NEUROSURGICAL FOCUS

Neurosurg Focus 46 (3):E10, 2019

Stem cell therapies for acute spinal cord injury in humans: a review

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Recent advances in stem cell biology present significant opportunities to advance clinical applications of stem cell–based therapies for spinal cord injury (SCI). In this review, the authors critically analyze the basic science and translational evidence that supports the use of various stem cell sources, including induced pluripotent stem cells, oligodendrocyte precursor cells, and mesenchymal stem cells. They subsequently explore recent advances in stem cell biology and discuss ongoing clinical translation efforts, including combinatorial strategies utilizing scaffolds, biogels, and growth factors to augment stem cell survival, function, and engraftment. Finally, the authors discuss the evolution of stem cell therapies for SCI by providing an overview of completed (n = 18) and ongoing (n = 9) clinical trials.

https://thejns.org/doi/abs/10.3171/2018.12.FOCUS18602

KEYWORDS stem cell; spinal cord injury; transplant; trauma; clinical trials

Spinal cord injury (SCI) is defined by a complex pathophysiological cascade provoked by mechanical injury to the spinal column. The global incidence of acute SCI is approximately 10 cases per 100,000 persons, resulting in over 700,000 new cases diagnosed per year worldwide.[28] The economic impact attributed to the care of SCI patients is substantial, with estimated first-year costs at over $500,000 per individual with additional annual charges of nearly $100,000 for the remainder of the patient's life.[10,36]

SCI pathophysiology consists of two distinct phases. Primary injury refers to the initial shearing or compression of the spinal cord tissue. The mechanical force of the primary injury causes hemorrhage, disruption of cell membrane integrity, and ion and neurotransmitter imbalance that immediately compromises neural function. Secondary injury pertains to the progressive inflammatory, ischemic, and apoptotic cascade that follows the initial mechanical assault.[52] Stem cell therapies for SCI seek to minimize the spread of secondary injury, augment the function of remaining cell populations, and facilitate regeneration of neuronal and glial populations. In this review article, we explore cell-based therapies targeting acute SCI, with a focus on completed and ongoing clinical trials.

History of Cell-Based Therapies

Stem cells have the unique ability to undergo asymmetrical division, generating a daughter stem cell and an additional progenitor cell. The repertoire of phenotypes that a stem cell is capable of maturing into defines its potency, with totipotency referring to the ability to differentiate into all terminal cell populations and multipotency defining stem cells only able to pursue a subset of lineages. Advances in stem cell biology have allowed for direct modulation of differentiation pathways and the ability to generate relatively homogeneous terminally differentiated cell populations from totipotent and multipotent cells. Transplanta-

ABBREVIATIONS AD-MSC = adipose-derived MSC; ASIA = American Spinal Injury Association; BDNF = brain-derived neurotrophic factor; BMP = bone morphogenetic protein; BM-MSC = bone marrow–derived MSC; ESC = embryonic stem cell; iPSC = induced pluripotent stem cell; MEP = motor evoked potential; MSC = mesenchymal stem cell; NPC = neural progenitor cell; OPC = oligodendrocyte progenitor cell; SCI = spinal cord injury; TGFβ = transforming growth factor–β; U-MSC = umbilical cord MSC.

SUBMITTED November 1, 2018. **ACCEPTED** December 11, 2018.
INCLUDE WHEN CITING DOI: 10.3171/2018.12.FOCUS18602.

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tion of multipotent neural progenitors has been shown in rodent models to be sufficient for promoting axon elongation and synapse formation in spite of the postinjury inhibitory milieu.[33] Early investigations into the potential of directed differentiation centered around deriving neural lineage cell populations from human embryonic stem cells (ESCs), with functional studies demonstrating transplantation of these derived populations encouraged behavioral and sensorimotor recovery in small rodent models of acute SCI.[15,25,35,47,59] Clinical exploration of cell transplant therapy in acute SCI patients led to the initiation of a 2010 Geron Corporation trial exploring introduction of human ESC–derived oligodendrocyte progenitor cells (OPCs) into the lesion site.[16] Since then, investigations into cell-based therapies have expanded on multiple frontiers, from the derivation of transplantable cells from neural progenitors to the establishment of a multitude of methods for optimizing transplant delivery (Table 1).

