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# Clinical translation of stem cell based interventions for spinal cord injury — Are we there yet?☆

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ABSTRACT

Recent advances in basic science in research related to spinal cord injury (SCI) and regeneration have led to a variety of novel experimental therapeutics designed to promote functionally effective axonal regrowth and sprouting. Stem cell and other cellular interventions have gained lot of attention due to their immense potential of regeneration. These interventions have been tested for their efficacy in case of SCI both at the pre-clinical and clinical level. In this review we critically discuss the published literature on the cellular interventions for SCI and their clinical applications with respect to the strength of evidence established by these studies. The need to curb unethical practice of offering unproven stem cell "therapies" for SCI at a global level is also discussed.



**Contents**



*Abbreviations:* SCI, spinal cord injury; ESC, embryonic stem cells; MSC, mesenchymal stem cells; CNS, central nervous system; NSPCs, neural stem/progenitor cells; OECs, olfactory ensheathing cells; PNS, peripheral nerve system; UCB, umbilical cord blood; SCP, Schwann cell precursors; SSEPs, somatosensory evoked potentials; MEP, motor evoked potential; SC, Schwann cells.

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## 1. Introduction

Injury to the spinal cord can lead to loss of sensation, paralysis, loss of bowel and bladder control and sexual dysfunction. It has a deep psychological, social and economic effect not only on the SCI individual but also on the whole family [1]. Thus it has been hailed as one of the most "devastating ailment" which could affect mankind [2]. The costs involved for the management of SCI have an overall impact on the society,

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hence efforts for prevention, management and cure of SCI are of global importance [3].

The therapeutic potential of cell transplantation for spinal cord injured patients has gained interest of clinicians and researchers due to the huge body of evidence supporting its effectiveness at pre-clinical level [4]. Approaches involving transplantation of fetal tissue, nerve tissue, stem cells and/or their derivatives have been a major focus for translation to the clinical situation [4,5]. A plethora of patient testimonials and case studies as well as a few clinical trials have reported the clinical safety and efficacy of cell transplantation after SCI [4,6]. A number of cell types have been tested in a clinical trial setting. These include Schwann cells (SCs), olfactory ensheathing glial cells (OECs), mesenchymal stem/stromal cells (MSCs), human umbilical cord blood cells (hUCBs), neural stem/progenitor cells (NSPCs) and human embryonic stem cells (hESCs) [4]. In this review we critically discuss the published literature on the cellular interventions for SCI and their clinical applications with respect to the strength of evidence established by these studies and the way forward.

## 2. Pathophysiology of SCI

To understand how these interventions might facilitate repair and regeneration following SCI, it is most important to know about the pathophysiology of SCI. Spinal cord injury in simple terms may be defined as an insult to the spinal cord which alters its normal motor, sensory or autonomic function [7]. The nature and extent of the injury varies widely, depending on the site of injury and its severity.

### *Primary injury mechanisms*

Primary injury is caused by rapid spinal cord compression due to bone displacement leading to acute spinal cord distraction, acceleration-deceleration with shearing or transection from penetrating injuries. Primary mechanical trauma is almost always unexpected and associated with inevitable treatment delays during the first few hours after injury.

### *2.2. Secondary injury mechanisms*

A primary injury to spine triggers a number of pathophysiological processes which may lead to a prolonged secondary injury phase that results in neurological impairment associated with loss of function [3]. The pathophysiological processes which are most affected relate to three major bodily systems — the nervous system, the immune system and the vascular system [4].

This phase may be further divided into acute, sub-acute and chronic phases depending upon the time elapsed since the primary injury. Initially, hemorrhage and rapid necrotic cell death occur followed by a number of interrelated biochemical and molecular events resulting in vascular insufficiency, neural excitotoxicity, toxic free radical production, inflammatory reactions and immunological responses, astrogliosis and demyelination, and apoptotic forms of neuronal as well as glial cell death [8]. This has been referred to as "death spiral" which comprises of numerous molecular and cellular/biochemical events following SCI. The major events following SCI include hemorrhage, ischemia, hypoxia, decrease in ATP, upregulation of stress genes, activation of local microglia and pro-inflammatory cytokines (e.g. TNF-, IL-1) leading to inflammation, downregulation of cytoskeleton gene expression (e.g. p38MAPK), increased glutamate excitotoxicity, free radicals production, edema and neutrophil invasion. This is followed by lipid peroxidation, nitric oxide production, activation of proteases and TGF-beta and CD-11 upregulation resulting in necrosis, neural apoptosis, astrogliosis, axon demyelination, axon degeneration and cyst formation. This cascade of events finally culminates into a permanent loss of spinal function [3,8]. Liverman et al. [3] and Steeves et al. [8] provide a detailed description of these events.

