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Mesenchymal stromal cell therapies for traumatic neurological injuries

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Abstract

Improved treatment options are urgently needed for neurological injuries resulting from trauma or iatrogenic events causing long-term disabilities that severely impact patients' quality of life. In vitro and animal studies have provided promising proof-of-concept examples of regenerative therapies using mesenchymal stromal cells (MSC) for a wide range of pathological conditions. Over the previous decade, various MSC-based therapies have been investigated in clinical trials to treat traumatic neurological injuries. However, while the safety and feasibility of MSC treatments has been established, the patient outcomes in these studies have not demonstrated significant success in the translation of MSC regenerative therapy for the treatment of human brain and spinal cord injuries. Herein, we have reviewed the literature and ongoing registered trials on the application of MSC for the treatment of traumatic brain injury, traumatic spinal cord injury, and peripheral nerve injury. We have focused on the shortcomings and technological hurdles that must be overcome to further advance clinical research to phase 3 trials, and we discuss recent advancements that represent potential solutions to these obstacles to progress.

Keywords Mesenchymal stem cells, Neurological injury, Peripheral nerve injury, Spinal cord injury, Traumatic brain injury

Background

Neurological injury refers to damage to the brain, spinal cord or peripheral nerves as a result of trauma, disease pathology or iatrogenic events. Global incidences to the population of traumatic brain injury (TBI) and traumatic spinal cord injury (TSCI) have been estimated to be 0.369% and 0.013%, respectively [1]. With approximately 69 million people suffering TBI worldwide each year, it is the greatest trauma-related cause of death and disability, with Southeast Asian and East Asian countries experiencing the greatest overall burden [2]. Peripheral nerve injuries (PNI) are most often the result of trauma or iatrogenic interventions [3], with the incidences of each varying according to the region and country [4–7]. Traumatic PNI of an extremity is most common, occurring at an incidence of 1.46–2.8% in various populations

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[4, 5, 8, 9]. An incidence of 0.16–7.6% has been reported for perioperative PNI [10, 11].

Traumatic neurological injuries most often involve tissue damage and loss of blood perfusion, followed soon thereafter by the localized induction of proinflammatory signaling cascades and the enhancement of local cell-mediated immune responses [12, 13]. If left unabated, these mechanisms can contribute to neuronal demyelination, permanent impairment of nerve action potential conduction and irreversible deterioration of sensory and motor neurological functions [14–16]. Advances in nerve transplantation, microsurgical techniques and acute neurological care have greatly improved treatments for neurological injuries in recent decades [12, 15]. Nonetheless, the global burden of these conditions on national health care systems and patients' families remains substantial, mainly due to the high prevalence of suboptimal treatment outcomes [1, 17].

Multipotent mesenchymal stem/stromal cells (MSC) [18] can be isolated from various adult human tissues [19, 20]. Exhibiting low immunogenicity and a high capacity for self-renewal, MSC can be induced to differentiate multi-directionally, and do not elicit host rejection responses after transplantation [21], highlighting their potential for regenerative therapies. Cellular studies have demonstrated the potential of MSC therapy to repair neurological injuries through immunomodulation [22] and differentiation of neural cell lines [23]. Animal experiments have shown that MSC express brain repair markers after transplantation [24]. Other animal studies have shown that MSC migrate to the sites of neurological pathology and improve neurological functions through the repair of damaged myelin and neurons, suppressing inflammation, and reducing glial scarring [25, 26]. Clinical trials have been undertaken to investigate the use of MSC-based therapies for various pathologies, including neurological disease and injury [27, 28]. Though clinical outcomes have not unequivocally demonstrated the clinical benefits of MSC treatment for neurological pathologies [29], MSC clinical trials have reported low incidences of adverse events [27, 30].

A number of recent reviews have been published that provide excellent in-depth discussions of clinical studies of MSC therapies for various pathologies, including neurological injuries [31–33]. We surveyed three major clinical trials databases to identify completed and ongoing registered trials using MSC therapy for the treatment of TBI, TSCI, and PNI, and found that most have not progressed to phase 3 studies and many have not produced published reports. To avoid duplicating the work of previous reviews, the purpose of our review is to (a) summarize the biotechnology used in MSC therapy for neurological injuries; (b) describe the major features of previous and ongoing clinical studies of MSC therapy for TBI, TSCI, and PNI; and (c) discuss the existing obstacles to progress in these assessments of the clinical efficacy of MSC therapy for neurological injuries to highlight the factors potentially blocking advancement to phase 3 clinical trials.

Biological properties of MSC

Cellular characteristics of MSC

The immunomodulatory properties of MSC are key elements for their application to regenerative medicine because the host immune response to tissue damage can result in neural cell death. Cell-to-cell contact and efferocytosis of MSC are known to contribute to immunosuppression [34]. Numerous molecules of the MSC secretome are critical to MSC-mediated immunomodulation in the context of neuronal injury, including the following: interferon-γ, soluble tumor necrosis factor (TNF)-α receptor, TNF stimulated gene-6, interleukin (IL)-6, stromal cell-derived factor-1, microRNA-21-5p, prostaglandin E2, IL-10, transforming growth factor-β, glial cell-derived neurotrophic factor, indoleamine 2,3-dioxygenase, and programmed cell death ligands 1 and 2 [34, 35]. Other MSC-expressed immunomodulatory factors include: IL-1 receptor antagonist; cyclooxygenase-2; inducible nitric oxide synthase; human leukocyte antigen molecule 5 [36]; hepatocyte growth factor; histocompatibility locus antigen-G (HLA-G); CD39; CD73; galectins; C-C motif chemokine ligand 2 (CCL2) [37]; heme-oxygenase 1 [38]; and complement-related factor H [39].

Molecules secreted by MSC also influence key regenerative processes [40, 41]. Exosomes and other extracellular vesicles secreted by MSC carry a variety of biomolecules, including signaling lipids, cytokines, growth factors, mRNA, miRNA and mtDNA, that have been shown to contribute to important paracrine signaling effects [28, 32, 42]. Cell culture experiments have shown that exosomes from bone marrow (BM)-MSC inhibit inflammatory factors, suppress oxidative cellular immune responses and stimulate cell differentiation and migration [43, 44]. Studies in an animal model of TSCI showed that neural progenitor cells treated with exosomes from BM-MSC inhibited inflammation and astrocyte-induced neurotoxicity [43]. Further analysis showed that exosome treatment induced angiogenesis, inhibited neural cell apoptosis, reduced glial scar formation and lesion size, and stimulated axon regeneration [43]. These findings have served as the rationale for studies that have investigated the direct application of MSC exosomes to neuroregenerative treatment strategies [28, 45].

MSC biomarkers

Criteria for defining MSC include plastic-adherence [46] and the capacity for multi-lineage differentiation, which

must include differentiation to osteoblasts, adipocytes and chondroblasts under standard induction conditions according to the minimum criteria for MSC designation [47]. Cell surface marker criteria for defining MSC have evolved considerably over time, and donor-related heterogeneity in marker expression has been reported [48]. In 2006, The International Society for Cellular Therapy suggested the following markers for MSC obtained from BM: (a) the presence of CD73, CD90 and CD105; (b) the absence of CD45, CD34 and HLA-DR; (c) the absence of CD14 or CD11b; and (d) the absence of CD79α or CD19 [47]. Subsequently, a number of additional markers have been proposed, and differences in marker expression have been reported for MSC obtained from different sources [49], leading to changes in the accepted criteria for defining MSC. These changes have been reviewed in detail elsewhere [47, 49–74]. The findings of studies on MSC markers are summarized in Table 1.