ESC-Derived Therapies

ESCs are regarded as the archetypal stem cell, with the capacity to endlessly self-renew and the ability to differentiate into any cell lineage.[26] Maintenance of this state is nontrivial, requiring stringent regulation of cell-cycle progression and conservation of genomic stability. Human ESCs specifically require the modulation of an intricate series of activating and inhibitory pathways, including but not limited to the inhibition of bone morphogenetic proteins (BMP2 and BMP4), activation of transforming growth factor–β (TGFβ) and involvement of Wnt pathway proteins.[13,47] Retention of genomic stability is largely associated with maintenance of telomere integrity by upregulation of telomerase activity and promotion of DNA repair pathways involved in replication error repair and oxidative stress.[2,13] Satisfaction of these two prerequisites, along with upregulation of the critical transcription factors Oct3/Oct4, Sox2, Klf4, and c-Myc, is sufficient for indefinite maintenance of a pluripotent state.[57]

The ability to direct differentiation along neural fates offers intriguing glimpses into the potential of stem cell therapy in acute SCI. The induced differentiation of ESCs into neural progenitors, cells restricted to neuronal and glial lineages, has been explored using various protocols to manipulate in vitro conditions to direct cell maturation.[18,60,68,70] Transplantation of these neural progenitors into animal models of acute SCI has yielded promising results, including transplant integration, axonal elongation, tract regeneration, oligodendrocyte-induced remyelination, and restoration of neuromuscular junctions.[15,18,35] Assessment of hindlimb functionality and gait suggests that the transplantation of ESC-derived neural progenitors encourages modest recovery of motor function.[15,25,35]

Significant functional, legal, and ethical shortcomings, however, have limited the application of ESCs in human SCI.[41] Acquisition of ESCs involves the isolation of embryonic cells from the inner cell mass of the developing blastocyst, one of the final phases in which germ cells retain pluripotency and self-renewing capabilities; this, however, results in the destruction of the blastocyst, raising significant ethical concerns.[62] Additionally, the formation of teratomas, tumors masses composed of structurally and compositionally heterogeneous aggregates of differentiated somatic tissue, has been observed in numerous animal models of ESC-derived cell therapy.[40,58] Molecular characterization of human ESC teratomas has provided insight into potentially targetable oncogenic pathways, allowing for future investigations into methods for ablation of tumorigenic potential.[4]

Transition to Alternative Stem Cell Types

Given the controversies surrounding ESCs, focus has transitioned to mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs) as multipotent alternatives to human ESCs. Unlike human ESCs, MSCs can be readily harvested from adults and are obtained from a number of organs and tissues, including bone marrow and adipose tissue.[64] In addition, the opportunity to harvest and transplant cells autologously greatly reduces concerns regarding immunogenicity and graft rejection. MSC-derived cell transplant therapies also have been shown in animal models to reduce spinal cord damage associated with immune activation by secondary injury.[1] Finally, the ability of MSCs to "home" to the injury site allows for noninvasive methods of cell transplantation, including peripheral injection.[44,65] Despite these advantages, MSCs also bring distinct limitations, including their inherent multipotency that restricts the repertoire of available cell fates.

In particular, studies have explored the therapeutic potential of OPCs, bone marrow–derived (BM-MSCs), adipose-derived (AD-MSCs), and umbilical cord (U-MSCs) MSCs in the context of SCI.

OPCs

Demyelination of axonal projections resulting from the destruction of local oligodendrocyte populations is a hallmark of secondary SCI. Transplantation of OPCs (also referred to as oligodendrocyte precursor cells) may mediate loss of myelination and attenuate further injury. In vivo studies have demonstrated significant therapeutic potential in the transplantation of OPCs in contusive SCI models. Implanted OPCs are capable of full differentiation into mature oligodendrocytes and promote remyelination of damaged axons near the injury site.[6] Phenotypic recovery of motor function has additionally suggested a restorative benefit associated with OPC transplantation. Histological findings correlate with this observed improvement, demonstrating preservation of white matter in experimental groups exhibiting the greatest functional improvement.[30] Evaluation of motor evoked potentials (MEPs) revealed reduced latency periods in animals receiving OPC transplants and confirmed recovery of motor system conduction.

Despite substantial research exploring OPC transplantation as a potential therapeutic avenue in SCI management, there remains a shortage of longitudinal clinical trials demonstrating efficacy in humans. An ongoing phase I/II dose-escalation trial by Asterias Biotherapeutics aims to evaluate human ESC–derived OPC transplants in cervical SCI and was expected to reach completion by December 2018 (Table 2; NCT02302157). Interim results from

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TABLE 1. Completed clinical trials on stem cell therapy in acute SCI