It is now well accepted that the final neurologic deficit is not just the result of the primary mechanical injury, but is the result of a combination of primary and secondary events [8].

Since logistical issues preclude immediate interventions after the primary injury, limiting the adverse effects of biochemical and molecular cascades activated during the secondary injury phase are the targets of choice for designing interventions aimed at achieving repair and regeneration after SCI [8].

## 3. How does SCI differ from other injuries in the body?

The greatest challenge for repair and regeneration after SCI has been the inability of central nervous system (CNS) neurons to regenerate with correct axonal and dendritic connections. For years it was thought that CNS neurons could not regenerate at all. However, this was initially disproved by RamoÂn y Cajal in 1928 and later confirmed by Aguayo et al. [9,10]. They demonstrated the intrinsic capacity of CNS neurons for regrowth over long distances, however, these neurons were actively inhibited by molecules in their extracellular environment. The extracellular environment may also lack molecules that promote or guide axon regrowth to its correct target site. Thus, CNS axons could regrow if their immediate environment is supportive [10]. This strongly suggests that failure of CNS neurons to regenerate is mainly due to the defects lying in the environment rather than within the CNS neurons.

## 4. Barriers to regeneration after SCI

A vast number of strategies have been employed in order to achieve regeneration of the damaged neurons. However, a number of challenges remain which need to be addressed satisfactorily to ensure that the experimental interventions for regeneration and repair after SCI are successful.

Regeneration of adult CNS neurons is not a one-step process rather it requires that the neuron survives (inhibits apoptosis), extends its processes toward its original neuronal target (site-directed migration), remyelinates and forms functional synapses [11].

Hence, a multitude of regenerative (cell growth and survival) as well as non-regenerative (physical and biochemical) events need to function in tandem to restore functionality of the damaged neuron [8,12].

Fig. 1 gives a schematic description of the cellular and molecular events following SCI which create a hostile environment for axonal regrowth and are the major barriers to overcome for achieving repair and regeneration.

## 5. Experimental interventions to facilitate recovery

The cellular and molecular events defined in Fig. 1, thus, are potential targets to facilitate neuronal recovery after SCI. Fig. 2 depicts the various strategies which have been tested in order to overcome the barriers to regeneration [12]. These include

- Inhibition of the voltage-dependent sodium channels, inhibition of neural injury induced by a surge of action potentials early in the injury phase and cell transplantation to overcome demyelination and conduction deficits.
- Inhibition/degradation of extracellular matrix proteins, elimination of astrocytes, local delivery of neurotrophins and directly targeting intracellular mechanisms for promoting neurite growth by improving the extracellular environment.
- Restoration of function by introduction of cells lost due to degeneration with an intent that these tissues/cells would rescue, replace, or provide a regenerative pathway for injured adult neurons, which would then integrate or promote the regeneration of the spinal cord circuitry and restore function after injury.
- Enabling nerve fibers with potential for regenerative growth or collateral sprouting (undamaged nerves cells that sprout) to overcome the