Table 1 Summary of call surface markers of human MSC obtained from different sources

MSC origin	hMSC biomarker	Not expressed in hMSC
Adipose tissue	CD9 [50], CD10 [50, 51], CD13 [53], CD29 [53], CD34 [50], CD44 [50, 51, 53], CD49d [50], CD54 [50, 51], CD55 [50], CD59 [50], CD71 [50], CD73 [52, 53], CD90 [51–53], CD105 [51–53], CD147 [51], CD166 [51, 53], STRO-1 [51]	CD14 [53], CD31 [51–53], CD34 [51, 53], CD45 [51–53], CD117 [51, 53]
Bone marrow	CD9 [56], CD10 [51], CD29 [54–56], CD44 [51, 54–56], CD54 [51], CD73 [56], CD90 [51, 54–56, CD105 [51, 54–57], CD106 [51, 54, 55, 57], CD117 [57], CD146 [56], CD147 [51], CD166 [51, 55, 56], STRO-1 [51]	CD14 [54], CD31 [54], CD34 [51, 54, 57], CD45 [51, 54, 57], CD54 [57], CD117 [51], HLA-DR [47]
Dental pulp	CD29 [58, 59], CD44 [58, 59], CD90 [58, 59], CD105 [58]	CD14 [58], CD34 [58, 59], CD45 [58, 59]
Peripheral blood	CD44 [60], CD90 [61], CD105 [60, 62], HLA ABC [63]	CD45 [60], CD133 [64]
Skin	CD44 [65, 66], CD73 [65], CD90 [65, 69], CD105 [65, 66], CD166 [66], SSEA-4 [67], vimentin [65]	CD34 [68], CD45 [65], HLA-DR [69]
Umbilical cord	CD13 [70], CD29 [70, 71], CD49e [70], CD54 [70], CD73 [71], CD90 [70, 71]	CD14 [70], CD31 [70], CD34 [70, 71], CD45 [70, 71], CD49d [70], CD106 [70]
Wharton's jelly	CD13 [72], CD19 [49], CD29 [72], CD44 [49, 72], CD73 [72], CD90 [49, 72], CD105 [49, 72], CD106 [49], CD146 [72], CD166 [72], HLA-ABC [72], STRO-1 [49]	CD14 [72], CD34 [72], CD45 [72], CD117 [72], CD133 [72], CD144 [72], CD326 [72], HLA-DR [72]
Amniotic fluid	CD44 [73], CD73 [73, 74], CD90 [73, 74], CD105 [73, 74], CD166 [73, 74]	CD14 [73, 74], CD19 [47], CD34 [73, 74], CD45 [73, 74], HLA-DR [74]

hMSC human mesenchymal stem cell

One study by Patrenko et al. [75] compared the cell surface markers of MSC derived from BM (BM-MSC), adipose tissue (AT-MSC) and Wharton's jelly (WJ-MSC). All three types of MSC expressed CD10, CD29, CD44, CD73, CD90, CD105 and HLA-ABC at similar levels, and all were negative for CD14, CD45, CD235a, CD271, HLA-DR and VEGFR2 expression. The expression of CD34, CD133, CD146, SSEA-4 and MSCA-1 varied significantly between sources [75]. MSC surface markers function in the modulation of immune responses and cell lineage differentiation [76]. However, previous studies have also found that CD34 expression was correlated with angiogenesis [77, 78], and that CD133 and CD146 were correlated with tumor progression [79, 80], both of which involve cellular mechanisms that also contribute to regenerative processes.

Initially, the MSC surface markers described above were used for the identification and isolation of MSC from source tissues by flow cytometry. These markers can also be used to assess the products of MSC expansion, which is sometimes performed to produce larger numbers of MSC by propagating newly isolated MSC in cell culture prior to transplantation. Specific cell markers can also identify the transition of MSC during induced neurogenesis [81]. Knowledge of the basic biology and functionality of MSC is a rapidly evolving field. MSC from essentially all sources, including MSC with neurogenic potential, are now known to possess both progenitor cell and paracrine signaling properties in the injury microenvironment [82]. Current knowledge of the mechanistic links between these processes have been thoroughly reviewed elsewhere [32, 34, 83]. Efforts to develop the techniques needed for assessing these properties have been undertaken, and will be discussed briefly in the section below entitled *Addressing treatment standards and technological gaps in MSC therapies*.

Variation in MSC according to source tissue

Currently, clinical studies using MSC-based therapies for neurological regenerative treatments have mainly used MSC derived from BM [75], AT [75], umbilical cord blood (UCB) [84], WJ [75] or dental pulp (DP) [85]. Therefore, we limit our discussion herein primarily to MSC derived from these sources, which are briefly summarized in Table 2. Autologous BM-MSC and AT-MSC have been used most often. However, no significant rejection has been reported for the use of allogenic BM-MSC, AT-MSC or MSC from UCB, WJ or DP. Though MSC can be isolated from amniotic tissues [91, 92], peripheral blood [93], skeletal muscle [94], testis, ovary, hair follicle [49], skin [95] and synovial tissues [96], no clinical studies have used MSC from these sources in therapies for TBI,

Table 2 Characteristics of MSC from different sources

Characteristics	Bone marrow	Adipose	Dental pulp	Umbilical cord blood	Wharton's jelly
Culture induction	Easy	Easy	Difficult	Difficult	Difficult
Neural differentiation	Low	Low	Low	Low	Low
Cell renewal	Low	Low	High	High	High
Allogeneic rejection	No	No	No	No	No
Clinical trial	Yes	Yes	Yes	Yes	Yes
References	[86]	[87]	[88]	[89]	[90]

MSC mesenchymal stem cell

TSCI or PNI, despite cellular and animal studies suggesting that MSC from amniotic tissues and peripheral blood possess properties potentially applicable to neurologic regenerative therapies [92, 97].

Though the expression of neural markers varies based on their source, essentially all human MSC express the neural cell marker nestin prior to induction [98–100], with each type displaying relatively good potential for differentiation to neuronal cell lineages [14]. Upon transfer to the site of injury, MSC stimulate immune pathways involved in responses to tissue damage, perhaps through Toll-like receptor-mediated signaling, while simultaneously expressing suppressors of the effects of proinflammatory mediators, autophagy processes, apoptosis and oxidative damage [37]. Though these characteristics of MSC should be considered with regard to their application for stem-cell therapy for neurological treatments, the degree to which these vary according to donor tissue source is not entirely clear.

Donor age is an important factor to consider for the use of BM-MSC, with donor age reducing long term MSC viability in cell culture and BM-MSC have been reported to be more susceptible to nutrient conditions compared to AT-MSC. The collection of BM requires an invasive procedure and the age of the BM donor affects the proliferation rate and long-term differentiation capacity of BM-MSC [101]. Though BM-MSC exhibit greater immunomodulatory activity than AT-MSC and WJ-MSC, they have lower expression of neurotrophic growth factors compared to AT-MSC and WJ-MSC [75]. Nevertheless, BM-MSC are the most frequently used MSC in clinical trials for the treatment of neurological disorders [102].

The MSC obtained from AT possess a high capacity for multilineage differentiation and their neurogenic potential is similar to that of BM-MSC. The use of AT-MSC in stem cell therapy has the advantages of source availability and reduced donor invasiveness because donor AT can be obtained from the aspirate of liposuction for body-fat reduction, which also yields greater numbers of MSC compared to the numbers collected from BM sources [103]. AT-MSC also exhibit better long-term stability in cell culture compared to BM-MSC, with donor age primarily affecting their osteogenic and chondrogenic potential [104].

The collection of DP from donors can make use of routinely extracted third molars, which are otherwise discarded as medical waste. The MSC obtained from DP have cellular characteristics and immune properties similar to those of AT-MSC. Originating from the neural crest during development, DP-MSC can be induced using various protocols [105] to differentiate into neuronal lineages expressing neurotrophic factors [106], such as microtubule-associated protein 2, Musashi-1, NGN2, neuron-specific enolase [107] and arginase I [108], as well as modulators of axonal regeneration including proteins involved in the RAS/ERK and PIK3/Akt signaling cascades [105].

Efforts to use UCB and WJ as sources of MSC for regenerative therapies have benefited from the widespread availability of these human afterbirth components, as well as the ease and reliability of sample collection [109, 110]. These UCB-derived MSC (UCB-MSC) express early neural cell markers, and can be induced to differentiate to Schwan cell and neural cell lineages [111]. UCB-MSC have been shown to retain the majority of their immunomodulatory and anti-oxidative activities following neural induction [112]. The WJ-MSC and UCB-MSC produce axon-like structures in cell culture [113], highlighting their potential use for axon regeneration in TSCI and PNI.