ClinicalTrials.gov Identifier	Title	Phase(s)	No. Enrolled	Completion Date	Primary End Point	Secondary End Point	Intervention	Injection Site	Status	Results Pub	Findings
NCT02482194	Autologous mesenchymal stem cells transplantation for spinal cord injury—a phase I clinical study	I	9	Mar 2016	Safety	NA	Autologous BM-MSCs	Intrathecal	Completed	Satti et al.	Intrathecal administration of BM-MSCs is safe w/ no adverse events[51]
NCT01186679	Safety and efficacy of autologous bone marrow stem cells in treating spinal cord injury	I/II	12	Aug 2010	Safety/ASIA score	NA	Autologous BM-MSCs	Intrathecal	Completed	NA	NA
NCT02027246	Safety and efficacy of stem cell therapy in spinal cord injury	I	166	Feb 2013	Safety	NA	Autologous BM-MSCs	Intrathecal	Completed	NA	NA
NCT01769872	Safety and effect of adipose tissue derived mesenchymal stem cell implantation in patients with spinal cord injury	I/II	15	Jan 2016	ASIA score	MRI; MEP/SSEPs; ADL; SF-36; ODI; safety	Autologous AD-MSCs	Intravenous; intrathecal	Completed	NA	NA
NCT01873547	Different efficacy between rehabilitation therapy and stem cells transplantation in patients with SCI in China	III	300	Dec 2015	ASIA score	McGill Pain Questionnaire; Barthel Index; SSEPs/MEPs	U-MSCs	Intrathecal	Completed	NA	NA
NCT01274975	Autologous adipose derived MSCs transplantation in patient with spinal cord injury	I	8	Feb 2010	Safety	NA	Autologous AD-MSCs	Intravenous	Completed	Ra et al.	Intravenous administration of AD-MSCs is safe w/ no adverse events[48]
NCT01624779	Intrathecal transplantation of autologous adipose tissue derived MSC in the patients with spinal cord injury	I	15	May 2014	MRI changes	NA	Autologous AD-MSCs	Intrathecal	Completed	NA	NA
NCT01328860	Autologous stem cells for spinal cord injury (SCI) in children	I	10	Jun 2016	ASIA score	Neuropathic pain	Autologous BM-MSCs	Intravenous	Terminated	NA	NA
NCT01162915	Transfer of bone marrow derived stem cells for the treatment of spinal cord injury	I	10	May 2014	Safety	NA	Autologous BM-MSCs	Intrathecal	Suspended	NA	NA
NCT02163876	Study of human central nervous system (CNS) stem cell transplantation in cervical spinal cord injury	II	31	May 2016	ISNC-SCI upper-extremity scores	Safety	Human CNS stem cells	Intramedullary	Terminated	NA	NA

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TABLE 1. Completed clinical trials on stem cell therapy in acute SCI

ClinicalTrials.gov Identifier	Title	Phase(s)	No. Enrolled	Completion Date	Primary End Point	Secondary End Point	Intervention	Injection Site	Status	Results Pub	Findings
NCT02237547	Safety and feasibility study of cell therapy in treatment of spinal cord injury	I/II	0	Oct 2019	Safety	ASIA score; Frankel grade	Autologous BM-MSCs; allogeneic AD-MSCs	Intrathecal; intravenous	Withdrawn	NA	NA
NCT01725880	Long-term follow-up of transplanted human central nervous system stem cells (HuCNS-SC) in spinal cord trauma subjects	I/II	12	May 2016	ASIA score	NA	Human CNS stem cells	Intramedullary	Terminated	NA	NA
NCT01393977	Difference between rehabilitation therapy and stem cells transplantation in patients with spinal cord injury in China	II	60	May 2012	EMG; ENP test	NA	U-MSCs	Intrathecal	Completed	Cheng et al.	Patients receiving U-MSCs demonstrate improved urinary control, muscle tension, motion, & self-care ability[11]
NCT01694927	Autologous mesenchymal stem cells in spinal cord injury (SCI) patients (MSC-SCI)	II	30	Jun 2014	Safety	Muscle, sphincter; spastic control	Autologous MSCs	Intralesional	Unknown	NA	NA
NCT01730183	To study the safety and efficacy of autologous bone marrow stem cells in patients with spinal cord injury (ABSCI)	I/II	15	Nov 2014	Safety	ASIA score	Autologous BM-MSCs	Intrathecal	Unknown	NA	NA
NCT01833975	Study the safety and efficacy of bone marrow derived autologous cells for the treatment of spinal cord injury (SCI)	I/II	50	Sept 2016	Frankel grade	Pain sensation; ASIA score	Autologous BM-MSCs	Intrathecal	Unknown	NA	NA
NCT01446640	Mesenchymal stem cells transplantation to patients with spinal cord injury (MSC)	I/II	20	Jun 2014	Safety	EMG; ENP test; ASIA & Frankel grade	Autologous BM-MSCs	Intravenous; intrathecal	Unknown	NA	NA
NCT02034669	Transplantation of autologous adipose derived stem cells (ADSCs) in spinal cord injury treatment	II	48	Mar 2015	Safety	MRI; urinary & bowel function; EMG; ASIA score	Autologous AD-MSCs	Intradural; intrathecal; intravenous	Unknown	NA	NA

ADL = activities of daily living; EMG = electromyography; ENP = electroneurophysiological; ISNC-SCI = International Standards for Neurological Classification of Spinal Cord Injury; NA = not applicable; ODI = Oswestry Disability Index; Pub = published; SSEP = somatosensory evoked potential.