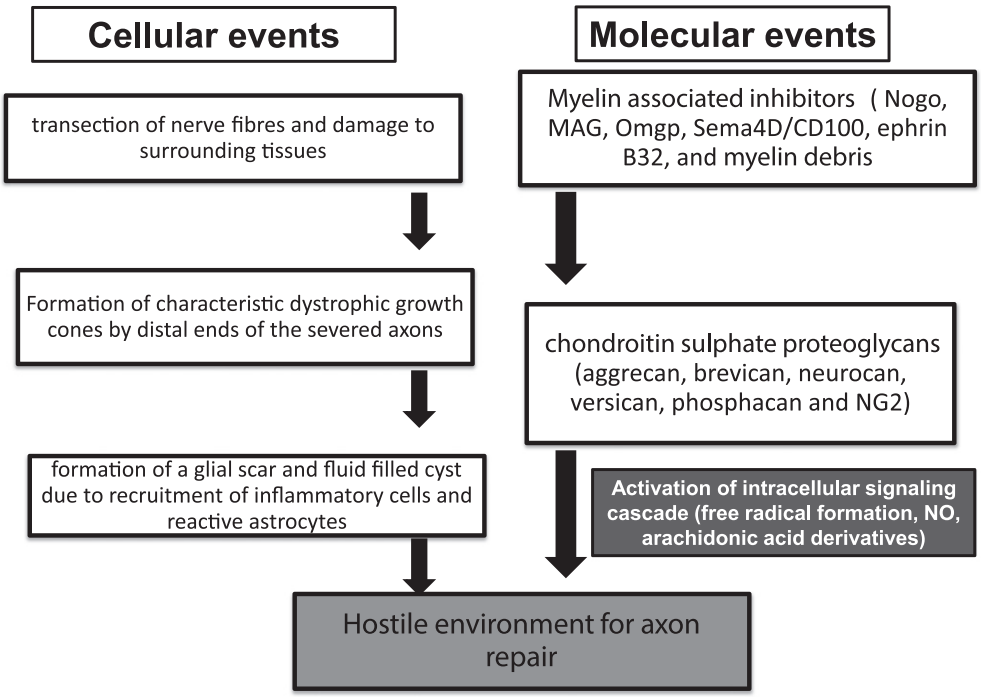


**Fig. 1.** A schematic description of the cellular and molecular events following SCI.

non-permissive physical gap by providing a permissive bridging substance. This includes the use of cells, fetal tissue en bloc, and artificial material/scaffolds, either alone or in combination along with various growth factors.

These strategies have been developed and tested for their safety and efficacy at pre-clinical as well as, in many cases, at the clinical level. The evidence base for these strategies is given in Table 1. In this review, we will discuss stem cell and other cellular interventions undertaken for the restoration of neurological and functional deficits arising after SCI.

## 6. Pre-clinical and clinical evidence base for cellular interventions

### *6.1. Pre-clinical studies*

Embryonic stem cells (ESC) were the first population of cells tested for its regenerative potential. The cells could differentiate into neuronal

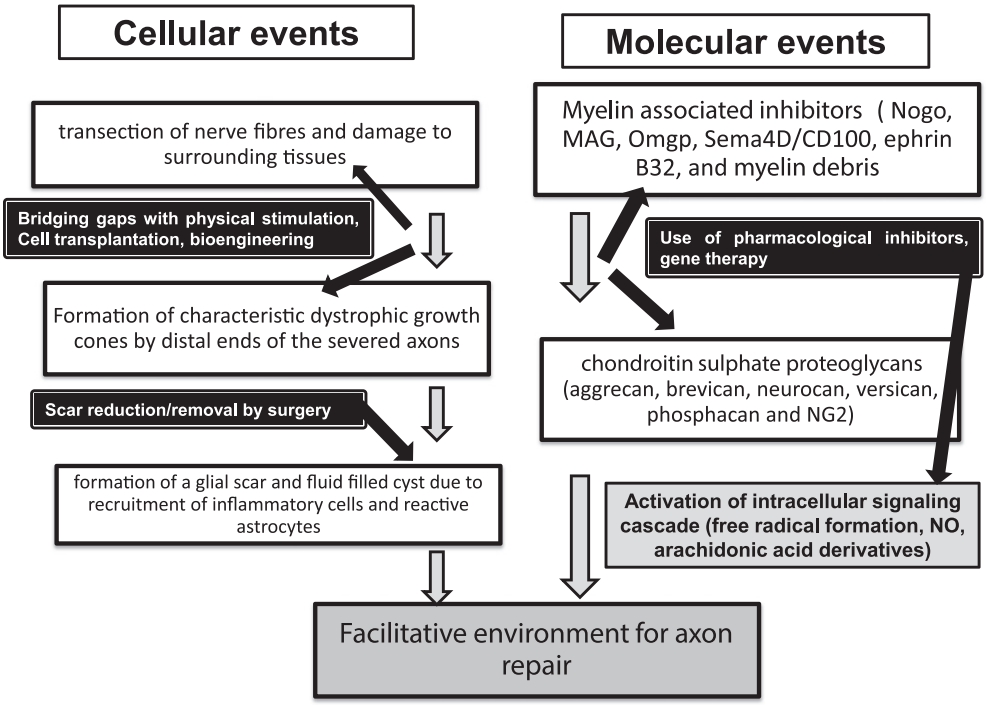


**Fig. 2.** Various strategies tested in order to overcome the barriers to regeneration. The strategies employed are given in black boxes. Solid arrows indicate the target(s) of the strategy employed.