The composition of secretome and exosome contents also vary according to the MSC source. Analysis of BM-MSC exosomes and other secreted factors found them to contain lower levels of neurotrophic factors, as well as fewer anti-inflammatory molecules that protect against oxidative stress, compared to those of exosomes secreted by AT-MSC and WJ-MSC [75]. However, further analysis in functional in vitro assays showed that the secretome from each type of MSC exhibited significant neurotrophic effects, protected neural progenitor cells against oxidative stress and induced neurite development in dorsal root ganglion neurons [75].

Clinical research in MSC regenerative therapy

MSC treatment for neurological injuries

Since BM-MSC were first described by Friedenstein et al. [114] in the 1970s, MSC treatments have been extensively investigated as regenerative treatments for various diseases and injuries. On the date of the production of this manuscript, a search of *clinicaltrials.gov* for studies using MSC-based therapies for neurological pathologies showed that 152 studies were registered as completed or in progress (excluding terminated, suspended, withdrawn

and unknown status studies), among which 82 used BM-MSC, 32 used AT-MSC, 31 used UCB-MSC, 4 used WJ-MSC and 3 used DP-MSC (the focus of our discussion herein). Among the total of 152 neurological studies identified, 13 were TBI studies, 19 were TSCI studies and none were PNI studies. These data highlight the need for increasing efforts to investigate the use of MSC to improve treatments specifically for traumatic and iatrogenic neurological injuries [30].

MSC therapy for TBI

In TBI, the initial physical damage to brain tissues usually induces a loss of blood perfusion and hemostasis resulting in further neuron and oligodendrocyte death, followed by demyelination and glial scar formation caused by astrocyte hypertrophy and proliferation, which spread outwards from the site of injury [115]. Much of the physical and cognitive impairment resulting from TBI is caused by the pro-inflammatory biochemical cascades that follow the traumatic primary injury. These pro-inflammatory responses to tissue damage lead to further neuron and oligodendrocyte loss and altered brain hemodynamics resulting in increased intracranial pressure. In MSC therapies for TBI, the secretion of neurotrophic factors by transplanted or infused MSC are important for stimulating neural cell differentiation and growth to repair damaged brain tissue, whereas the immunomodulatory properties of MSC are equally beneficial in suppressing the negative effects of acute inflammation [116].

Fundamental overview of clinical trials for TBI

The safety and efficacy of MSC treatments for TBI have been investigated in previous clinical research investigations. In one small study, pediatric TBI patients ($n=10$), with Glasgow coma scale scores of 5 to 8, were treated intravenously with autologous BM-MSC at 2 days post-injury [117]. At the 6-month follow-up, 7 patients had good clinical outcomes and 3 had moderate to severe disability, indicating improvement over conventional treatment methods [117]. Later, the same investigators used similar autologous BM-MSC methods in adult TBI patients ($n=15$) and found that neurologic functional assessments correlated with brain magnetic resonance imaging (MRI) data showing preservation of critical brain tissue structure with a moderate treatment effect (Cohen's d: 0.5–0.8) [118]. At 4 days post-treatment, plasma levels of TNF-α, IL-1b, IL-10, and IFN-γ were reduced in the high dose group ($n=5$), relative to pretreatment levels, demonstrating the anti-inflammatory effects of the BM-MSC treatment [118]. Both of these studies reported no serious adverse events. In another small study, approximately 10^8 autologous BM-MSC were delivered directly to the site of injury in TBI patients ($n=7$), which was followed by intravenous (IV) re-infusion of approximately 10^9 autologous BM-MSC [119]. At 6-months post-treatment, all patients had improved neurological outcomes with no serious adverse events [119].

In a larger clinical study, TBI patients ($n=97$) received a single autologous BM-MSC re-infusion via lumbar puncture at approximately 1 to 3 months following the onset of injury [120]. At 2 weeks post-treatment, assessments of clinical outcomes showed that 39.2% of patients had improved neurological outcomes, with younger patients and those who were treated earlier in the treatment window showing greater improvement [120]. No serious adverse events were reported. The efficacy of UCB-MSC treatment for TBI was investigated in a study in which TBI patients ($n=20$) received 4 infusions administered via lumbar puncture [121]. The UCB-MSC treated patients had significant improvements in extremity motor functions, sensation and balance at 6-months post-treatment, and displayed significant improvements in self-care, sphincter control, locomotion and mobility, communication and social cognition, whereas the control group did not display any significant improvements [121]. No severe adverse events were reported.

These studies provide evidence for the safety of MSC therapies and preliminary findings to serve as the basis for future studies. However, the statistical significance of the findings in all of these studies was limited by small sample sizes. Furthermore, the confounding effects of injury heterogeneity are a challenging aspect of research for TBI treatment. The implementation of standardized methods for evaluating the severity of neurological impairment before and after treatment will improve the reliability of estimates of treatment efficacy and comparisons of treatment protocols, especially with regard to evaluating differences in MSC delivery techniques, such as the re-infusion route, number of re-infusions, MSC source and the injury-to-treatment interval.

Critical summary of registered trials of MSC therapy for TBI

Comprehensive evaluations of both previous and active trials are needed to better guide the future directions of clinical research to improve treatment strategies for TBI and advance our knowledge of the properties of transplanted MSC. Rather than merely describing the results of previous studies, we wish to discuss the overall state of research in MSC-based therapies for TBI, with a vision to the future beyond that of ongoing studies. To provide a broader perspective of both past and ongoing clinical research efforts, we searched the major clinical trials databases for studies investigating neurological conditions, and the results were then searched manually to identify clinical trials that investigated the safety and/or efficacy of MSC-based treatments for TBI or conditions directly related to TBI, such as sequelae caused by severe

brain injury. Only active or completed studies were selected for analysis.

We identified 11 relevant TBI studies registered on the ClinicalTrials.gov registry (https://www.clinicaltrials.gov). We also identified an additional study in the European Union Clinical Trials Register (https://www.clinicaltrialsregister.eu/) and one further study in the Chinese Clinical Trials Registry (https://www.chictr.org.cn/). A search of the International Clinical Trials Registry (https://www.isrctn.com/) yielded no relevant results. The total of 13 studies identified are summarized in Table 3. With combined study periods spanning 19 years (2006–2025), the relatively low total number of studies ($n=13$) is indicative of a slow rate of progress in the investigation of MSC-based therapy for TBI.

Seven of these studies describe TBI as the condition treated. Two studies (NCT02795052 and NCT03724136) investigated multiple neurological conditions that included TBI and two studies (NCT01649700 and ChiCTR-TNRC-11001528) investigated sequelae caused by severe brain injury. One study (NCT02742857) investigated brain death resulting from TBI. Two of the studies were phase 1 trials, five studies were designated as phase 1/phase 2 trials, and six as phase 2 trials, while the phase-levels of two currently active studies (NCT02795052 and NCT03724136) had not yet been designated, but the primary outcome measures in the study descriptions suggest these are phase 2 trials. Seven of these studies gave completion dates, and six are ongoing (active). Thus, the majority of these studies provide, or will provide, information regarding the effects of MSC treatments on neurological outcomes in TBI patients. However, eleven of these studies have enrollments of less than 100 patients, among which eight studies have enrollments of less than 50 patients. Small cohort sizes present obvious difficulties to the analysis of outcomes of any study. The studies including multiple neurological conditions (NCT02795052 and NCT03724136) have larger sample sizes compared to the remaining studies, but it remains unclear whether TBI subgroup analyses of sufficient statistical power will be possible.

Two studies in Table 3 (NCT01851083 and NCT00254722) are pediatric studies. Ten of the remaining studies investigated TBI in adults only, and one study (ChiCTR-TNRC-11001528) included both children and adults. It is uncertain whether differences in the ages of patients might contribute to heterogeneity in treatment outcomes. Eight of the TBI studies use interventions involving the administration of BM-MSC, among which seven used autologous BM-MSC and one uses allogenic BM-MSC. Three of the TBI studies used interventions involving autologous AT-MSC, whereas UCB-MSC were administered in one study. The information provided for one study was unclear regarding the MSC donor source (NCT02742857), and the results of that study have not been published. A previous review of cell based therapies for TBI did, however, report that NCT02742857 administered allogenic MSC [127]. The earliest investigations of MSC treatments for TBI used autologous BM-MSC. Four of the BM-MSC studies have been completed. One AT-MSC study and one UCB-MSC study have been completed. Though the results of these studies will allow some comparisons of treatment efficacy, evidence remains lacking for a direct comparison of the efficacies of different MSC therapies based on the donor source, highlighting the need for multi-arm study designs in future clinical trials that will investigate MSC from multiple sources.