Despite the scarcity of published results outlining findings in cell-based SCI therapy trials, early trials suggest a lack of serious adverse effects associated with the introduction of MSC-derived therapies.[11,48,51] The majority of completed studies evaluated MSC-derived cell transplantation, necessitating additional inquiry into iPSC-centered methods and combinatorial approaches. (Results were queried from the NIH clinical trial repository [clinicaltrials.gov] using the key terms "spinal cord injuries" and "stem cell." Filtering was done to only include trials addressing acute or subacute SCI. Completed, suspended, and terminated trials are included the table. Unknown trials with a past expected end date are also included.)

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TABLE 2. Currently active/recruiting trials exploring cell therapy in acute SCI

ClinicalTrials.gov Identifier	Title	Phase(s)	No. Enrolled	Completion Date	Primary End Point	Secondary End Point	Intervention	Injection Site	Status
NCT02326662	Neural stem cell transplantation in traumatic spinal cord injury	I/II	30	Dec 2018	Feasibility/safety	324-point ASIA; MRI	Autologous NSCs + 3D matrix	Intraspinal; intrathecal	Active, not recruiting
NCT02481440	Umbilical cord mesenchymal stem cells transplantation to patients with spinal cord injury	I/II	44	Dec 2018	ASIA score; IANR-SCIRFS score	Adverse events; EMG/ENP test; MRI	Allogeneic UC-MSCs	Intrathecal	Recruiting
NCT03521336	Intrathecal transplantation of UC-MSC in patients with sub-acute spinal cord injury	II	130	Dec 2022	ASIA score	IANR-SCIRFS score; EMG; residual urine	Allogeneic UC-MSCs	Intrathecal	Recruiting
NCT02981576	Safety and effectiveness of BM-MSC vs AT-MSC in the treatment of SCI patients	I/II	14	Jan 2019	ASIA score; MRI	Safety & effectiveness	Autologous BM-MSC; autologous AD-MSCs	Intrathecal	Active, not recruiting
NCT03308565	Adipose stem cells for traumatic spinal cord injury	I	10	Nov 2023	Acute adverse events	ASIA; MEPs; SSEPs; MRI; functional changes	Autologous AD-MSCs	Intrathecal	Recruiting
NCT02009124	Stem cell therapy in spinal cord injury	II	500	Dec 2018	Change in clinical symptoms	Functional Independence Measure score	Autologous BM-MSCs	Intrathecal	Recruiting
NCT03225625	Stem cell spinal cord injury exoskeleton and virtual reality treatment study	NA	40	Jul 2022	ASIA score	ANS function; general well-being	Autologous BM-MSCs	Paraspinal; intravenous; intranasal	Recruiting
NCT02917291	Safety and preliminary efficacy of FAB117-HC in patients with acute traumatic spinal cord injury	I/II	46	Jan 2020	Safety	ISNC-SCI; SCIM III; SSEPs; MEPs	Autologous AD-MSCs	Intramedullary	Recruiting
NCT02302157	Dose escalation study of AST-OPC1 in spinal cord injury	I/II	35	Dec 2018	Safety	ISNC-SCI	ESC-derived OPCs	Unknown	Active, not recruiting

ANS = autonomic nervous system; AT = adipose tissue; IANR-SCIRFS = International Association of Neural Restoration Spinal Cord Injury Functional Rating Scale; NSC = neural stem cell; SCIM III = Spinal Cord Independence Measure III; UC = umbilical cord.

Currently active clinical trials are primarily early phase and are aimed at expanding understanding of the safety profile of stem cell therapies in SCI. Only two studies (NCT03521336 and NCT02009124) plan to enroll more than 50 subjects, highlighting a need for large, controlled clinical trials. (Trials were identified from the NIH repository of clinical trials [clinicaltrials.gov]. Results were queried using the key terms "spinal cord injuries" and "stem cell." Filtering was done to only include trials addressing acute or subacute SCI. Only active or recruiting trials are included.)