**Table 1**
Strategies for overcoming the barriers to regeneration.

| Deficit to be repaired | Strategy | Mediators/interventions explored | Evidence base | Reference |
|---|---|---|---|---|
| Demyelination and conduction deficits | Inhibition of voltage-dependent sodium channels | $Na^+$ channel blocker tetrodotoxin (2,3-dihydroxy-6-nitro-7-sulfamoyl-benzo(f)quinoxaline) | Pre-clinical:<br>Rescue of neural tissue and improved behavioral recovery | [84] |
| | Inhibition of barrage of action potentials | Voltage-sensitive $K^+$ channel blocker 4-aminopyridine (4AP) | Clinical:<br>Phases II & III clinical trials at Acorda and Washington Univ | [85] |
| | Cell transplantation | • Olfactory ensheathing cells<br>• Oligodendrocytes<br>• Schwann cells | Pre-clinical:<br>Demonstrates efficacy | [46,86] |
| Inhibition of neurite growth | Inhibition/degradation of ECM proteins | • Chondroitinase ABC<br>• IN-1 (Anti-Nogo) antibody | Pre-clinical:<br>Rescue of neural tissue and improved behavioral recovery by chondroitinase<br>Clinical:<br>Phase I & multicentric, multinational Phase II clinical trial applying anti-Nogo-A antibody to subjects with acute SCI has been successfully conducted.<br>http://clinicaltrials.gov/ct2/show/NCT00406016 | [87,88] |
| | Elimination of astrocytes | • Ethidium bromide<br>• X-irradiation<br>• Glial cytotoxins | Pre-clinical:<br>Experimental only due to associated risks | [89] |
| | Local delivery of neurotropins | • NGF<br>• NT-3<br>• GDNF<br>• BDNF | Pre-clinical:<br>Intrathecal infusion demonstrated some success in regeneration of cut dorsal roots.<br>GDNF demonstrated the best anatomical, functional, and behavioral recovery. | [90] |
| | Target direct intracellular mechanisms | • Inosine, a purine nucleoside and cAMP | Pre-clinical:<br>Neurite outgrowth promotion *in vitro* and in the rodent spinal cord.<br>Clinical:<br>AIT-082, a synthetic hypoxanthine derivative containing a para-aminobenzoic acid moiety (Neotrofin; NeoTherapeutics) shown to promote both axonal sprouting and the production of NGF, NT-3, and bFGF in astrocytes in culture systems and *in vivo*. Four rehabilitation centres testing Neotrofin in subacute (21 days of injury) spinal cord injuries: Ranchos Los Amigos, Gaylord, Craig, and Thomas Jefferson Rehabilitation Centres. | [91–94] |
| Loss of function | Restoration of function by introduction of cells lost due to degeneration | • Olfactory ensheathing cells<br>• Schwann cells<br>• Processed Schwann cells<br>• Transplanted conduits of Schwann cells<br>• Dorsal root ganglia<br>• Adrenal tissue<br>• Hybridomas<br>• Peripheral nerves | • Cells showing success in animal models include olfactory ensheathing cells, oligodendrocytes, Schwann cells and stem cells.<br>• Vast preclinical data is available elucidating some level of functional restoration by each cell type. However, only few human trials have been conducted. Since trial design was not appropriate in some cases, conclusive data not yet obtained. | [5,95] |
| | Gene therapy | Cells transfected with<br>• NGF<br>• NT3 | Pre-clinical:<br>• Rodent syngenic fibroblast cells transfected with NGF demonstrated some success with neurite growth of cells that respond to NT3<br>• Other cells were transfected with neurotrophins and demonstrated some success in terms of promoting neurite growth and some behavioral recovery including Schwann cells and embryonic neural precursors | [96,97] |
| Glial scar/"Gap" | Overcome the non-permissive physical gap by providing a permissive bridging substance | • Cell transplants<br>• Schwann cells,<br>• Multiple grafting of intracostal nerves<br>• Olfactory ensheathing cells<br>• Human neural progenitor cells<br>• Bone marrow mononuclear cells<br>• Mesenchymal stem cells<br>• Umbilical cord blood stem cells<br>• Embryonic stem cells | Pre-clinical:<br>Promising evidence<br>Clinical:<br>Absence of robust Level 1 evidence. | [5,98] |
| | | • Fetal tissue en bloc, or | Pre-clinical:<br>Promising results have been reported using fetal spinal cord transplants into the adult spinal cord in rats, mice, and primates<br>Clinical:<br>Used in chronic SCI patients with post-traumatic syringomyelia. Poor design therefore no conclusive result | [95,99,100] |