Transplantation methods in MSC therapy for TBI

Little data is currently available regarding differences in clinical benefits based on the MSC infusion route and frequency of administrations in TBI patients. One completed study (NCT02416492) described significant improvement in the Fugl-Meyer Motor Scale (FMMS) score using stereotactic intracranial injection of MSC [128]. In ten of the studies in Table 3, the intervention involved IV administration of MSC. Animal studies have shown that the majority of IV-administered MSC accumulate in the lungs before passing onward to the brain [129]. Intrathecal, intranasal and intracranial administration seek to circumvent this effect. However, the proportion of MSC reaching the brain following intranasal administration in humans is unclear and intracranial injection requires focal lesions which are often absent in certain types of TBI. Two of the studies in Table 3 (NCT02742857 and ChiCTR-TNRC-11001528) used intrathecal MSC transplantation for the intervention. In two other studies (NCT02795052 and NCT03724136), both i.v. and intranasal administration were used in a single study group. While NCT02795052 was a single arm study, the results of NCT03724136 should provide a direct comparison of i.v. administration with i.v. and intranasal treatments combined, but it remains to be established whether a subgroup analysis of the TBI patients will have sufficient statistical power.

The administration of multiple boluses has been shown to increase the number of MSC reaching the brain [129]. Two studies used multiple infusions of AT-MSC for the intervention (NCT05951777, $n=3$; NCT01649700, $n=5$). While NCT05951777 study is ongoing, NCT01649700 had a completion date of May 2013, but we could find no publication in which the results of the study were described in detail. Differences in the pretreatment interval from injury onset are another potential problematic aspect of study designs for MSC therapy for TBI. Among the studies in Table 3, this interval ranged from as little as 24 h in NCT00254722 to >1 year in NCT02416492,

Table 3 Summary of clinical trials of MSC therapy for TBI

Registration ID, study phase	Publication	Location	Diagnosis, enrolled, ITI	Donor type, source	Administered: Route, dosing*	MSC methods described†	Primary outcomes
NCT01575470[a]; phase 1, 2	Cox et al. 2017 [118]	USA	TBI, $n=25$, ≤ 36 h	Autologous BM	IV; 6, 9, or 12×10^6 cells/kg BW	Isolation, viability, identity, and counting	Safety endpoints for AE monitoring. GCS at baseline and 12 h to 21 days.
NCT02525432[a], phase 2	NA	USA	TBI, $n=37$, ≤ 48 h	Autologous BM	IV; 6×10^6 to 9×10^6 cells/kg BW	NA	3T-MRI at 0, 1, and 6 mos.
NCT02416492[a], phase 2	McCrea et al. 2021 [122]	USA	TBI, $n=63$, > 1 y	Allogenic BM	IC; 2.5×10^6, 5.0×10^6, 10×10^6 cells	NA	DRS and FMMS subscales (FM-UE and FM-LE) at 0, 24, and 48 wk.
NCT00254722[a], phase 1	Liao 2015 [123]	USA	TBI, $n=10$, ≤ 48 h	Autologous BM	IV; 6×10^6 cells/kg BW	Isolation, viability, identity, and counting	Safety endpoints for AE monitoring. PILOT score daily from 0–21 days.
NCT01851083[a], phase 2	Cox et al. 2024 [124]	USA	TBI, $n=47$, ≤ 48 h	Autologous BM	IV; 10×10^6 cells/kg BW	Isolation, viability, identity, and counting	Volume of WM and GM in CC and CC microstructure at 0, 1, and 6 mos.
NCT04063215[a]; phase 1, 2	NA	USA	TBI, $n=24$, > 6 mos	Autologous AT	IV; 2×10^8 cells every 14 days for 6 wk.	NA	Safety endpoints for AE monitoring. Macro- and micro-structure of GM and WM in CC and corticospinal tracts at 0 and 6 mos.
NCT02742857[a], phase 1	NA	India	Brain death, $n=20$, NA	NA	IT; Dose: NA	NA	Safety endpoints for AE monitoring. Brain death reversal based on clinical exam or EEG results at 15 days.
NCT02795052[a]; phase 1, 2	Weiss and Levy 2016 [125]	USA	Multiple including TBI, $n=500$, > 6 mos	Autologous BM	IV + IN, 16 mL of filtered BM aspirate	NA	Safety endpoints for AE monitoring. Neuro-QOL score at 0, 1,3, 6, and 12 mos.
NCT03724136[a]; phase 1, 2	NA	USA	Multiple including TBI, $n=100$, NA	Autologous BM	IV and IV + IN; IV dose: 14 cc, IN dose: 1 cc	Isolation	Safety endpoints for AE monitoring. MMSE and ASQE scores at 0, 1,3,6, and 12 mos.
NCT05951777[a], phase 2	NA	USA	TBI, $n=51$, > 6 mos	Autologous AT	IV; 2×10^8 cells at 0, 2, 4, and 6 wk	NA	Whole brain MRI and PET/DT-MRI at 0 and 6 mos. GOS, TBIQOL-SF, and BREF-A at 0, 6, and 12 mos.
NCT01649700[a]; phase 1, 2	NA	Taiwan	Sequelae of severe brain injury, $n=1$, NA	Autologous AT	IV; 5×10^7 to 7×10^7 cells at 0, 1, 2, and 3 mos	NA	Vital signs and clinical lab tests for AE monitoring (frequency NA).
ChiCTR-TNRC-11,001,528[b], phase 2	Wang et al. 2013 [121]	China	Sequelae of severe brain injury, $n=20$, > 2 y	Allogenic UCB	IT; 4 doses of 1×10^7 cells over 5–7 days	Propagation, isolation, identity, and counting.	FMA subscales (FM-UE, FM-LE, sensitivity, and balance) at 0 and 6 mos.
2022-000680-49[c], phase 2	Zanier et al. 2023 [126]	Italy	TBI, $n=78$, < 48 h	Autologous BM	IV; 8×10^7 to 16×10^7 cells	NA	Safety endpoints for AE monitoring. Plasma NFL at baseline, 4, 14, 180, 360 mos after TBI.

*Treatments were administered at baseline only unless otherwise noted. For studies that propagated MSC, dates of subsequent administrations and outcomes reflect the date of first treatment as baseline or 0 days, wk, mos, y as applicable

†Isolation: Isolation of MSC from source tissue specimen; Identity: Identification of MSC using phenotypic biomarkers; Counting: Quantification of MSC; Viability: Confirmation of live MSC; Propagation: Proliferation of MSC in tissue culture. Only the methods reported in the publication or trials registry record are listed herein

[a] https://clinicaltrials.gov

[b] https://www.chictr.org.cn

[c] https://www.clinicaltrialsregister.eu

AE adverse event, *ASQE* Autism Spectrum Quotient Exam, *AT* adipose tissue, *BM* bone marrow, *BREF-A* behavior rating of executive functions-adult, *BW* body weight, *CBC* complete blood count, *CC* corpus callosum, *DT-MRI* diffusion tensor-magnetic resonance imaging, *EEG* electroencephalogram, *FMA* Fugl-Meyer Assessment, *FM-LE* Fugl-Meyer Lower Extremity Subscale, *FMMS* Fugl-Meyer Motor Scale, *FM-UE* Fugl-Meyer Upper Extremity Subscale, *GCS* Glasgow coma score, *GM* grey matter, *GOS* Glasgow outcome score, *IC* intracranial, *IN* intranasal, *IT* intrathecal, *ITI* injury-to-treatment interval, *IV* intravenous, *MMSE* Mini-Mental Status Exam, *mos* months, *MRI* magnetic resonance imaging, *MSC* mesenchymal stromal cells, *NA* not available, not provided, or non-existent, *Neuro-QOL* Neurology Quality of Life questionnaire, *NFL* Neurofilament Light Protein, *PET* positron emission tomography, *PILOT* Pediatric Intensity Level of Therapy, *TBI* traumatic brain injury, *TBIQOL-SF* traumatic brain injury quality of life-short form, *UCB* umbilical cord blood, *wk* week, *WM* white matter, *y* year

with five studies using an interval of 36 h or less and three studies an interval of ≥6 months. It remains to be determined how differences in the pretreatment interval might affect patient outcomes.

