinical trials using MSCs for ALS.

Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events
			Trial	Control						
Berry et al. [42]	ALS (Phase 2)	BM-NTF	36	12	51.1 (26–71)	IM + IT	IM: 48 × 10 ⁶ cells IT: 125 × 10 ⁶ cells	1	Improvement in the rate of disease progression after 6 months	Headache, fever, back pain, injection site bruising
Syková et al. [44]	ALS (Phase 1/2)	BM	26	0	51.2 (33–64)	IT	15 ± 4.5 × 10 ⁶ cells	1	Slowing down of the disease progression after 3, 6, 9 months	Headache
Staff et al. [46]	ALS (Phase 1)	AD	27	0	36–75	IT	1 × 10 ⁷ , 5 × 10 ⁷ , 5 × 10 ⁷ × 2, 1 × 10 ⁸ , 1 × 10 ⁸ × 2	1 or 2	Only safety assessment	Temporary back and leg pain in the highest dose
Petrou et al. [43]	ALS (Phase 1/2)	BM-NTF	26	0	48.1, 50.8 (23–65)	IM IT IM + IT	IM: 2.4–4.8 × 10 ⁷ cells IT: 1.0–	1	Improvement in the rate of disease progression after 6 months	Fever, vomiting, headache

Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events
			Trial	Control						
Rushkevich et al. [47]	ALS	BM- MSC and neural induced MSC	10	15	54.5, 55.0 (37–66)	IV + IT	2.0 × 10 ⁶ /kg	1 or 2	Slowing down of the disease progression after 12 months	Fever, headache
							0.5–1.5 × 10 ⁶ /kg × 5.0–9.7 × 10 ⁶ cells at 5–7-month intervals			
Oh et al. [45]	ALS (Phase 1)	BM	8	0	45.7 (29–62)	IT	1 × 10 ⁶ /kg at 26-day intervals	2	No efficacy after 6 months	Fever, pain, headache
Kim et al. [48]	ALS	BM	37	0	52.7, 48.8	IT	1 × 10 ⁶ /kg at one-month intervals	2	Trophic factors associated with a positive response to treat	No
Mazzini et al. [49]	ALS (Phase 1)	BM	19	0	20–75	Direct injection into spinal cord	7–152 × 10 ⁶ cells	1	No long-term adverse effect after nearly 9 years	No

failure in the MSC-IT and MSC-IV groups compared with those in the sham-treatment group. During the 1-year follow-up period, no evidence of disease activity was observed in 58.6% and 40.6% of patients treated with MSC-IT and MSC-IV, respectively, compared with 9.7% in the sham-treated group. MSC-IT transplantation induced additional benefits regarding the relapse rate, and the researchers concluded that the IT administration was more efficacious than the IV administration regarding several parameters of the disease. Furthermore, a safety and feasibility study was completed, focusing on the use of UC-MSCs for treating multiple sclerosis. Twenty subjects were enrolled in the study, and symptom improvements were most notable a month after treatment [51]. Infusion with MSCs is considered safe and feasible in patients with multiple sclerosis. However, larger studies investigating IV, intravenous injection, IT, intrathecal injection, IM, intramuscular injection, BM, bone marrow, AD, adipose. progressively by years. Petrou et aggressive y (IT) or treatment

Table 5. Summary of recent clinical trials using MSCs for multiple sclerosis.

Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events
			Trial	Control						
Petrou et al. [50]	Multiple sclerosis (Phase 2)	BM	16, 16	16	47.6 (37.9–57.3)	IT or IV	1 × 10 ⁶ /kg at 6-month intervals	1 or 2	Improvement in the course of the disease and comprehensive functional recovery after	No