**Table 1** (*continued*)

| Deficit to be repaired | Strategy | Mediators/interventions explored | Evidence base | Reference |
|---|---|---|---|---|
| | | • Artificial material/scaffolds | Pre-clinical:<br>Potential to enhance the survival of NPCs | [101] |
| | | • Axon guidance devices | – Often used in combination with other tissue engineering strategies<br>– Have been used, with varying success for PNS nerve regrowth, spinal cord and brain nerve tract repair<br>– PNS repair has been more successful<br>• Upregulation of regeneration-associated genes (c-Jun, GAP-43, etc.)<br>• Presence of Schwann cells (produce myelin, but also provide nutrients and aid in guidance) | [102] |

cell types both *in vitro* and *in vivo* in animal models. However, due to their capability to differentiate into all cell types they were found to be tumorigenic [13]. Several groups have derived neural progenitor/stem cells [14,15], motor neurons [16], oligodendrocyte progenitor cells [17], and olfactory ensheathing cells from ESCs *in vitro* [16], and then transplanted these cells into various animal models to study restoration of neural function. Embryonic stem cell-derived populations have also been utilized for many combinatorial strategies [5].

Mesenchymal stem cells have been reported to differentiate into osteoblasts, chondrocytes, adipocytes, neural cells and myoblasts, *in vitro* [18,19]. Due to their multipotent nature, source availability and comparative safety, these cells have been advocated as a promising cell source for repair. Transplantation of MSCs in SCI animal models has been reported to promote sensorimotor function recovery and bladder function recovery *via* neural lineage differentiation, neurotrophic paracrine effects and post-trauma inflammation regulation [20–27]. The major limitations in the therapeutic *in vivo* application of MSCs for spinal cord injury is their low survival rate after graft, the lack of neural differentiation, glial scar formation, cystic cavity formation, the inhibitory cellular environment, the transplantation time point, and the graft/host immune responses [4]. Also, significant effects on the outcome are observed depending upon the route of transplantation of MSCs. In order to overcome the limitations of direct MSC transplantation, several strategies have been employed that include pre-transplantation neural differentiation, neurotrophic gene transduction, glial cell co-transplantation, and tissue engineering [24,28–30]. Sources of MSCs other than bone marrow have also been identified by researchers, such as adipose tissue, amniotic fluid, placenta, umbilical cord blood (UCB), and in several fetal tissues including liver, lung, and spleen [4]. Of these the MSCs from UCB and adipose tissue are sources of choice with many advantages such as ease of collection, availability and proliferative capacity [31–33] One of the major barriers to spinal cord regeneration is the glial scar, which hampers the movement of regenerating cells and does not support the survival of implanted cells and their neural differentiation [34]. Biological scaffolds are now gaining importance for providing support as well as neurotropins to aid cell survival, differentiation , and proliferation [35,36].

Neural stem/progenitor cells are capable of self-renewal and generating the main phenotypes (neurons, astrocytes, and oligodendrocytes) of CNS cells *in vitro* and *in vivo* [37]. After transplantation into the injured spinal cord, NSPCs generate mature neural phenotypes and provide neural functional recovery in some SCI models [38]. *In vivo* transplanted neural stem cells (NSCs), in most cases, have shown a preferential capability of differentiating into glial lineages, especially astrocytes [38]. However, the direct transplantation of NSCs or neural progenitor cells has not been always efficient for functional recovery after SCI.

Olfactory ensheathing cells are present in the olfactory epithelium and are considered a special class of glial cells which exist in both the peripheral nervous system (PNS) and CNS, and share certain features and functions with astrocytes as well as SC [39]. Studies have shown that rodent OECs are able to support axonal regrowth when transplanted into experimental models of spinal cord injury [39] and are also able to form myelin sheaths around regenerated or demyelinated axons, thereby permitting rapid saltatory conduction to occur [40]. Olfactory ensheathing cells promoted regeneration after complete transection of the spinal cord [41] and restored rapid and secure conduction across the transected dorsal columns of the rat spinal cord with the recovery of motor function [42]. Human olfactory ensheathing cells were also shown to remyelinate the demyelinated spinal cord of the rat [43]. Other groups have shed doubt on the functional improvements induced by OEC grafts, and have suggested that they are caused by a trophic support mechanism and not the birth of new neurons, which means that the therapeutic potential of OECs after SCI may be limited [44,45].