In two studies in Table 3 (NCT02742857 and NCT03724136), the interventions involved adjuvant treatments. In NCT02742857, the MSC were suspended in medium containing a proprietary peptide extract and transcranial laser therapy and median nerve stimulation were used as adjuvant treatments. As stated previously, no results of NCT02742857 have been published. In the ongoing NCT03724136 study, near infrared (IR) light therapy was used as a treatment adjuvant in one treatment arm, whereas two additional treatment arms received an MSC transplant without IR therapy. Preliminary results for NCT03724136 have not yet been published. Thus, the clinical benefits of these adjuvants remain unclear. However, the study design of NCT03724136 should allow an evaluation of the benefits of the IR adjuvant. The overall analysis of previous and ongoing clinical trials highlights the importance of choosing study designs for future clinical trials that allow more direct comparisons, based on the MSC donor source, transplant methods and adjuvant treatments to identify optimal treatment strategies for TBI.

Variation in clinical outcomes in TBI patients

Quantifying the effects of treatments on neurological functions is always a challenging aspect of clinical research. Several different outcome measures are used in the studies listed in Table 3. A partial list of the clinical assessments employed included: the FMMS, disability rating score, quality of life in neurological disorders, activities of daily living, action research arm test, global rating of perceived change, Glascow coma scale, Galveston orientation and amnesia test, Rivermead post-concussion symptoms questionnaire, automated neuropsychological assessment, brain injury functional outcome measure, behavior rating of executive functions, and TBI quality of life questionnaire. The use of different clinical assessments contributes to the difficulty in making intra-study comparisons of outcome measures and treatment efficacy. Four studies used MRI data for outcome measures. The use of MRI-based imaging data in the post-treatment assessment of TBI patients, such as the supratentorial and corpus callosal volumes and the fractional anisotropy and mean diffusivity of the corpus callosum and corticospinal tract used by Cox et al. (2017) [118], might also improve the quality of study findings by providing additional means of objective intra-study comparisons of patient outcomes and treatment efficacy.

MSC treatment for TSCI

Spinal cord injury is arguably the most challenging trauma-related neurological injury, and current therapeutic approaches have mainly been ineffective for improving patient outcomes. Given that MSC have been shown to promote axon elongation and synapse formation in animal models, much research has been conducted to investigate the application of MSC therapies in patients with spinal cord injury [130]. The number of clinical trials undertaken for the investigation of MSC-based therapies for TSCI exceeds that for TBI. A search of the American, European, and Chinese clinical trials registries identified 27 completed or ongoing clinical trials Table 4). These studies investigated the use of MSC from various sources, with MSC infusions being administered to TSCI patients intrathecally and i.v. Similar to TBI studies, the results of only 13 of the 27 trials were published from which the majority were phase 1/2 trials with one pilot study.

Most sample sizes were between 5 and 20 cases, with the exception of NCT00816803 which enrolled 70 patients and NCT02481440 with 41 patients for efficacy and safety, as well as 102 patients for additional safety evaluations. Apart from five studies that solely focused on safety, the remaining studies mainly assessed efficacies of the treatments using American Spinal Injury Association (ASIA) scores. All treated patients showed improvements after treatment with various degrees of efficacy (NCT04288934 NCT03308565 NCT02481440 NCT02152657 NCT01325103 NCT00816803 and NCT02570932). These studies also reported that MSC infusions in patients with spinal cord injury were safe and well-tolerated. Upper limb motility, sensation within the damaged area, reduction in neuropathic pain, bladder function, and sphincter control were positively achieved. In one study, the mean values of brain-derived neurotrophic factor, glial-derived neurotrophic factor, ciliary neurotrophic factor, and neurotrophin 3 and 4 appeared to show slight increases after three MSC administrations, but the differences did not reach statistical significance (NCT02165904). Though more studies of TSCI have been undertaken, compared with those of TBI, it is clear that these trials are beset with the same general obstacles to progress as the TBI studies, including small sample sizes and variability in injury duration, transplantation methods, MSC culturing/analysis techniques, and clinical outcomes, which are likely confounding analyses of treatment efficacy.

MSC treatment for PNI

PNI is a common neurological injury characterized by sensory, motor and autonomic nervous system dysfunctions that affect the trunk and/or limbs. In contrast to neurological injuries of the central nervous system

Table 4 Summary of clinical trials of MSC therapy for TSCI

Registration ID, study phase	Publication	Location	Diagnosis, enrolled, ITI	Donor type, source	Administered: Route, dosing*	MSC methods described†	Primary outcomes*
NCT02352077, phase 1	Zhao et al. 2017 [131]	China	TSCI, $n=8$, 2–36 mos	Allogenic UCB	Perilesional; 4×10^7 cells	Propagation, isolation, identity, and counting.	Safety endpoints for AE monitoring. ASIA and MEP testing at 0, 1, 3, 6, and 12 mos.
NCT02482194, phase 1	Satti et al. 2016 [132]	Pakistan	TSCI, $n=6$, >2 wk	Autologous BM	IT; 2–3 doses of 1×10^6 cells/kg BW at 0 and 4–8 wk	Propagation, isolation, identity, and counting. Adipogenic, chondrogenic, and osteogenic characterization.	Safety endpoints for AE monitoring.
NCT02165904; phase 1, 2	Vaquero et al. 2017 [133]	Spain	TSCI, $n=10$, 2–35 y	Autologous BM	IT; 30×10^6 cells at 0, 4, 7, and 10 mos.	NA	Safety endpoints for AE monitoring. ASIA, IANR-SCIFRS, FIM, Barthel, ADL, VASP, Penn, modified Ashworth, Geffner, and NBD scales at 0, 3, 6, 9 and 12 mos.
NCT02570932, phase 2	Vaquero et al. 2018 [134]	Spain	TSCI, $n=11$, 13.65 ± 14.79 y	Autologous BM	IT; 3 doses of 100×10^6 cells at 0, 4, and 7 mos.	Propagation, isolation, identity, viability, and counting.	ASIA, IANR-SCIFRS, Ashworth, Penn, VASP, Geffner, and NBD scales at baseline, 4, 7, and 10 mos.
NCT02152657, phase 1	Larocca et al. 2017 [135]	Brazil	TSCI, $n=5$, >6 mos	Autologous BM	Perilesional; 2×10^7 cells	Propagation, isolation, identity, and counting. Adipogenic and chondrogenic characterization. Cytogenetic evaluation.	Safety endpoints for AE monitoring. VASP, MPQ, and ASIA scores; urodynamics; MEP and SEP tests; and SCIM and FIM assessments at 0, 1, 3, and 6 mos.
NCT05152290, phase 1	NA	Argentina	TSCI, NA, NA	Allogenic UCB	IV + IT; 100×10^6 cells (total)	NA	Safety endpoints for AE monitoring at 1, 6, 12, 24, 36, and 48 mos.
NCT02481440; phase 1, 2	Yang et al. 2021 [136]	China	TSCI, $n=102$, ≥2 mos	Allogenic UCB	IT; 1×10^6 cells at 0, 1, 2, 3 mos	Propagation, isolation, identity, counting, and viability. Adipogenic, chondrogenic, and osteogenic characterization.	Safety endpoints for AE monitoring at 1, 3, 6, and 12 mos ($n=102$). ASIA and IANR-SCIFRS scores at 0, 1, 3, and 6 mos ($n=41$).
NCT02981576; phase 1, 2	NA	Jordan	TSCI, $n=14$, ≥2 wk	Autologous BM and AT	IT; 3 doses (amount and frequency: NA)	NA	Safety endpoints for AE monitoring. ASIA-AIS score and MRI results at 0 and 12 mos.
NCT01274975, phase 1	Ra et al. 2011 [137]	ROK	TSCI, $n=8$, >12 mos	Autologous AT	IV; 4×10^8 cells	Viability	Safety endpoints for AE monitoring.
NCT01909154; phase 1, 2	Vaquero et al. 2016 [138]	Spain	TSCI, $n=12$, ≥6 mos	Autologous BM	Iintramedullary; 5×10^6 to 150×10^6 cells at baseline; IT, 30×10^6 cells at 3 mos.	Propagation, identity, isolation, counting, and viability.	Safety endpoints for AE monitoring.
NCT04288934; phase 1, 2	Awidi et al. 2024 [139]	Jordan	TSCI, $n=20$, ≥1 y	Autologous BM and Allogenic UCB	Perilesional (BM-MSC) at baseline and IT (UCB-MSC) at 1, 2, and 3 mos.	Propagation, identity, isolation, counting, and viability. Adipogenic, chondrogenic, and osteogenic characterization. Cytogenetic evaluation.	Safety endpoints for AE monitoring. ASIA-AIS score at 0, 1, 2, and 3 y.