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the first cohort of patients evaluated suggest a promising safety profile, with no reported severe adverse side effects 24 months following treatment.[3] Continued evaluation is ongoing, but preliminary reports include MRI evidence of cell attachment and tissue formation. Longitudinal evaluation of changes in American Spinal Injury Association (ASIA) motor score indicates upper-extremity motor improvements in 5 of 6 patients. Despite promising initial results, additional validation is needed in the form of larger transplant cohorts and additional phase II and III trials.

BM-MSCs

BM-MSCs are partially differentiated progenitor cells that reside within adult bone marrow and support continual hematopoiesis and bone regeneration.[9] Originally believed to be tripotent, additional studies have shown that BM-MSCs are capable of pursing a broad range of lineages and can propagate populations expressing a variety of neural markers.[66] Early in vivo research established that the introduction of BM-MSCs into the injury site of rats suffering from spinal cord contusion resulted in the robust formation of tissue bundles hosting populations of astrocyte and neuronal predecessors.[21] Delayed introduction of BM-MSCs into the injury site was found to improve functional recovery of hindlimb motility and strength. Further molecular characterization of BM-MSC intravenous transplantation models suggested that functional recovery was preceded by expanded production of neurotropic factors (brain-derived neurotrophic factor [BDNF] and nerve growth factor) and vascular endothelial growth factor.[12] BDNF and nerve growth factor have previously been demonstrated to be critical regulators in neuronal differentiation, while vascular endothelial growth factor is known to be a key contributor to the initiation and continued induction of angiogenesis and vasculogenesis.[20,31]

In one of the first longitudinal studies examining BM-MSC–based therapy in patients with cervical SCI, autologous BM-MSCs isolated from the iliac bone of each patient were expanded and introduced via injection (both intramedullary and intradural). Within 6 months of transplantation, improved upper-extremity motor function and MRI changes were observed in 6 and 7 of the 10 candidate patients, respectively.[23] These patients were tracked for over 3 years posttransplantation, and continued observation of recovery progress demonstrated continuous improvement in upper-extremity functionality with no evidence of complications or tumor formation.[46] Additional trials would help confirm the clinical efficacy of BM-MSCs, especially in light of conflicting reports disputing the extent to which patients respond to BM-MSC treatment.[45,55] In addition to completed studies, we identified 3 ongoing phase I and II trials exploring BM-MSC–based therapies in acute SCI patients (Table 2). For each of these studies, functional improvements were measured according to a graded scale (e.g., ASIA) and, combined, they seek to enroll 554 total patients. One study in particular, named SciExVR, aims to integrate other therapeutic modalities, namely exoskeletal stimulation and virtual reality visualization, following paraspinal, intravenous, and intranasal application of BM-MSCs to explore the potential benefit of combinatorial therapies centered around BM-MSCs (NCT03225625). The completion of these studies will provide much-needed information to initiate larger-scale efforts scrutinizing the functional efficacy of BM-MSC–derived therapies.

U-MSCs

Recent investigations have also examined the utility of MSCs recovered from tissue sources outside of bone marrow, including umbilical cord and adipose tissue.[7,32] U-MSCs specifically demonstrate the potential to mature into relatively homogeneous populations expressing neural markers, acquiring phenotypic traits, such as end branching and bipolar extensions, that are characteristic of terminally differentiated neurons and their predecessors. Furthermore, immunostaining for neural biomarkers demonstrates extensive expression of cytoskeletal proteins specific to neurons and astrocytes.[19] In an early study of intravenous transplantation of human U-MSCs, rats suffering from compressive SCI demonstrated significant functional recovery.[50] Additionally, U-MSCs were found to migrate to the injury site within 4 weeks of transplantation. Later studies demonstrated additional benefit associated with coinjection of BDNF with U-MSCs compared to injection of only U-MSCs. Immunohistochemistry for GFAP/MAP2 confirmed differentiation into the astrocytic and neural lineages, respectively.[27] Anatomical improvements at the injury site were also observed after transplantation of U-MSCs, noting increased angiogenesis and reduced glial scar formation due to upregulation of matrix metalloproteinases.[37,63]

Clinically, injection of U-MSCs into the subarachnoid, intradural, and extradural spaces of the spinal cord in a patient suffering from a compressive fracture has demonstrated improved motor function in the lower extremities, and CT and MRI demonstrated expansion of the atrophied spinal cord, particularly at the injured level.[24] However, additional efforts are needed to more comprehensively evaluate the effectiveness of U-MSC transplantation in acute SCI. A recently initiated phase II trial has started enrollment of patients into a multicenter, randomized, sham-controlled study evaluating the safety and efficacy of intrathecal transplantation of U-MSCs into patients with acute, subacute, and chronic SCI (Table 2; NCT03521336). Functional progress scores based on the ASIA Scale, the International Association of Neural Restoration of Spinal Cord Injury Rating Scale, and electromyogram testing serve as clinical end points and completion of the study is expected by late 2022.