It has been demonstrated that after SCI if the injured neurons are grafted into a peripheral neural environment, which facilitates growth and remyelination, they can recover their morphology and electrophysiological function [46]. SCs are an important part of the peripheral nerve system (PNS) and are vital for the myelination of peripheral axons. In the past studies, SCs used were isolated from peripheral nerves and cultured *in vitro* to provide enough number of cells for the transplantation. Recently, alternate sources for SCs have been used. The SCs have been derived from different stem cell populations or neural progenitors like mesenchymal stem cells [47], adipose-derived stem cells [48] and skin-derived precursors [49]. SC transplantation has been reported to lead to remyelination of demyelinated axons and axonal sprouting [49]. A successful integration of SC precursors (SCPs) into the host tissue, and a robust bridging effect which extended rostrocaudally into the lesion site after surgery has been reported [50]. However, no significant difference in motor function was observed between the SCPs and control group. Improved axonal regeneration and motor function have also been reported following transplantation of SCs which were genetically modified to secrete neurotrophin in combination with chondroitinase [51].

Based on the pre-clinical evidence of efficacy, the discussed cell populations have been tested for their efficacy in case of human SCI.

### 6.2. Clinical studies

Although pre-clinical evidence provides a good basis for undertaking testing of putative cell populations in humans, at times the clinical translation is hindered due to limitations of the experimental models used for the pre-clinical studies and the trial design. These include anatomical differences in the experimental injuries and human SCI, choice of the animal model, cell population and cell numbers used, subject selection criteria, confounding factors like spontaneous recovery and absence of standardized outcome measures.

Xian-Hu et al. reported recovery within their 6 clinical cases post SC transplantation. However, the study results have limitations due to poor

subject selection criteria and post assessments [52]. Saberi et al. undertook a 2-year follow-up for the safety assessment of SC transplantation therapy. Transient paresthesia or increased muscle spasm has been reported following transplantation of purified SCs in persons with chronic SCI (28–80 months post-trauma) [53].

Huang et al. transplanted OEGs in 16 individuals with chronic SCI. They concluded that their protocol is feasible and safe to treat persons with chronic SCI within 38 months after the injury. Olfactory mucosa autografts were transplanted into lesions after a myelotomy and scar removal in AIS A individuals between 18 and 32 years of age, 6 months to 6.5 years post-injury. The authors concluded that the study was feasible, relatively safe and potentially beneficial. However, the efficacy of the reported procedure could not be replicated in human chronic thoracic SCI [54]. Recently neurological improvements have been reported in a 38-year old male with a complete chronic SCI after transplantation with a mix of OECs and olfactory nerve fibroblasts along with sural nerve grafts. However, further studies with larger population need to be conducted before the efficacy of this approach is established [55,56].

In a case report, Ichim et al. transplanted MSCs and CD34 cells in combination with a total of 13 intrathecal administrations and 2 IV injections in 3 cycles of treatment into a 29-year old AIS A individual within a period of 10 months. Significant improvements in sensory function and lower limb muscle strength recovery were reported at the end of treatment. The individual was classified as AIS D six months post-transplantation with no adverse immunological reactions. However, there was insufficient evidence in the study to support that the recovery was due to cell graft and not spontaneous [57].

In another study, the effect of intrathecal administration of MSCs was studied in persons with chronic complete SCI. Monthly administration of autologous MSCs for 6 to 12 months in 45 persons did not lead to any significant improvements over the controls. Additionally, neuropathic pain was reported in 23 of the treated cases, leading the authors to conclude that further preclinical data was necessary before commencing with large scale clinical trials using MSCs [58]. In a similar study, Bhanot et al. reported equivocal results following administration of autologous MSCs at the lesion site after laminectomy in persons with chronic SCI [59].