Table 4 (continued)

Registration ID, study phase	Publication	Location	Diagnosis, enrolled, ITI	Donor type, source	Administered: Route, dosing*	MSC methods described†	Primary outcomes*
NCT04520373, phase 2	NA	USA	TSCI, $n=40$, < 1 y	Autologous AT	Group 1: IT at baseline; Group 2: IT at 6 mos post-enrollment; Dose: NA	NA	ASIA-AIS score at 1 y post-treatment in both groups.
NCT01769872, phase 1, 2	NA	ROK	TSCI, $n=15$, > 3 mos	Autologous AT	IV, 2×10^8 cells; IT, 5×10^7 cells; and perilesional, 2×10^7 cells	NA	Safety endpoints for AE monitoring. ASIA-AIS score at 0, 3, and 6 mos.
NCT01624779, phase 1	NA	ROK	TSCI, $n=15$, > 4 wk	Autologous AT	IT; 9×10^7cells at 0, 1, and 2 mos.	NA	Safety endpoints for AE monitoring. MRI results at 6 mos.
NCT01325103, phase 1	Mendonça et al. 2014 [140]	Brazil	TSCI, $n=14$, > 6 mos	Autologous BM	Perilesional;5×10^6 cells/cm^3 at baseline.	Propagation, identity, isolation, and counting. Differentiation (cell types: NA) and cytogenetic analyses.	Safety endpoints for AE monitoring.
NCT01873547, phase 3	NA	China	TSCI, $n=300$, > 1 y	Allogenic UCB	IT at baseline and 3 subsequent intervals (Dose/Frequency: NA).	NA	ASIA-AIS and ISNCSCI scores at baseline, 6 mos, and 1 y.
NCT03308565, phase 1	Bydon et al. 2024 [141]	USA	TSCI, $n=10$, < 1 y	Autologous AT	IT; 100×10^6 cells at baseline.	Propagation and cytogenetic analysis.	Safety endpoints for AE monitoring.
NCT03003364; phase 1, 2a	Albu et al. 2021 [142]	Spain	TSCI, $n=10$, 1–5 y	Allogenic WJ	IT; 10×10^6 cells at 0 and 6 mos.	Propagation, identity, isolation, counting, and viability.	Safety endpoints for AE monitoring. ISNCSCI, Modified Ashworth, VASP, SCIM III, ADL, WHOQOL-BREF, MEP and SEP at baseline, 1, 3, and 6 mos.
NCT00816803; phase 1, 2	El-Kheir et al. 2014 [143]	Egypt	TSCI, $n=70$, 10–36 mos	Autologous BM	IT; 2×10^6 cells/kg BW at baseline.	Propagation, identity, isolation, counting, and viability. Adipogenic, chondrogenic, and osteogenic characterization.	Safety endpoints for AE monitoring. ASIA-AIS, FIM-FRS, and SEP monthly and MRI every 6 mos for 18 mos.
NCT05054803; phase 1, 2	NA	Spain	TSCI, $n=18$, 1–5 y	Allogenic WJ	IT; 1×10^6 cells/kg at baseline and 3 mos.	NA	Safety endpoints for AE monitoring. ASIA-AIS at 1, 3, 4, 6 and 12 mos. MEP, SEP, EPTP, modified Ashworth, SCIM III, and WHOQOL-BREF at 6 and 12 mos.
NCT03225625, NA	NA	USA	TSCI, $n=40$, NA	Autologous BM	Two paraspinal injections, IV, and IN (dose: NA).	NA	ASIA-AIS at 0, 1, 3, 6, and 12 mos.
ChiCTR2200061962; phase 1, 2	NA	China	TSCI, $n=10$, NA	Allogenic UCB	IT and perilesional (dose/schedule: NA)	NA	Safety endpoints for AE monitoring. ASIA-AIS, IANR-SCI-FRS, and WISCI (Schedule: NA).
ChiCTR-INR-17,012,152; phase 1, 2	NA	China	TSCI, $n=18$, < 3 mos	NA	NA	NA	Safety endpoints for AE monitoring. ASIA-AIS, urodynamic, and MRI (schedule: NA).
ChiCTR-TCH-11,001,421, phase 2	NA	China	TSCI, $n=20$, NA	NA, BM	NA	NA	FIM an electrophysiological tests (schedule: NA).
ChiCTR-ONRC-12,002,478, phase 2	NA	China	TSCI, $n=20$, > 1 y	NA, BM	Perilesional (dose/schedule: NA)	NA	ASIA-AIS, urodynamic, electromyography, and SEP (schedule: NA).

Table 4 (continued)

Registration ID, study phase	Publication	Location	Diagnosis, enrolled, ITI	Donor type, source	Administered: Route, dosing*	MSC methods described†	Primary outcomes*
ChiCTR-ONC-12,002,005, phase 2	NA	China	TSCI, $n=20$, >1 y	Allogenic UCB	IV via femoral artery (dose/schedule: NA)	NA	MEP and SEP (schedule: NA).
2021-000346-18; phase 1, 2	NA	Spain	TSCI-I, $n=18$, 1–5 y	Allogenic WJ	IT; 7×10^5 to 1×10^6 cells/kg BW (schedule: NA)	Propagation.	Safety endpoints for AE monitoring. ASIA at 1, 3, 4, 6, and 12 mos. EPTP at 3, 6, and 12 mos. WISCI-II, VASP, modified Ashworth, SCIM-III, and WHOQOL-BREF at 6 and 12 mos.

*Treatments were administered at baseline only unless otherwise noted. For studies that propagated MSC, dates of subsequent administrations and outcomes reflect the date of first treatment as baseline or 0 days, wk, mos, y as applicable

†Isolation: Isolation of MSC from source tissue specimen; Identity: Identification of MSC using phenotypic biomarkers; Counting: Quantification of MSC; Viability: Confirmation of live MSC; Propagation: Proliferation of MSC in tissue culture. Only the methods reported in the publication or trials registry record are listed herein

[a]https://clinicaltrials.gov

[b]https://www.chictr.org.cn

[c]https://www.clinicaltrialsregister.eu

ADL activities of daily life, *AE* adverse events, *ASIA-AIS* American Spinal Injury Association Impairment Scale, *AT* adipose tissue, *BM* bone marrow, *BW* body weight, *EPTP* electrical pain threshold perception, *FIM* functional independence measure, *FRS* Functional Rating Scale, *IANR* International Association of Neurorestoratology, *ISNCSCI* International Standards for Neurological Classification of Spinal Cord Injury, *IT* intrathecal, *ITI* injury-to-treatment interval, *IV* intravenous, *MEP* motor evoked potential, *MPQ* McGill Pain Questionnaire, *MSC* mesenchymal stromal cells, *NA* not available, not provided, or non-existent, *NBD* Neurogenic Bowel Dysfunction, *ROK* Republic of Korea, South Korea, *SCI* spinal cord injury, *SCIM* spinal cord independence measure, *SEP* somatosensory evoked potential, *TSCI* traumatic spinal cord injury, *TSC-I* traumatic incomplete spinal cord injury, *UCB* umbilical cord blood, *VASP* visual analog scale for neuropathic pain, *WHOQOL-BREF* World Health Organization Quality of Life Brief Version, *WISCI* Spinal Cord Injury Walking Index, *WJ* Wharton Jelly

(CNS), damaged peripheral nerves can either spontaneously regenerate or be 'repaired' surgically [144]. Alternative treatment options have been investigated, of which one refers to cell therapy using MSC [145]. An early study compared the outcomes of PNI treatment with silicon tubes versus silicon tubes filled with autologous MSC. The authors concluded that MSC application led to superior nerve recovery, but due to study design biases the results could not be deemed definitive [146]. Subsequently, only a few case reports have been published describing the utilization of MSC to treat PNI. A significant improvement in finger movements in a patient with traumatic total brachial plexus injury (BPI) was found after injection of AT-MSC [147]. There was also an increase in the upper extremity range of motions, with return of functions of the hand in a patient with BPI sustained during a road traffic accident, and furthermore ongoing recovery in motor and sensory functions in patients with median and ulnar nerve injury [148]. However, more clinical research is required to determine whether MSC treatment for PNI can provide therapeutic benefits. Such future efforts might be additionally bolstered by ongoing research designed to address the current shortcomings in MSC treatments for other types of neurological injuries, such as TSCI.