AD-MSCs

AD-MSC transplants have also been explored as an alternative to ESC-based therapy. Compared to bone marrow, adipose tissue contains a greater population of somatic stem cells, which, combined with the ubiquitous availability of adipose tissue, has made AD-MSCs an attractive source of transplantable MSCs.[14,71] Functional experiments indicate that intravenous application of AD-MSCs improve hindlimb motor function through activation of angiogenesis along with upregulation of upstream kinase protein activity, such as ERK1/2 and Akt, in turn promoting cellular survival pathways and tissue-repair mechanisms.[42] However, while AD-MSC transplantation has been evaluated

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in animal SCI models, there remains a paucity of large, longitudinal clinical trials utilizing stem cells derived from adipose tissue. Early studies examining the safety of intravenous injection of AD-MSCs reported no adverse side effects, including no observed tumorigenicity.[48] One recent study investigated the effect of intrathecal transplantation of autologously collected AD-MSCs in 14 patients with SCI.[22] Functionality was measured using the ASIA motor and sensory scores, while corresponding electrophysiological studies included electromyography and MRI examinations. Following treatment, 10 of the 14 patients exhibited sensory improvement; however, lesion size, as visualized by MRI, remained stable. Severe adverse events were also absent from all of the patients treated with AD-MSCs. While 3 patients developed minor side effects following therapy, these events were thought to be unrelated to the treatment itself.

We identified 3 ongoing clinical trials exploring the safety and efficacy of AD-MSCs and AD-MSC–derived therapies (Table 2; NCT02917291). The most comprehensive of these is a phase I/II trial investigating FAB117-HC in patients with traumatic thoracic SCI. FAB117-HC is a putative therapeutic product whose active ingredient is expanded allogeneic AD-MSCs, and the current study design has partitioned participants into cohorts exploring FAB117-HC effectiveness in a randomized, controlled double-blind fashion. The estimated study completion date is in December of 2020 and, pending the publication of study results, could initiate broader clinical trials focusing on efficacy evaluation of AD-MSC–derived cell transplants in acute SCI.

iPSCs

Expanded understanding of biochemical modulators of stem cell maturation has allowed for the "un-differentiation" of terminally differentiated somatic cells, such as fibroblasts and peripheral blood cells, into pluripotent cells termed induced pluripotent stem cells. iPSCs were first generated by Drs. Takahashi and Yamanaka, who defined Oct3/4, Sox2, c-Myc, and Klf4 as the 4 factors necessary to reverse differentiate adult fibroblasts into a stemlike cell.[56,57] Concurrently, the authors identified Oct4, Sox2, NANOG, and LIN28 as being sufficient to reprogram fully differentiated somatic cells to express ESC-like qualities.[69] As our understanding of differentiation and developmental biology has advanced, studies have increasingly turned to iPSCs as an ethical and readily obtainable alternative to ESCs. iPSC-derived neural progenitor cells (NPCs) have been shown to exhibit ESC-like neural differentiation potentials both in vitro and in vivo.[61] In animal models of SCI, transplantation of these iPSC-derived NPCs has been associated with a reduced injury profile, tract regeneration, remyelination, and serotonergic reinnervation.[34,39] In one study, prescreening of NPCs was required as a subset of transplanted NPC neurospheres resulted in formation of teratomas and subsequent functional deterioration. This increased tumorigenic potential has been associated with the viral mechanism used to generate iPSCs, as constitutional reactivation of the c-Myc transgene frequently occurs due to viral integration into the host cell genome.[43] Recent solutions for overcoming this conundrum include the development of nonviral methods for creating iPSCs utilizing transposon-based reprogramming.[67] Transplantation of transposon-induced, iPSC-derived NPCs has been shown to be safe while similarly promoting recovery of motor function in murine SCI models.[49]

Although human clinical trials studying the feasibility of iPSC-based cell therapy in SCI have yet to be finished, recent investigations have explored iPSC-derived NPC grafts in larger systems, including minipig SCI models.[54] iPSC-derived NPCs were generated using a nonintegrating viral model and grafted into syngeneic recipients to investigate changes in functional recovery. Immunofluorescence staining for NeuN, synaptophysin, and GFAP, markers for identifying terminal neural cell subtypes, confirmed differentiated cell populations, while subsequent gene expression analysis revealed distinct neuronal and glial subtypes resembling the cellular organization of non-SCI mature pig CNS tissue. Further safety evaluation of iPSC-derived transplant therapies is required prior to administration in human acute SCI patients; however, positive results from diverse in vivo models hints to their therapeutic potential.