Autologous MSCs were transplanted by Karamouzian et al. into the cerebrospinal fluid *via* lumbar puncture for eleven SCI individuals with complete thoracic and compared with 20 SCI individuals in the control group. Although, no adverse reaction and complications in control and interventional groups were experienced by subjects, the functional improvement between the two groups was not significant [60].

Improvement in motor and/or sensory functions was observed within 3 months in 5 of 6 individuals with intra-arterial application, in 5 of 7 acute, and in 1 of 13 chronic individuals following the transplantation of unmanipulated autologous bone marrow in individuals with SCI [61].

A phase I/II open-label and nonrandomized study on 35 individuals with complete SCI has also been conducted. The AIS grade was reported to increase in 30.4% of the acute and subacute treated individuals (AIS A to B or C), whereas no significant improvement was observed in the chronic treatment group [62].

Jarocha et al. in a preliminary study have reported safety and feasibility of transplantation of autologous bone marrow mononuclear cells in children with chronic SCI. Though the authors claim to a certain degree of neurological improvement due to the cell transplant, this evidence base provided is inconclusive [63].

In a case series of 14 individuals with SCI, Amr et al. have reported co-transplantation of bone marrow derived MSCs, chitosan-laminin scaffold and peripheral nerve grafts after chronic SCI. The authors have reported sensory and neurological improvements and proposed that the combined treatment helps in bridging the glial scar and thus facilitates functional and neurological recovery [64].

Pal et al. undertook to transplant BMC *via* lumbar puncture in 20 individuals who had been injured for less than 6 months and 10 who had suffered injury for more than 6 months. No adverse effects were reported. There were no significant differences in the MRI scans taken at baseline and at the 1-year follow- up. Similarly, somatosensory evoked potentials (SSEPs), motor evoked potentials (MEPs) and nerve conduction velocity (NCV) measurements revealed no significant changes [65].

In our experience transplantation of autologous bone marrow cells *via* intrathecal or intralesional route in persons with acute complete (AIS A) SCI did not demonstrate significant improvement in the neurological, electrophysiological or urodynamic efficacy variables as compared to controls [66].

Autologous transplantation of MSCs derived from adipose tissue has also been undertaken. In a study by Ra et al., 8 individuals with chronic SCI received autologous transplantation of MSCs derived from adipose tissue. Several adverse effects following transplantation were reported and there were no changes in electrophysiological (SSEP and MEP) recordings [67].

Preclinical studies suggest behavioral efficacy due to hUCB transplantation and suggest that benefits may come from secretion of factors by transplanted cells. However, only a few small "open label" human studies have been conducted with varying claims of benefit [68,69].

Due to ethical and safety issues of harvesting NSPCs from fetal material, transplantation of these cells has been limited. Despite these challenges, a part of the scientific community believes that NSPCs represent an ideal candidate for cell-based treatment of SCI due to functional improvement noticed after their transplantation, low rates of tumorigenesis, and the opportunity for autologous transplantation. Two trials one by StemCells Inc. [CT #NCT01321333] and the other by Neuralstem Inc. [CT #NCT01772810]. involve transplantation of these cells.

The potential use of ESCs in clinical applications has garnered the attention of researchers as well as clinicians. However, several issues remain to be addressed regarding their safety and efficacy [13,70,71]. One of the most widely publicized trials has been the transplantation of human ESC-derived oligodendrocyte progenitor cells, GRNOPC1, in persons who were suffering from complete thoracic level paraplegia. To date, there are no reports of serious adverse events in the long-term follow-up [72].

Treatment of patients with SCI by human ES transplantation (NTECH-2000 n/nn) in SCI has been reported to be safe and effective. However, due to the lack of controls, the absence of validated outcome measures as well as the lack standardized treatment plan and heterogeneous population, the reported efficacy needs to be confirmed within a validated clinical trial setting before these cells may be used as a standard therapy [73,74].

Most of the published studies exploring the role of cellular interventions in case of human SCI have the following features in common which limit their claims of efficacy

- Most are from emerging nations
- Most are open label studies
- Most are uncontrolled studies

Due to these limitations, the level of evidence regarding the efficacy of cellular interventions tested in these studies is low. A comprehensive list of published clinical trials and their limitations is discussed in Sarda and Chhabra in 2015 [5]. With the publication of guidelines for the conduct of clinical trials in case of SCI, recent ongoing and upcoming trials for testing cellular interventions for SCI have addressed these limitations. One may look forward to the outcomes of these trials for providing scientific and validated data for the role of cellular interventions in repair and regeneration after human SCI. An updated list of these trials may be found in the website of Spinal Cord Outcomes Partnership Endeavor (www.scope-sci.org).