Addressing treatment standards and technological gaps in MSC therapies

Coordination of future studies of neurological injuries

Despite the great potential benefits of MSC therapy for neurological injuries, significant progress in treatment efficacies has not been demonstrated for TBI or TSCI. The application of MSC-based therapies for TBI and TSCI relies on extremely new technology to treat conditions that clinicians have only recently come to understand. Our limited knowledge of the properties of MSC after their localization to the sites of brain and spinal cord injuries in humans is an unavoidable impediment to efforts to design studies capable of yielding clinically meaningful efficacy data. Further innovation in the application of our present knowledge of MSC is therefore needed to overcome obstacles to progress that are inherently associated with MSC-based therapies, as represented in Fig. 1.

The small sizes of the study populations in previous and ongoing studies are likely to compound the effects of intra-study heterogeneity introduced by differences in recruitment criteria, treatment methods and outcome measures, thereby confounding comparisons of outcomes and efficacy. Multi-center studies would allow meaningful subgroup analyses based on injury type or severity, if sufficiently large study populations can be achieved, thereby providing protection against such potential confounding factors. Nonetheless, some degree of standardization of outcome measures would likely improve the quality of the research findings of future MSC therapy

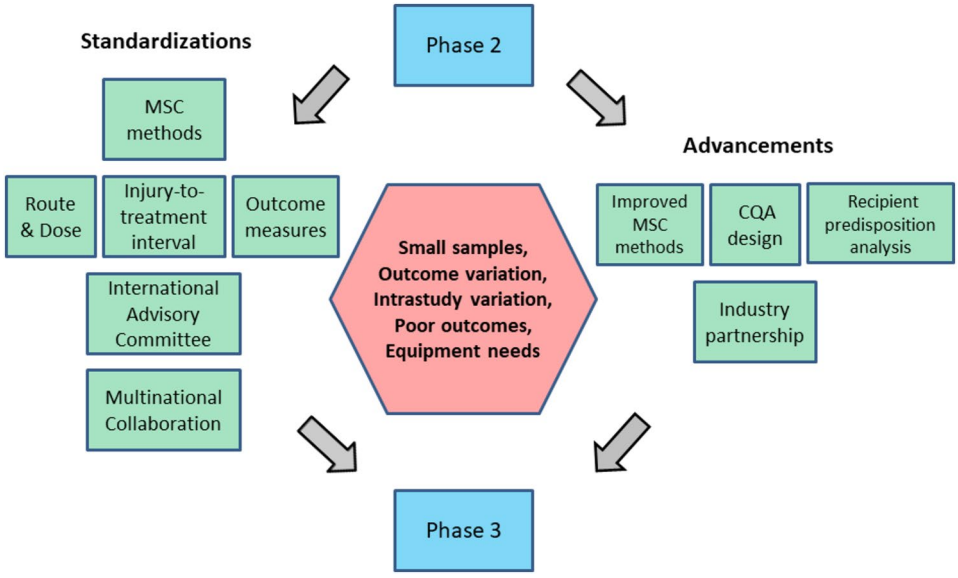

Fig. 1 Schematic diagram of potential flow of progress toward phase 3 trials of mesenchymal stromal cells (MSC) therapy for traumatic neurological injuries. Current obstacles to progress (red, center) prevent the progression of research toward phase 3 trials for traumatic brain and spinal cord injuries. Standardizations in study design and methodologies (green, left), aided in part by the benefits of an international advisory committee and multinational collaborations, can mitigate the effects of such obstacles. Likewise, advancements in technologies, such as improved methods for rapid MSC identification, isolation, counting, and functional characterization, can mitigate the effects of variation by improving both qualitative and quantitative methods. Advancements in the knowledge of critical quality attributes (CAQ) of MSC (green, right), the ability to manipulate CAQs by altering culturing conditions, and the matching of CAQ sets to specific types of tissue repair will improve clinical outcomes. Improved knowledge of recipient predisposition to MSC therapy (green, right) will further allow the matching of CAQ sets to specific injury conditions associated with injury conditions, such as the injury-to-treatment interval or the type of traumatic damage (e.g., crushing versus penetrating injuries), which will also improve clinical outcomes. Industry partnerships can make these technological advancements available to researchers globally, thereby facilitating multinational collaborations and alleviating lack of research infrastructure and equipment shortages at study locations

studies. Achieving further progress might also require more stringent patient selection criteria aimed at identifying those with injuries that are more neurologically similar.

Efforts to standardize selection criteria, outcome measures and/or methods of data analysis might also limit the extent to which research efforts are undermined by shortcomings in study designs or unexpected factors negatively impacting study completion or data analysis. Of the seven trials in Table 4 that were completed, we found publications describing the results of only five of them. Furthermore, we identified two TBI clinical trials (NCT02028104 and NCT02959294) which have been withdrawn from the clinical trial registries. Though we identified two publications [149, 150] reporting results of the TBI clinical trial NCT02028104, its status in the trials registry has since been designated as 'withdrawn'. The trials registry provides no information about the reasons for either withdrawal. We do not wish to speculate inappropriately on the reasons for this high proportion of unpublished and withdrawn studies of MSC therapy for TBI. However, the lack of clinically meaningful results is one obvious possibility. Regarding TSCI treatments with MSC-based therapies, though the number of studies and publications with reported results is higher than for TBI, the mainly phase 1/2 trials also involved only small cohorts of patients and were focused mainly on safety, but reported varying efficacies within small subgroups. Our review highlights the need for future studies to incorporate means of avoiding similar obstacles to progress.

We believe that the creation of an international body of experts in the fields of clinical neurology and MSC-based therapies would benefit future research efforts in MSC treatment for neurological injuries in a number of ways. This type of committee could provide useful advice regarding trial registry applications and regulatory issues, the latter of which can be quite complex in the context of trauma medicine. Perhaps the most important example of such benefits to both the investigator and the research community would be recommendations for standardized patient outcomes specific to the type of neurological injury to better facilitate comparisons with the results of other studies. Recommendations regarding patient selection criteria and intervention methods will also likely be beneficial in some circumstances.

It might also be helpful to include industry representatives on such a committee to provide feedback regarding the roles companies can fulfill to best support researchers using their newly developed products or services.

Implementing the involvement of a non-authoritative, non-regulatory advisory committee for MSC therapies for neurological injuries could be problematic in some instances. However, we believe that any benefit to the overall progress of research would justify its role. It is also important to consider that such a committee might also benefit researchers investigating MSC-based therapies for other types of neurological injuries, such as ischemic stroke, cerebral palsy and others, because these areas of research are also beset by the same types of obstacles to progress that have thus far impeded progress in research for MSC therapies for TBI and TSCI.

Identification and quantification of MSC

Current methods of MSC identification and quantification using cell markers cannot efficiently discriminate between the early stages of differentiation [151]. Another recent review noted that, despite the known phenotypic complexity of MSC, many studies of MSC therapies have not performed cell counting methods uniformly, including studies in which MSC propagation was performed [151]. Twenty-six of the 40 trials we reviewed herein did not report counting methods, and five described using a propagation step prior to MSC identification, counting, and isolation by flow cytometry (Tables 3 and 4). Changes in MSC phenotype are known to occur during cell culture expansion [152], thereby possibly creating subpopulations of MSC with altered stemness and/or paracrine signaling properties. More thorough quantification and the examination of possible MSC subpopulations within newly isolated MSC and expanded MSC specimens might also be beneficial toward optimizing administration dosages.