The Future of Cell Therapy Strategies for Treating Acute SCI

While scientific explorations into cell-based therapies for acute SCI has encouraged optimism for future therapeutic utility, clinical evaluation of stem cell transplants in traumatic SCI has moved slowly. Despite advances in the underlying biology of cell-based therapies in acute SCI, there has been a marked lack of large phase III trials exploring the therapeutic efficacy of stem cell transplantation. This paucity may exist for a number of reasons, including but not limited to the ethical challenges concerning the use of ESCs, the financial logistics associated with continued longitudinal functional and imaging analyses of patients receiving transplants, and patients' willingness to receive relatively novel therapies without extensive demonstration of safety.

Furthermore, advancement of cell transplant therapies into the clinical sphere has been hindered by modest efficacy or poor study design in a number of completed trials. A phase III study examining the effectiveness of cell-based therapy in patients with chronic SCI reported injection of BM-MSCs into the intramedullary and subdural spaces resulted in a weak therapeutic effect in only 2 of 16 patients.[41] Despite the negative implication of this result, the limitations of this study encourage optimism for future clinical trials. The aforementioned study did not contain a control arm, preventing coordinators from identifying potential functional improvements in a controlled fashion. Additionally, it had been previously found that the application of multiple MSC injections was required to enhance neurological recovery.[46] However, in the case of this study, only a single administration was given, due to government regulatory policy. Given these concerns, it stands to reason that additional clinical trials are required to validate the potential of stem cell–based therapy in treating acute SCI.

Currently, clinical efforts have focused on validating the safety and efficacy of somatic MSCs; a review of active and ongoing clinical trials in cell-based therapy in acute

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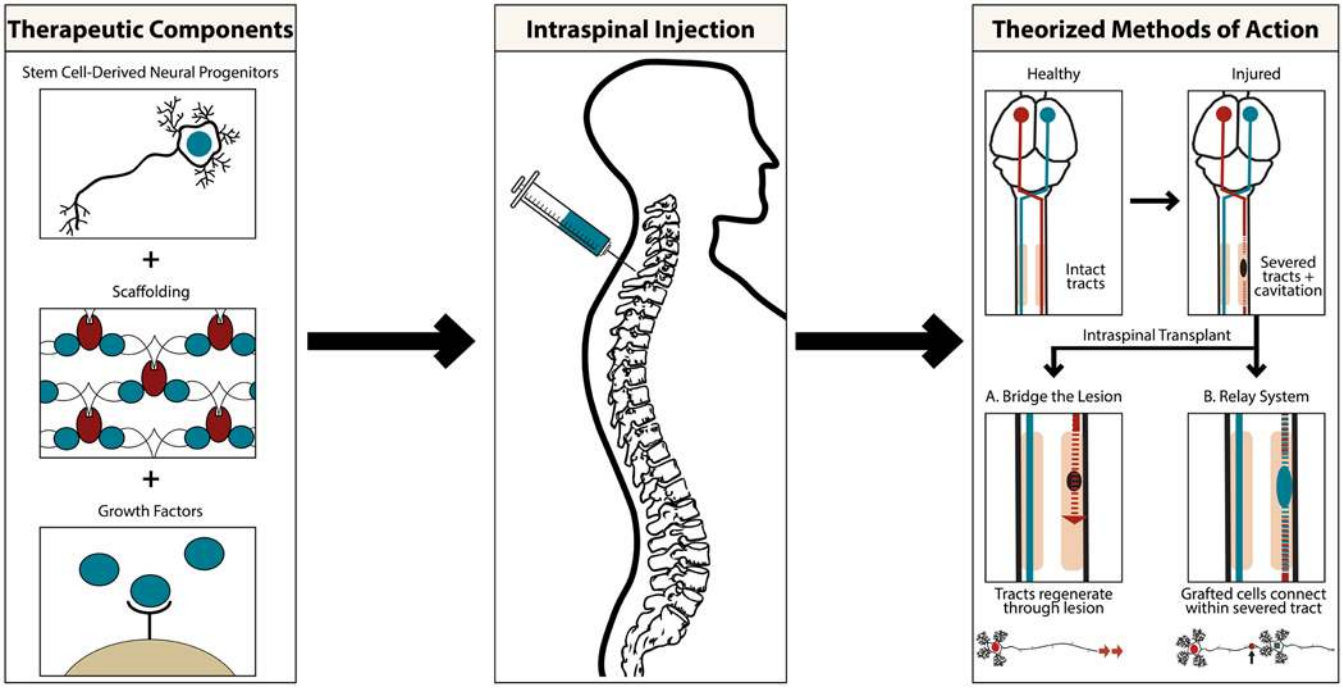