## 7. Unproven "treatments"

In the past two decades or so "stem cell transplantation" has gained considerable attention. It has been touted as a "cure-all" therapy for a large variety of conditions. Some experimental therapies have been

introduced into clinical practice without a valid clinical trial being completed [75,76]. Worldwide a number of centres offer such non-validated interventions as an alternative to standard mode of therapy. A rise in so-called stem cell tourism with patients from the countries with strict oversight and legislation regarding the use of such unproven "therapies" traveling to countries with less defined regulations for "treatment" has been a particular cause for concern in international community [77]. Most of the positive clinical improvements claimed due to such "therapies" are testimonials provided by these centres. Such testimonials are mostly subjective in nature since the individuals undergoing transplants are generally not subjected to any validated and objective assessments to measure the outcome of the "treatment". There is generally no evidence that the reported improvements in such cases are related to the actual stem cell/cellular transplantation. It may as well be attributed to the 'placebo effect', accompanying treatments, and natural history of the condition. If the patients with spinal cord injuries are not properly counseled, they may feel that the functional improvements experienced by them are due to the transplant.

Use of stem cells or other cellular interventions in the absence of scientifically validated evidence of safety and efficacy at both the pre-clinical and clinical levels may lead to adverse effects which may develop many years after the interventions [78]. Thus, it is essential to curb the use of cellular interventions outside of validated clinical trials.

Worldwide various societies engaged in SCI management and care have issued position statements and guidelines in order to educate healthcare workers as well as the SCI individuals to create awareness regarding the current evidence of efficacy of stem cells and curb the malpractices by these "stem cell treatment centres" [78–81].

Internationally those involved in exploring cellular interventions for achieving repair and regeneration after SCI acknowledge that these interventions have a "very high potential to translate into the clinical setting" [5,6,78,79,82,83]. However, it is important to establish their efficacy through a recognized framework of clinical trials.

Due to the involvement of multiple cell types and the complexity of SCI, it is becoming increasingly clear that a multi-factorial approach involving cell populations, scaffolding matrix, growth factor supplementation and scar removal may be more successful in achieving SCI repair. It can be envisioned that future trials would involve an amalgamation of inputs from clinicians, pharmacologists, cell biologists and biomaterial engineers to come up with multi-pronged strategies for achieving repair and regeneration after SCI.

It is also essential that all countries unite to form legislation and have strict oversight mechanisms in order to curb the sprouting of stem cell "treatment" centres which offer unproven stem cell "therapies" as a cure.

To date, cellular interventions for SCI remain experimental and it is unethical to offer such unproven transplantations as therapies and to charge for it.

## 8. Conclusion

The list of experimental therapies that have been developed in animal models to improve functional outcomes after spinal cord injury is extensive. There is a vast body of pre-clinical evidence which supports the therapeutic potential of cell transplant in facilitating spinal cord regeneration and/or repair after SCI. However, pre-clinical studies have their inherent limitations dependent upon the mechanism of injury and the animal model used. The reported efficacy in most of the published clinical trials is also limited due to poor trial design and absence of controls. A number of questions remain regarding the choice of cells, their safety, the number of cells to be transplanted and long-term safety. The complex pathophysiology of SCI has to be kept in mind before designing any clinical study. From the clinical viewpoint it is necessary to address the time point of transplantation, too early would probably result in transplant death due to the pro-apoptotic environment and later time points may be ineffective due to loss of plasticity of the cells at the point of injury and the glial scar. Approaches which are designed to combine scaffold matrices, neutrotrophic factors and neural precursor cells might show more promising results. These approaches need to be combined with better imaging techniques and robust outcome measures at the clinical level. This would decrease the heterogeneity of the study population and hence provide concise data for evaluating the effect of stem cell transplantation in case of SCI.

One may look forward to the findings of recent clinical trials for understanding the role of cellular interventions for repair and regeneration after SCI. It may be envisioned that future clinical studies would involve a collaborative network of clinicians, researchers, pharmacologists and biomaterial engineers to address the issue of facilitating repair and regeneration after SCI. This along with global participation for forming legislation to curb the misuse of cellular interventions as "cure" would pave the way for delineating the role of cellular interventions in case of SCI.

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