Reference	Disease	Source	Number Trial Control		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events
									3, 6, 12 months. IT is more efficacious than IV	
Fernández et al. [52]	Multiple sclerosis (phase 1/2)	AD	10, 9	11	44.8 47.8 46.3	IV	$1 \times 10^6/\text{kg}$ or $4 \times 10^6/\text{kg}$	1	Partial efficacy in the imaging studies and evoked potentials after 12 months	urinary infection
Riordan et al. [51]	Multiple sclerosis (phase 1/2)	UC	20	0	41.15	IV	20×10^6 cells at 1–4-day intervals	7	Comprehensive functional recovery after one month	Headache, fatigue
Harris et al. [53]	Multiple sclerosis (Phase 1)	BM MSC - derived neural progenitors	20	0	27–65	IT	$5.3\text{--}10 \times 10^6$ cells at 3-month intervals	3	Motor, bladder and comprehensive functional recovery after 3 months	headache, fever
Dahbour et al. [54]	Multiple sclerosis (Phase 1/2)	BM MSC-CM	10	0	34.9 (18–54)	IT	$93\text{--}168 \times 10^6$ cells CM:13–20 mL at 1-month intervals	1 + 1	Comprehensive functional recovery after 12 months	Pain, headache, fever
Llufriu et al. [55]	Multiple sclerosis (Phase 2)	BM	9	0	36.8 (23–48)	IV	$1\text{--}2 \times 10^6/\text{kg}$	1	Improvement in the imaging studies after 6 months	No
Li et al. [56]	Multiple sclerosis	UC	13	10	41.7, 39.4	IV	4×10^6 cells/kg at 2-week intervals	3	Improvement in the overall symptoms and fewer incidences of relapse during 12 months	No
Bonab et al. [57]	Multiple sclerosis	BM	25	0	34.7 (23–50)	IT	2.95×10^7 cells	1	Improvement or stabilization in the course of	Fever, nausea, weakness

2.6. Parkinson's Disease

Parkinson's disease is the common and progressive neurodegenerative disease with major symptoms such as bradykinesia, impaired posture, and tremor. Some studies have reported on the safety and feasibility of MSCs in patients with Parkinson's disease (**Table 6**). Canesi et al. demonstrated the feasibility of BM-MSC in Parkinson's disease patients. One year after cell infusion, all treated patients were alive, except one, who died 9 months after the infusion for reasons not related to cell administration or to disease progression (accidental fall), and in all

Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events	Follow-up
			Trial	Control							
[60]	(Phase 2)								the disease during 12 months	in the lower limbs, headache	observed
[61]											
Lee et al.	Multiple sclerosis	BM	16	17	56.1,	IA (intra-	IA: 4 × 10 ⁷ cells IV: 4 × 10 ⁶ cells	1 + 3	Efficacy in preventing the progression of	Small ischemic	
Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events	
			Trial	Control							
Canesi et al. [60]	Progressive supranuclear palsy (Phase 1)	BM	5	0	60–68	IA (intra-arterial) via catheterization	1.7 (1.2–2.0) × 10 ⁶ /kg	1	Clinical stabilization for at least 6 months during the one-year follow-up	Transient left hemiparesis	
Carstens et al. [61]	Parkinson's disease (Case studies)	AD MSC-derived stromal vascular fraction	2	0	72, 50	Facial and nasal transplantation	6.0 × 10 ⁷ cells	1	Subjective functional recovery after 2 weeks and up to 5 years	No	

2.7. Traumatic Brain Injury

Traumatic brain injury is one of the major serious diseases that threaten human life and health, causing traffic accidents, collisions with hard objects, and falls from high places. With improving medical technology, the survival rate of patients with traumatic brain injury has increased significantly. However, the prognosis for patients with severe TBI remains poor, such as disturbance of consciousness and motor disorder. The recent clinical reports using MSCs for the treatment of traumatic brain injury are summarized in **Table 7**. Wang et al. showed the results of a phase 2 clinical trial using UC-MSCs for traumatic brain injury patients [62]. Forty patients with sequelae of traumatic brain injury were randomly assigned to the stem cell treatment group or the control group, and UC-MSCs administration improved the neurological function and self-care in patients after 6 months. On the other hand, Tian et al. explored the clinical therapeutic effects and safety of autologous BM-MSCs therapy for traumatic brain injury by lumbar puncture [63]. The results showed improvement in the function of brain in the form of post-therapeutic improvements in consciousness and motor functions. In addition, they showed the age of patients and the time elapsed between injury and therapy had effects on the outcomes of the cellular therapy, and no correlation was found between the number of cell injections and improvements.

Table 7. Summary of recent clinical trials using MSCs for traumatic brain injury.

Reference	Disease	Source	Number		Mean Age (Range), Year	Route of Administration	Number of Cells	Number of Treatments	Results	Adverse Events
Wang et al. [62]	Traumatic brain injury (Phase 2)	UC	20	20	27.5 ± 9.4 28.6 ± 10.1	IT	6.0 × 10 ⁷ cells	4	Comprehensive functional recovery and improvement in the ADL after 6 months	Mild dizziness, headache
Tian et al. [63]	Traumatic brain injury	BM	97	0	-	IT	3.0–5.0 × 10 ⁶ cells	1	Improvement of consciousness and motor function after 14 days	No

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