FIG. 1. A combinatorial strategy for cell-based therapies in SCI. Cellular transplantation may be augmented with a combination of growth factors, scaffolds, or other biomaterials that improve cell survival, engraftment, and differentiation. Intraspinal application of these therapies leads to engraftment of transplanted cells, which may promote neural regeneration through several proposed mechanisms. Engrafted cells may provide a conduit for host axonal outgrowth across the site of injury. Alternatively, engrafted cells may act as a relay system by synapsing with neurons located cranial and caudal to the injury site.

SCI revealed 8 of 9 studies (89%) are focusing on MSC transplant as opposed to ESC-centric modalities (Table 2). Additionally, while most of these studies are administering stem cells intrathecally, exploration of other administration routes is also underway and would provide additional understanding on the optimal mode of treatment delivery. Finally, while the vast majority of completed and ongoing studies are phase I/II, preliminary evaluation of neuromuscular functionality using predefined scales of neurological impairment should prime the expansion of later-phase trials aimed at conclusively determining the effectiveness of current and future cell-based therapies for acute SCI.

Therapeutic Adjuncts to Stem Cell Transplantation

Therapeutic adjuncts including scaffolds, biomaterials, and immunotherapies could further promote spinal cord regeneration by augmenting stem cell survival, engraftment, and growth.

Immunotherapy

A major challenge following trauma to the spinal cord is the inhibitory nature of the posttrauma milieu, which is maintained by the presence of growth-suppressive molecules and signaling pathways. Despite the complexity of these inhibitory interactions, investigations have shown promise for immunotherapy in the treatment of acute SCI through both modulation of molecular signaling and regulation of the broader injury environment.[5,29] When applied in rodent models of SCI, antibodies targeting a class of inhibitory molecules called myelin-associated inhibitors (MAIs) support increased locomotor function after injury.[5] Other studies have explored controlling injury-associated inflammation through the administration of B-cell–depleting antibodies, demonstrating reduction of cell death, inflammatory signaling, and hindlimb dysfunction.[8] However, before these therapies can be translated for use in patients, their safety must be clearly demonstrated by showing that these antibodies do not attack healthy myelin and do not elicit detrimental immunological responses.

Biomaterial Scaffolds and Hydrogels

Scaffolds and injectable hydrogels have been designed to augment stem cell engraftment, survival, and direct differentiation toward desired cell types after SCI (Fig. 1). Early work in synergistic treatment approaches involved implantation of extramedullary chitosan channels seeded with NPCs, theorizing that the channels would provide a supportive microenvironment for continued neural cell regrowth and axon extension.[38] Since then, advances in biomaterials research, along with an improved understanding of stem cell biology, have allowed for diverse biomaterial-cellular combinatorial approaches. A recent study examining methods to improve the survival of iPSC-derived OPCs posttransplantation demonstrated that simultaneous injection of a peptide-modified hyaluronan/methylcellulose-based hydrogel improved cell survival and proliferation in Sprague-Dawley rats subjected to compressive spinal injury.[17] Additional assays demonstrated increased OPC migration and reduced teratoma formation in the rats

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receiving both OPCs and the injectable hydrogel. Another study demonstrated that co-introduction of a gelatin/methylacrylate hydrogel with NPCs decreased glial scar formation, reduced local inflammatory responses, and accelerated functional recovery after SCI.[53]

Conclusions

Cell-based therapies for acute SCI offer intriguing therapeutic solutions for a complex pathology. Recent advances in stem cell research have positioned cell-based approaches to SCI as potential therapeutic options for restoring sensorimotor function following acute SCI. Furthermore, combination approaches synergizing biomaterial constructs with stem cell transplants have proved promising. While more extensive validation is required before transitioning cell-based therapies into the clinic, current results and ongoing efforts suggest that stem cell–based approaches may play a major role in improving acute SCI therapy.

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Disclosures

Dr. Veeravagu reports being a consultant for NuVasive, Medtronic, and Johnson & Johnson.

Author Contributions

Conception and design: Veeravagu, Jin, Medress. Acquisition of data: Jin, Medress. Analysis and interpretation of data: Jin, Medress, Azad, Doulames. Drafting the article: Jin, Medress. Critically revising the article: all authors. Reviewed submitted version of manuscript: all authors. Study supervision: Veeravagu.

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