The developing field of MSC applicability addresses the need for accurate MSC phenotyping and counting methods that can be standardized to meet clinical research requirements [151]. The products of MSC propagation have been deemed advanced therapy medicinal products (ATMPs) by regulatory agencies in the USA and Europe, and are therefore subject to certain quality assurance regulations that result in a more expensive and time-consuming process of MSC propagation. This added burden has been compounded by the manufacturing and quality assurance issues encountered by the majority of companies producing ATMPs [153]. The net effect of ATMP regulatory requirements has therefore increased the appeal of single-step preparations for MSC therapies. Due to the sparseness of MSC in donor tissues, the accurate counting of newly isolated MSC is especially important for such single-step methodologies to ensure consistently sufficient numbers of MSC are administered. For regenerative therapy studies using autologous MSC with short injury-to-treatment intervals, perhaps even same day interventions, cell counting methods must be both accurate and rapid to mitigate variation in the period required for the transportation, evaluation, and stabilization of injured patients.

A recent study used immunofluorescence images of AT-MSC to train deep-learning convolutional neural network models to quantify the stemness properties of MSC based on nuclear structure and actin architecture [154]. The analysis showed that certain changes in chromatin appearance, especially with regard to the extent and positioning of heterochromatin features, were indicative of the early differentiation of AT-MSC during the first 6 to 24 h of adipogenesis. Though their fluorescence imaging methods cannot be used for the evaluation of living cells due to the deleterious effects of DNA-intercalating dyes, the authors of this study proposed that recent advancements in phase contrast, differential interference contrast, Raman scattering, and light scattering microscopy technologies allow the production of images of living cells that are similarly capable of training deep-learning models to identify early differentiation in AT-MSC. It is possible that this extension of their research might also provide a means of rapidly evaluating MSC to detect early differentiation in neurogenesis as a means of optimizing MSC isolation and/or propagation methods for MSC therapies for neurological injuries.

Assessments of MSC viability and clinical attributes

Efforts to assess the viability and clinical attributes of MSC are also vital to the advancement of MSC therapies. A recent analysis of 84 published reports of clinical trials of MSC therapies for a variety of diseases found that one-third of the studies reported no characterization of MSC functionality or viability, and assessments in the remaining studies were overly generalized and inconsistent across studies [155]. Standardized assays, such as trypan blue staining and fibroblast colony-forming unit (CFU-F) assays, can be used to assess the viability and self-renewal capacity of MSC, respectively [156]. A viability of >90% is recommended for most MSC therapies [156]. Only 9 of the 40 clinical trials in Tables 3 and 4 reported viability testing. Differentiation assays also assess the progenitor potential of MSC to transition to specific cell types, which is critical indicator of stemness. Only 6 of the studies in Tables 3 and 4 reported performing differentiation assays. As clinical research in MSC therapies has progressed over the past decade, institutional review committees have made cell counting, viability, and CFU-F assays standard requirements for most MSC therapy clinical trials. These types of assessments do not, however, measure the specific cellular properties involved in MSC-mediated tissue repair, which are described collectively as critical quality attributes (CQAs).

Recent studies have proposed metrics to assess the immunomodulatory and angiogenic properties of MSC.

Phinney et al. [34] developed a clinical indications prediction (CLIP) scale based on the population mean level of *TWIST1* mRNA expression, in which increased *TWIST1* expression across an MSC population correlated with greater angiogenic activity and stem/progenitor self-maintenance, whereas reduced *TWIST1* expression correlated with increased stimulus-induced differentiation and greater anti-inflammatory and immunomodulatory activities. The level of *TWIST1* expression was also shown to be directly proportional to CFU-F score [34], suggesting that CFU-F could be used to estimate the critical quality attributes of MSC. The CLIP scale can therefore be used to align the desired critical quality attributes of MSC with optimal clinical benefits for a specified pathological condition. Based on this range of MSC functional activities, the treatment of neurological injuries would seem to require intermediate to low CLIP scores for the most clinically beneficial mix of critical quality attributes.

The application of this continuum of MSC functional activities describing CQAs was taken further by Robb et al. [157] who used a multivariate matrix to define the specific critical processing parameters (CPPs) that could be manipulated based on cell culture conditions to enhance the fitness of AT-MSC toward either immunomodulatory or angiogenic potency. In another study published during the production of our manuscript, Krupczak et al. [158] demonstrated that CPPs could be modified using a microcarrier-microbioreactor platform to reliably propagate populations of BM-MSC with desired CQAs based on the expression of predefined sets of well-characterized genes known to be involved in MSC functional activities, with their results showing reasonable repeatability (donor-to-donor) and reliable reproducibility (batch-to-batch), suggesting that these procedures can be performed by investigators at the institutional level.

Predisposition of patients to MSC therapy

Among the clinical trials of MSC therapy for neurological injuries reviewed herein, substantial variation occurred with regard to the injury-to-treatment interval (Tables 3 and 4). The post-injury period might be an important contributing factor to the predisposition of a patient to regenerative MSC therapy. It remains unclear how the biochemical links between the progenitor and paracrine functions of MSC might differ between the acute and chronic neurological injury microenvironments. However, the application of MSC therapy in the period immediately following injury would seem to better reflect a time course of natural healing processes, compared with similar application to a long-term injury subjected to chronic inflammation, necrosis, and glial scarring. The next frontier in MSC therapy will likely center on determining which host biomarkers provide predictive insight into the favorability of a patient's response to MSC therapy [34]. However, in the absence of standardized assays for such predictive markers, the effects of variation in host predisposition to MSC therapy in clinical trials might be mitigated, at least in part, by selecting patients with comparable injury-to-treatment intervals measured in days or weeks rather than years. If predictive biomarkers of response to MSC therapy can be identified in the future, determining differences between the predispositions of patients with acute versus chronic neurological damage could then become possible. In the interim, patients who are unlikely to respond favorably to MSC therapy based on the current understanding of CNS injury physiology can pivot to other available treatments, rather than being subjected to the futility of invasive procedures that provide no meaningful improvement in their quality of life.

Conclusions

Evidence from animal studies has provided exciting potential for the use of MSC therapy to improve outcomes for patients with traumatic neurological injuries. Heroic efforts have been undertaken by researchers to harness the potential of MSC therapy despite our lack of a complete understanding of the functional properties of MSC administered in the neurological injury microenvironment. While the results of clinical trials for MSC therapy for TBI and TSCI clearly show that many challenges must be met before such treatments can become a reality for patients stricken with these devastating injuries, recent research has made substantial progress in addressing the knowledge and technological gaps in MSC therapy. It is our hope that the combination of improved treatments standards and technological advancements will facilitate the tayloring of MSC therapy to that most beneficial for neurological injury and reduce the potential variation in treatment response that has undoubtedly hampered the advancement of clinical research thus far.

Abbreviations

ASIA	American Spinal Injury Association
AT	Adipose tissue
ATMPs	Advanced therapy medicinal products
BM	Bone marrow
BPI	Brachial plexus injury
CCL2	C-C motif chemokine ligand 2
CFU-F	Fibroblast colony-forming unit
CLIP	Clinical indications prediction
CNS	Central nervous system
CPPs	Critical processing parameters
CQAs	Critical quality attributes
DP	Dental pulp
FMMS	Fugl-Meyer Motor Scale
HLA-G	Histocompatibility locus antigen-G
IL	Interleukin
IR	Infrared
IV	Intravenous
MRI	Magnetic resonance imaging
MSC	Mesenchymal stem/stromal cell

PNI	Peripheral nerve injury
TBI	Traumatic brain injury
TNF	Tumor necrosis factor
TSCI	Traumatic spinal cord injury
UCB	Umbilical cord blood
WJ	Wharton's jelly

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Author contributions
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Data availability
The data supporting this review are from previously reported studies and datasets, which have been cited.

Declarations

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Not applicable.

Consent for publication
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Xiujuan Wang, Ying Yang and Yongsheng Xu are employees of Tianjin Everunion Biotechnology Co., Ltd. Qian Wang and Jiaxian Wang are employees of HELP Therapeutics Co., Ltd. The remaining authors declare no competing interests.

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